EU Risk Management Plan for
Pelgraz* 6 mg solution for injection in pre-filled syringe and
Pelgraz 6 mg solution for injection in pre-filled injector
(pegfilgrastim)

RMP version to be assessed as part of this application:

RMP Version number	3.0
Data lock point for this RMP	02-Jan-2026
Date of final sign off	13-Mar-2026

*Note:

1. In clinical/non-clinical study data, the product brand name of test product has been mentioned as "APO-Peg", "Pegylated Apo-Filgrastim" instead of "Pelgraz" to be in-line the product brand name with the finalised protocols/clinical study reports.
2. Throughout the RMP, "Pegylated Apo-Filgrastim" will be referred as "Pelgraz"

Rationale for submitting an updated RMP: This RMP has been updated in line with EPAR Risk-management-plan of Neulasta (Pegfilgrastim) (Version 11.0, dated 20-May-2025) published by the EMA on 08-Dec-2025.

Summary of significant changes in this RMP: Significant changes have been done in following sections of RMP: Part II (, SVII, SVIII), Part V, Part VI, Part VII (annex 7, annex 8)

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP

Version number	Procedure	Date of approval
2.0	EMEA/H/C/003961	26-Apr-2023

QPPV name: Arletta Werynska

QPPV signature: [redacted]

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Pegfilgrastim
Pharmacotherapeutic group(s) (ATC Code)	**Pharmacotherapeutic group(s):** Immunostimulants, colony stimulating factor **ATC Code**: L03AA13
Marketing Authorisation Holder	Accord Healthcare S.L.U.
Medicinal products to which this RMP refers	02
Invented name(s) in the European Economic Area (EEA)	Pelgraz 6 mg solution for injection in pre-filled syringe Pelgraz 6 mg solution for injection in pre-filled injector
Marketing authorisation procedure	Centralised Procedure (EMEA/H/C/003961)
Brief description of the product	Chemical class: Hematopoietic Agents (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 (PEG) 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 within 24 hours, 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. As with other haematopoietic growth factors, G-CSF has shown *in vitro* stimulating properties on human endothelial cells. 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*.
	Important information about its composition Each pre-filled syringe / injector contains 6 mg of pegfilgrastim* in 0.6 ml solution for injection. The concentration is 10 mg/mL based on protein only**. *Produced in *Escherichia coli* cells by recombinant DNA technology followed by conjugation with polyethylene glycol (PEG). ** The concentration is 20 mg/mL if the PEG moiety is included. *Excipient(s) with known effect:* Sorbitol Each pre-filled syringe / injector contains 30 mg sorbitol (E420) Sodium Pelgraz contains less than 1 mmol sodium (23 mg) per 6 mg dose, that is to say essentially 'sodium-free'.
Hyperlink to the Product Information	Refer Module 1.3.1 for SmPC and PIL.
Indication(s) in the EEA	***Current*** Pelgraz is indicated to reduce the duration of neutropenia and the incidence of febrile neutropenia (FN) in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Dosage in the EEA	***Current*** Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. **Posology:** One 6 mg dose (a single pre-filled syringe or pre-filled injector) of Pelgraz is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy. **Method of administration:** Pelgraz is for subcutaneous use. The injections should be given subcutaneously into the thigh, abdomen or upper arm.
Pharmaceutical form(s) and strengths	***Current*** **Pharmaceutical form(s):** Solution for injection in pre-filled syringe & Solution for injection in pre-filled injector **Strengths:** 6 mg of pegfilgrastim in 0.6 mL solution for injection
Is the product subject to additional monitoring in the EU?	No

Part II: Safety specification

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

Not applicable for biosimilar medicinal products.

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

In accordance with the Guidelines on Biosimilars when the non-clinical studies were conducted, the nonclinical development program of Pelgraz included comparative pharmacodynamic, repeat-dose toxicokinetics and local tolerance studies to demonstrate the safety and comparability of Pelgraz and Neulasta.

Table 2: Non-clinical studies of Pegylated Apo-Filgrastim

Non- clinical study details	**Relevance to human usage**
Study No.: 410.419.1796: *EU-approved and US-licensed Neulasta Pivotal Comparative In-Vivo Efficacy Testing of Pegylated Apo-Filgrastim versus EU-approved and US-licensed Neulasta.* **Route of administration:** Subcutaneous **Species:** Neutropenic BALB/C mice Module 4.2.1.1	Preclinical data revealed no special hazard likely for humans. • The parallel line analysis of Pegylated Apo-Filgrastim with EU-approved Neulasta and US-licensed Neulasta showed the relative potency of Pegylated Apo-Filgrastim to US-licensed Neulasta as 1.006 and as 1.024 with EU-approved Neulasta. These results fall well within the acceptable potency criteria of 0.8-1.25 for comparability, thereby demonstrating that Pegylated Apo-Filgrastim, EU-approved Neulasta EU and US-licensed Neulasta are equally potent in the pharmacological effects of restoration of neutrophil counts.
Study No.: BIO-EF- 697: *Pivotal Comparative In-Vivo Efficacy Study of Pegfilgrastim Drug Products and Neulasta.* **Route of administration:** Subcutaneous **Species:** Neutropenic Swiss Albino mice Module 4.2.1.1	Preclinical data revealed no special hazard likely for humans. • Study showed a comparable dose-dependent increase in absolute neutrophil counts with both Pegylated Apo-Filgrastim EU-approved Neulasta, thereby demonstrating the comparability in pharmacodynamic effects. Toxicokinetic analyses of the active moiety, pegfilgrastim, showed parallel plasma profiles of the Pegylated Apo-Filgrastim and EU-approved Neulasta, consistent with the similarity of the observed pharmacological effect.

Non- clinical study details	**Relevance to human usage**
Study No.: 410.120.1797: *Pivotal Comparative Repeat-Dose 28 days toxicity study in rats (comparability) also including 14 day toxicokinetic assessment: Pegylated Apo-Filgrastim vs EU-approved Neulasta.* The effect on neutrophil counts was also assessed in a pivotal 28-day repeat-dose toxicity study in Wistar rats. **Route of administration:** Subcutaneous **Species:** Wistar rats Module 4.2.3.2	Preclinical data revealed no special hazard likely for humans. • 28-day repeated dose toxicity study at dose of Pegylated Apo-Filgrastim 30 µg/kg, 180 µg/kg, or 1100 µg/kg showed a comparable dose-dependent increase in absolute neutrophil counts accompanied by an increase in myeloid hyperplasia in bone marrow, an increase in circulating alkaline phosphatase, spleen weight and hematopoiesis in the liver and spleen with both Pegylated Apo-Filgrastim and EU-approved Neulasta. • With regard to immunogenicity, signals slightly above the Lower Limit of Quantification (LLOQ) of the anti-drug antibody assay were measured in single animals of the Pegylated Apo-Filgrastim and low dose EU-approved Neulasta groups as well as in the Vehicle group suggesting that these signals seen in both Pegylated Apo-Filgrastim and EU-approved Neulasta treated animals were at the border of specificity and therefore considered not treatment-related. This deduction is further supported by the absence of an increase in IgG or IgM levels detected in samples from both Pegylated Apo-Filgrastim and Neulasta treatment groups.
Study No.: 410.542.4251: *Pivotal, comparative Local tolerance: Pegylated Apo-Filgrastim **vs.** EU-approved Neulasta and US-licensed Neulasta.* **Route of administration:** Intrarterial, intramuscular, intravenous, paravenous, subcutaneous **Species:** New Zealand rabbit Module 4.2.3.6	Preclinical data revealed no special hazard likely for humans. • This study demonstrated the comparable local tolerance of Pegylated Apo-Filgrastim as compared to US-licensed Neulasta and EU-approved Neulasta in female New Zealand White rabbits. • Pegylated Apo-Filgrastim caused no adverse local skin reactions after intravenous, subcutaneous, intraarterial, paravenous and intramuscular injection. Slight to moderate to hematoma formation was noted in some animals after intravenous, intraarterial, paravenous and subcutaneous injection. Most

Non- clinical study details	Relevance to human usage
	of the observed findings were caused by the treatment procedures.
Study No.: 410.552.4252: *Pivotal Comparative, Skin Sensitization study of Pegylated Apo-Filgrastim vs EU-approved Neulasta and US-licensed Neulasta* **Route of administration:** Intradermal, dermal **Species:** Guinea pigs Module 4.2.3.6	Preclinical data revealed no special hazard likely for humans. • When challenged, none of the treatment groups (Pegylated Apo-Filgrastim, US-licensed Neulasta, EU-approved Neulasta, or any of the saline controls) demonstrated visible dermal reactions at the challenge sites • There was no evidence of sensitisation potential with Pegylated Apo-Filgrastim and EU-approved Neulasta or US licensed Neulasta.

Overall, the pharmacodynamic and toxicology studies of Pegylated Apo-Filgrastim confirmed that the activity, toxicity and tolerance of Pegylated Apo-Filgrastim, the proposed biosimilar, is similar to that of the US-licensed Neulasta and EU-approved Neulasta.

Furthermore, considering the totality of the comparative data from the primary pharmacodynamic studies, Study Report 410.419.1796, and Study Report BIO-EF-697, as well as the repeat-dose toxicity Study Report 410.120.1797, local tolerance, and sensitization studies of Pegylated Apo-Filgrastim versus US-licensed Neulasta and EU-approved Neulasta, it can be justifiably concluded that the physiological responses to Pegylated Apo-Filgrastim and Neulasta are not meaningfully different.

Part II: Module SIII - Clinical trial exposure

Pegylated Apo-Filgrastim has been developed as a proposed biosimilar to both the US-licensed and EU-approved Neulasta. Consistent with biosimilar guidance which were current at the time of product development, the development program for Pegylated Apo-Filgrastim as a proposed biosimilar to Neulasta, includes a comprehensive comparative analytical similarity assessment program to Neulasta, comparative PK and PD assessments in a Phase I study in healthy volunteers, and comparative efficacy, safety and immunogenicity assessments in a Phase III study conducted in breast cancer patients. Details of the clinical program are provided in Table 4 below:

Table 3: Clinical studies with Pegylated Apo-Filgrastim

Clinical Study Design	Study treatment	Comment
Phase I (APO-Peg-02) Single-dose, randomized 2-way crossover, assessor-blinded, active-controlled, PK/PD study in healthy volunteer subjects to assess and compare the PK and PD parameters of Pegylated Apo-Filgrastim with US licensed Neulasta in healthy volunteers following subcutaneous administration of a single 6 mg dose.	**Reference product**: US-Licensed Neulasta (Amgen Inc.); 6 mg Single Fixed dose (6 mg/0.6 mL); subcutaneous **Test product**: Pegylated Apo-Filgrastim; 6 mg Single Fixed dose (6 mg/0.6 mL); subcutaneous	Study site: Single site in Canada Study status: Completed Of the total 66 healthy volunteers (Male/Female; 18-55 years old), 56 completed the study.
Phase III (APO-Peg-03) Randomized, active controlled, assessor blinded, safety and efficacy three arm study conducted in patients with stage IIa,	**Test product**: Pegylated Apo-Filgrastim **Reference product:** US-Licensed Neulasta (Amgen	Study site: Multiple sites in Central and Eastern Europe Study status: Completed A total of 595 female subjects ≥18 years of age were randomized, 589 were dosed, and 547 subjects completed the treatment phase of the

[redacted]

Clinical Study Design	Study treatment	Comment
IIb or IIIa breast cancer receiving TAC (docetaxel, doxorubicin, cyclophosphamide) anticancer chemotherapy. Patients were randomized to either Pegylated Apo-Filgrastim or US-licensed Neulasta or EU-approved Neulasta in a 2:1:1 ratio.	Inc.); EU-Approved Neulasta (Amgen Europe B.V.) 6 mg fixed dose (6 mg/0.6 mL), administered once per chemotherapy cycle for 6 cycles; subcutaneous	study. Similar total numbers of subjects were exposed to APO-Peg, 294 subjects, as were exposed to the combined total of US-Neulasta (148 subjects) and EU-Neulasta (147 subjects) (295 subjects in the combined Neulasta arms).
Phase I (154-14) supportive study Assessor-blind, balanced, randomized, 2-treatment, 2-period, single dose, 2-way crossover, comparative, SC, 2 dose levels of either of 3 mg/0.3 mL (either INTP5, Test Product-T1 or Neulasta, Reference Product-R1) or 6 mg/0.6 mL (either of INTP5, Test Product-T2 or Neulasta, Reference Product-R2) PK and PD study in healthy, normal, adult, human subjects under fasting conditions.	**Test product**: INTP5 (Pegylated Apo-Filgrastim) 3 mg/0.3 mL single subcutaneous fixed dose; INTP5 (Pegylated Apo-Filgrastim) 6 mg/0.6 mL single subcutaneous fixed dose **Reference product:** EU-Approved Neulasta (Amgen Europe B.V.); 3 mg/0.3 mL or 6 mg/0.6 mL single subcutaneous fixed dose	Study site: One site in Gujarat, India Study status: Completed A total of 344 subjects (172 subjects per dose level group) were planned to be enrolled. As per the plan, 344 subjects (172 subjects per dose level group) were enrolled in the study, and 299 subjects completed the study (there were 148 completers for the 3 mg/0.3 mL dose level and 151 completers for the 6 mg/0.6 mL dose level).

Table 5 and Table 6 provide an overview of the exposure to Pegylated Apo-Filgrastim and Neulasta (US-licensed and EU-approved Neulasta) in the three clinical trials conducted.

[redacted]

Table 4. Summary of Exposure in the Clinical Studies Conducted with Pegylated Apo-Filgrastim Drug Product

	Cumulative Dose	Pegylated Apo-Filgrastim 6 mg	US-Neulasta, 6 mg	EU-Neulasta, 6 mg
Number of Healthy Volunteer Subjects (APO-Peg-02) – Period 1	6 mg	33	33	-
Number of Healthy Volunteer Subjects (APO-Peg-02) –Period 2	6 mg	27	30	-
Number of Cancer Subjects (APO-Peg-03) – Cycle 1	6 mg	294	148	147
Number of Cancer Subjects (APO-Peg-03) – Cycle 2	12 mg	288	146	144
Number of Cancer Subjects (APO-Peg-03) – Cycle 3	18 mg	285	146	144
Number of Cancer Subjects (APO-Peg-03) – Cycle 4	24 mg	284	144	144
Number of Cancer Subjects (APO-Peg-03) – Cycle 5	30 mg	276	143	142
Number of Cancer Subjects (APO-Peg-03) – Cycle 6	36 mg	270	143	139

Table 5. Summary of Exposure in the Supportive Phase I Clinical Study 154-14 Conducted with Pegylated Apo-Filgrastim Drug Product

	INTP5 (Pegylated Apo-Filgrastim) 3 mg/0.3 mL	**INTP5 (Pegylated Apo-Filgrastim) 6 mg/0.6 mL**	**EU-Neulasta 3 mg/0.3 mL**	**EU-Neulasta 6 mg/0.6 mL**
Number of subjects	172	172	172	172
Number of doses	161	160	159	163

In each dose level group, a single dose of pegfilgrastim 3 mg/0.3 mL (INTP5 and EU-Neulasta) or 6 mg/0.6 mL (INTP5 and Neulasta) was administered subcutaneously to each subject in each period.

All of the subjects were exposed to at least one dose of study drug. For the discontinued/withdrawn subjects (n = 45), subjects did not receive a dose of both study drugs.

[redacted]

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

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

The clinical studies for Pegylated Apo-Filgrastim were conducted on healthy volunteers and adult female patients suffering from stage IIa, IIb or IIIa breast cancer. There were no specific studies done to assess effects of pegfilgrastim in pregnant women, nursing mothers, children and the elderly.

Pregnancy

There are no clinical data on the safety of Pegylated Apo-Filgrastim in pregnancy, or on the development of the fetus. Preclinical studies on reproductive and developmental toxicity have not been performed. There were no adverse effects observed in offspring from pregnant rats given pegfilgrastim subcutaneously, but in rabbits pegfilgrastim has been shown to cause embryo/foetal toxicity (embryo loss) at cumulative doses approximately 4 times the recommended human dose, which were not seen when pregnant rabbits were exposed to the recommended human dose. In rat studies, it was shown that pegfilgrastim may cross the placenta. Studies in rats indicated that reproductive performance, fertility, oestrous cycling, days between pairing and coitus, and intrauterine survival were unaffected by pegfilgrastim given subcutaneously. The relevance of these findings for humans is not known (Neulasta SmPC). Consistent with the labelling for Neulasta (Neulasta SmPC), Pegylated Apo-Filgrastim is not recommended during pregnancy and in women of childbearing potential not using contraception.

Nursing Mothers

As there is insufficient information on the excretion of pegfilgrastim / 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 Pegylated Apo-Filgrastim therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman (Neulasta SmPC).

Pediatric Use

No specific studies have been conducted with Pegylated Apo-Filgrastim in children <18 years of age.

The Neulasta SmPC notes that the safety and efficacy of pegfilgrastim has not yet been established. 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. As such, Pegylated Apo-Filgrastim is not indicated for pediatric patients.

The Neulasta USPI, Section 8.4 Pediatric Use, notes that the safety and effectiveness of Neulasta have been established in pediatric patients. No overall differences in safety were identified between adult and pediatric patients based on postmarketing surveillance and review of the scientific literature. The use of Neulasta in pediatric patients for chemotherapy-induced neutropenia is based on adequate and well controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients with sarcoma (Neulasta USPI).

Neulasta has been extensively characterized pharmacologically, with >14 years of clinical and postmarketing experience from both an efficacy and safety standpoint, all of which are reported in the prescribing information for the reference product and the literature. The cumulative use of Neulasta in pediatric patients (0-16 years) from 2006-2009 was 330 patients, and since the approval of Neulasta in January 2002 up to August 31, 2010, there have been 24 Adverse Event Reports following use of Neulasta in the pediatric population (PREA: Pediatric Postmarketing Adverse Event Review, 2010).

The mechanism of action of pegfilgrastim, and hence its selective and specific biological effects on the neutrophil lineage are the same in healthy and a diseased population, and the same in an adult and pediatric population as evidenced by the reported similarity in pharmacokinetics, safety and efficacy of pegfilgrastim reported in Section 8.4 of the Neulasta product label (Neulasta USPI).

As reported in the US labelling for Neulasta, a Phase II study was conducted to evaluate the efficacy, safety, and pharmacokinetics of Neulasta in pediatric and young adult patients with sarcoma (aged 0 to 21 years), patients were randomized in a 6:1 allocation to receive subcutaneous Neulasta as a single dose of 100 mcg/kg (n= 37) or subcutaneous filgrastim at a dose 5 mcg/kg/day (n=6) following myelosuppressive chemotherapy. Results demonstrated that pegfilgrastim and filgrastim were similar for all efficacy and safety end points, and their pharmacokinetic profiles were consistent with those in adults. Younger children experienced more protracted neutropenia and had higher median pegfilgrastim exposure than older children (Neulasta USPI, and Spunt et al. 2010).

Elderly

No specific studies on the use of pegfilgrastim in the elderly population have been performed. For APO-Peg-03, subgroup analyses by age for the primary efficacy endpoint, the Duration of Sever Neutropenia in Cycle 1 was conducted by categorizing subjects into two subgroups based on age: < 65 and ≥ 65 years of age at baseline. A review of the data from the age subgroup analyses demonstrates consistency across treatment arms for each age subgroup. These results are consistent with Neulasta product labelling, which notes that overall differences in safety or effectiveness were not observed between patients aged 65 and older and younger patients (Neulasta SmPC).

Exclusion criteria	**Reason for Exclusion**	**Is it considered to be included as missing information**	**Rationale (if not include as missing information)**
Pregnancy or breast feeding	Consistent with the labelling for Neulasta (Neulasta SmPC), Pegylated Apo-Filgrastim is not recommended during pregnancy and in women of childbearing potential not using contraception. There is insufficient information on the excretion of Neulasta/metabolites in human milk, a risk to the newborns/infants cannot be excluded. Standard exclusion criteria to exclude any foetal exposure or exposure during pregnancy or breastfeeding.	Yes	Not applicable
Pediatric Use	No differences in safety were identified between adult and pediatric patients based on post-marketing surveillance and review of the scientific literature. (Neulasta USPI).	Yes	Not applicable
Elderly	Of the 932 patients with cancer who received Neulasta in clinical studies, 139 (15%) were aged 65 and over, and 18 (2%) were aged 75 and over (Neulasta USPI).	No	As per Neulasta USPI, overall differences in safety or effectiveness were not observed between patients

[redacted]

Exclusion criteria	Reason for Exclusion	Is it considered to be included as missing information	Rationale (if not include as missing information)
			aged 65 and older and younger patients

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Table 6: Limitations to detect adverse reactions in clinical trial development programmes

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Common and very common adverse drug reactions could be detected based on exposure number in clinical trials	589 breast-cancer patients and 66 healthy subjects were exposed to pegfilgrastim	Safety profile of Pegylated Apo-Filgrastim is comparable to the safety profile of pegfilgrastim as known from available literature.
Limitations to detect rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure	Clinical trial have been conducted with implied inclusion / exclusion criteria in a selected population for a limited time period with randomized study design	

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 7: Exposure of special populations included or not in clinical trial development programmes

[redacted]

Type of special population	**Exposure**
Pediatric Use	No specific studies have been conducted with Pegylated Apo-Filgrastim in children <18 years of age and elderly population. For APO-Peg-03, subgroup analyses by age for the primary efficacy endpoint, the Duration of Severe Neutropenia in Cycle 1 was conducted by categorizing subjects into two subgroups based on age: < 65 and ≥ 65 years of age at baseline. A review of the data from the age subgroup analyses demonstrates consistency across treatment arms for each age subgroup.
Elderly	
Pregnant women	Not included in the clinical development program. Pegylated Apo-Filgrastim is not recommended during pregnancy and in women of childbearing potential not using contraception.
Breastfeeding women	Women who are breastfeeding should not take Pegylated Apo-Filgrastim. It is not known if pegfilgrastim is excreted in human milk.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Patients with pulmonary impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program As per the brand Neulasta SmPC, no dose change is recommended in patients with renal impairment, including those with end stage renal disease. As per the brand Neulasta SmPC, pulmonary adverse events are uncommon (≥1/1,000 to <1/100). Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.

Type of special population	**Exposure**
Population with relevant different ethnic origin	The Phase I study (APO-Peg-02) included 66 subjects of different ethnic origins (White, Black or African American, Asian, Multi-Racial and Aboriginal). The Phase III study (APO-Peg-03) included 595 white female subjects.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Other	Not included in the clinical development program

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

One 6 mg dose (a single pre-filled syringe/injector) of Pelgraz is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy and Pelgraz syringes/injector are for single use only.

Based on the sales data presented in below table, assuming that each individual patient administered one pre-filled syringe/injector of Pelgraz injection, hence the total number of injection sold provides an approximate estimate of the patient exposure i.e. total patient exposure is estimated approximately 369,140.

SV.1.2 Exposure

Total sales of Pegfilgrastim is provided in below table:

Region	Product Name	Strength (mg)	Pack Size	Total Pack Sold	Total Unit Sold
EU Countries	Pegfilgrastim pre-filled Syringe/Injector	6 mg	1	To be updated	To be updated
UK			1	To be updated	To be updated
Non-EU countries			1	369,140	369,140
Grand Total					369,140

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

Accord proposal for ensuring the traceability of Pegylated Apo-Filgrastim is summarized below:

- Labelling: In order to enhance prescribers' knowledge about traceability, the following sentence is included under Section 4.4, Special warnings and precautions, in the Pegylated Apo-Filgrastim SmPC: "In order to improve the traceability of granulocyte-

colony stimulating factors (G-CSFs), the trade name of the administered syringe / injector should be clearly recorded in the patient file".

- Education of prescribers/consumers: Sales representatives and other customer interfacing staff will be trained about the importance of requesting/recording/ providing trade names and batch numbers when an adverse event associated with Pegylated Apo-Filgrastim is reported, or follow-up information about an event is requested.
- As part of the routine pharmacovigilance procedures for biologics, information about trade name and batch numbers will be required as part of case validation. Relevant work instruction document will be updated to enable Accord to proactively gather and record relevant information (such as trade names, batch numbers) of any adverse events reported in association with the use of any Accord biologic products including Pegylated Apo-Filgrastim.

SVI.1 Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes

SVI.2 Potential for harm from overdose

Based on current data, there is no clear definition/threshold for overdose. The maximum amount of pegfilgrastim that can be safely administered as a single dose has not been determined. The effects of overdose of pegfilgrastim are unknown. There were no events of overdose in the APO-Peg-02 or APO-Peg-03 clinical trials with Pegylated Apo-Filgrastim. As per the Pegylated Apo-Filgrastim SmPC, the maximum amount of pegfilgrastim that can be safely administered in single or multiple doses has not been determined. Single doses of 300 µg/kg have been administered subcutaneously to a limited number of healthy volunteers and patients with non-small cell lung cancer without serious adverse reactions. The adverse events were similar to those in subjects receiving lower doses of pegfilgrastim.

SVI.3 Potential for medication errors

The intended Pegylated Apo-Filgrastim administration is via subcutaneous route. There is a slight risk of accidental administration by an incorrect route, e.g. intradermal and intramuscular

administration, or i.v. self-administration instead of s.c. and vice versa. The incorrect self-administration of the medication could potentially lead to lack of efficacy.

Pegylated Apo-Filgrastim should be administered at least 24 hours after administration of cytotoxic chemotherapy therefore, there is potential for medication error and administration of the product just after chemotherapy.

Description of medication errors during the clinical trial programme

There were no events of medication error reported in the APO-Peg-02 or APO-Peg-03 clinical trials with Pegylated Apo-Filgrastim.

Preventive measures for the final product(s) being marketed

As per the Guideline on the Readability of the Labelling and Package Leaflet of Medicinal Products for Human Use, 2009, each labeling component for pegfilgrastim (the pre-filled syringe / injector label, the outer carton and package leaflet) contains the:

- name of the medicine;
- strength and total content;
- route of administration.

The text for each of these elements is clearly written in a plain typeface using at least 7 -point font on each component. The name of the product uses black text to ensure a good contrast between the text and the background.

Pegylated Apo-Filgrastim is only available as a ready-to-use 6-mg prefilled syringe / injector and is given at a single dose of 6 mg; there is no requirement to reconstitute the product, or perform any dose calculation steps.

Given the nature of the treatment and close monitoring of patients undergoing such treatment, the probability of incorrect route of self-administration is very low. The physician would determine that the patient can safely and effectively self-administer Pegylated Apo-Filgrastim, and the patients performing self-administration will be adequately trained by their physicians/nurses prior to being allowed to self-administer the medication. In addition, the Pegylated Apo-Filgrastim PIL will provide pictorial presentation of the detailed process to self-administer the medication.

SVI.4 Potential for off-label use

As physicians make care decisions, there is a potential for off label use. Accord expects that risks associated with off label use would be the same as those in patients treated for approved indications.

The potential for off-label use exists in patients undergoing myeloablative therapy followed by bone marrow transplantation; in healthy donors for the mobilization of peripheral blood progenitor cells (PBPC); in patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an ANC of $\leqslant$ 0.5 x 10^9/L, and a history of severe or recurrent infections; and in patients with advanced HIV infection. The Pegylated Apo-Filgrastim SmPC states that the safety and efficacy of pegfilgrastim have not been investigated in patients with MDS, CML, and in patients with secondary AML; therefore, it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of CML from AML.

The safety and efficacy of pegfilgrastim administration in de novo AML patients aged < 55 years with cytogenetics t (15;17) have not been established.

In addition, the SmPC states that the safety and efficacy of pegfilgrastim have not been investigated in patients receiving high-dose chemotherapy. Pegfilgrastim should not be used to increase the dose of cytotoxic chemotherapy beyond the established dosage regimen. The safety and efficacy of pegfilgrastim for the mobilization of blood progenitor cells in patients or healthy donors have not been adequately evaluated.

Potential for paediatric off-label use

Pegfilgrastim is not indicated in the pediatric population. The potential for off-label use exists in children.

Part II: Module SVII - Identified and potential risks

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

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Reversible, mild to moderate elevations in uric acid and alkaline phosphatase, with no associated clinical effects, frequency: uncommon (≥ 1/1000 to < 1/100). These are listed event in Summary of Product Characteristic (SmPC) section 4.8.
- Reversible, mild to moderate elevations in lactate dehydrogenase, with no associated clinical effects, frequency: uncommon (≥ 1/1000 to < 1/100). This is a listed event in SmPC section 4.8.
- Reversible, mild to moderate nausea and headaches; frequency: very common (≥ 1/10). These are listed event in SmPC section 4.8.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Elevations in liver function tests (LFTs) for ALT (alanine aminotransferase) or AST (aspartate aminotransferase). These elevations are transient and return to baseline. Frequency: uncommon (≥ 1/1000 to < 1/100). These are listed event in SmPC section 4.8.
- Injection site reactions, including injection site erythema. Frequency: uncommon (≥ 1/1000 to < 1/100). These are listed event in SmPC section 4.8.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- None

Known risks that do not impact the risk-benefit profile:

- None

Other reasons for considering the risks not important:

- None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

The information presented in Table 9 includes identified, potential and newly identified risks with pegfilgrastim. The information is based on the risks observed in clinical trials with pegfilgrastim as well as clinical trials with Pegylated Apo-Filgrastim. Since the clinical trials with Pegylated Apo-Filgrastim were limited to short-term use in healthy volunteers and breast cancer patients, the table also contains information on identified and potential risks based on the data presented in the SmPC for Neulasta, other biosimilars approved in the EU, and literature articles.

Table 8: Risks considered important for inclusion in the list of safety concerns in the RMP

Risks considered important for inclusion in the list of safety concerns in the RMP	Risk-benefit impact
Important Identified Risks	
Acute Respiratory Distress Syndrome (ARDS)	Not reported in clinical trials with Pegylated Apo-Filgrastim. Uncommon. Serious pulmonary adverse events including interstitial pneumonia and ARDS have been identified in clinical studies and in the postmarketing setting with the use of Neulasta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. As per the Neulasta SmPC, pulmonary adverse events are uncommon (≥1/1,000 to < 1/100). Pulmonary adverse reactions, in particular interstitial pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.
Capillary leak syndrome (CLS)	Not reported in clinical trials with Pegylated Apo-Filgrastim.

Risks considered important for inclusion in the list of safety concerns in the RMP	**Risk-benefit impact**
	Uncommon. CLS has been identified in clinical studies and through postmarketing adverse event reporting with the use of Neulasta. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Capillary leak syndrome is characterised by severe hypotension, hypoalbuminaemia, oedema and hemoconcentration. 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. Capillary Leak Syndrome is serious/potentially life-threatening.
Important Potential Risks	
Cytokine release syndrome (CRS)	Not reported in clinical trials with Pegylated Apo-Filgrastim. No information on background rates is available for the target populations for filgrastim. This risk has been identified from PRAC review of case reports submitted for Neulasta in EudraVigilance and scientific literature.
Missing information	
None	-

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

'Acute myeloid leukaemia/ myelodysplastic syndrome' previously classified as an important potential risk is removed from the list of safety concerns in line with the refernce product Neulasta, as per PRAC PSUR assessment report of Pegfilgrastim (EMEA/H/C/PSUSA/00002326/202201) dated 29-Sep-2022.

[redacted]

“Sickle cell crisis in patients with sickle cell disease” and “Glomerulonephritis” previously classified as important identified risks have been removed from the list of safety concerns in line with the Reference Medicinal Product Neulasta (Pegfilgrastim) RMP (Version 11.0, dated 20-May-2025), published by EMA on 08-Dec-2025.

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

Table 9: Details of important identified risks

Important identified risk: Acute Respiratory Distress Syndrome (ARDS)	
MedDRA terms (Preferred Terms)	ARDS: Acute respiratory distress syndrome; Acute interstitial pneumonitis, Acute lung injury; Acute pulmonary oedema, Lung infiltration; Noncardiogenic pulmonary oedema; Pulmonary function test decreased
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.
Evidence source(s) and strength of evidence	This safety concern was identified in clinical studies and in the post-marketing setting with Neulasta.
Characterisation of the risk	ARDS is a clinical syndrome of severe dyspnea of rapid onset, hypoxemia, and diffuse pulmonary infiltrates leading to respiratory failure. ARDS is caused by diffuse lung injury from many underlying medical and surgical disorders, most commonly pneumonia, sepsis, aspiration, trauma with shock, and cytotoxic drugs. Human G-CSF is the most important regulatory cytokine capable of stimulating neutrophil production from committed hematopoietic progenitor cells, both in vitro and in vivo. There have been several reports of acute respiratory failure during G-CSF-induced neutropenia recovery (Takatsuka et al, 2002; Azoulay et al, 2001). G-CSF is believed to enhance cytokine production and to activate the oxidative

Important identified risk: Acute Respiratory Distress Syndrome (ARDS)	
	burst within circulating or resident alveolar neutrophils and macrophages (Karlin et al, 2005).
Background incidence/prevalence	The age-adjusted incidence of ARDS in the US is estimated to be 64.0 per 100,000 person-years (Rubenfeld et al, 2005). Incidence information for interstitial pneumonia in patients with cancer and HIV was available only for specific drugs. Between January 2000 and May 2009, in a study of 529 consecutive patients with diffuse large B-cell lymphoma receiving first-line therapy with CHOP-based chemotherapy with or without rituximab, interstitial pneumonia was observed in 26 patients (4.9%), 6 of whom were confirmed with Pneumocystis jirovecii pneumonia (Huang et al, 2011). In a Japanese study of 2 different time periods in the same hospital, patients with CD20-positive B-cell NHL were observed (105 patients received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) between June 2000 and December 2004, and 90 received R-CHOP (CHOP with rituximab) between April 2005 and October 2006 (Ennishi et al, 2008). None of the 105 CHOP-treated patients developed interstitial pneumonia, but 13 of the 90 (14%) R-CHOP-treated patients developed interstitial pneumonia. In a prospective cohort study of 8090 participants in the HIV outpatient study at 12 US HIV clinics, the incidence of pneumonia due to Pneumocystis jirovecii as the AIDS-defining illness was 29.9 (95% CI: 25.7, 34.5) per 1000 person-years in 1994-1997, 7.7 (95% CI: 6.2,9.5) per 1000 person-years in 1998-2002, and 3.9 (95% C: 2.9, 5.2) per 1000 person-years in 2003-2007 (Buchacz et al, 2010).
Risk factors and risk groups	Risk factors include concurrent chemotherapy and infections. A number of studies have showed that elevated risk of interstitial pneumonia is associated with use of rituximab in NHL (Katsuya et al, 2009; Huang et al, 2011). Interstitial pneumonitis and other interstitial lung diseases have been seen with other chemotherapy agents in the setting of lung cancer

Important identified risk: Acute Respiratory Distress Syndrome (ARDS)	
	(Zimmerman et al, 1984), particularly in Japan (Camus et al, 2004).
Preventability	Monitor for pulmonary signs such as cough, fever and dyspnoea. For ARDS, association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs. Pegylated Apo-Filgrastim should be discontinued at the discretion of the physician and appropriate treatment is given.
Impact on the risk-benefit balance of the product	Complications such as respiratory failure or ARDS are serious with potential impact on the patient and therefore require immediate attention. ARDS is also a potentially fatal event and it might have significant adverse impact on individual patient.
Public health impact	Mortality rates of approximately 40% were reported for patients with acute respiratory failure, with similar or slightly lower rates reported for patients with acute lung injury and ARDS (Lewandowski, 2003).

Important identified risk: Capillary leak syndrome (CLS)	
MedDRA terms (Preferred Terms)	Capillary leak syndrome, capillary permeability increased.
Potential mechanisms	The exact mechanism remains unclear. The potential mechanism is damage to the endothelial cells, resulting in extravasation of plasma proteins and fluid from the capillaries into the extravascular space, and/or an increase of the neutrophil count and their phagocytic and cytotoxic functions and their expression of adhesion molecules.
Evidence source(s) and strength of evidence	Clinical studies and postmarketing adverse event reporting for Neulasta.

Important identified risk: Capillary leak syndrome (CLS)	
Characterisation of the risk	Capillary leak syndrome is characterized by episodes of severe hypotension, hypoalbuminemia, edema, and hemoconcentration. In cancer patients, due to pre-existing anemia, hemoconcentration may be variable (Druey and Greipp, 2010). During "attacks" of capillary leak syndrome, profound derangement of the vascular endothelium results in leakage of plasma and proteins into the interstitial compartment resulting in edema. Episodes vary in severity and frequency and may be fatal (Clarkson et al, 1960; Marks et al, 1973).
Background incidence/prevalence	This condition, which can be life-threatening if treatment is delayed, has been reported as uncommon (affecting less than 1 patient in 100) with pegfilgrastim treatment.
Risk factors and risk groups	Cancer patients undergoing chemotherapy (patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications). High white cell count might be contributory. Capillary leak syndrome has been reported after administration of multiple drugs, some of which include interleukins (Kai-Feng et al, 2011), gemcitabine (Baron et al, 2006), doxorubicin (Krzesinski et al, 2010), granulocyte-macrophage colony-stimulating (AI-Homaidhi et al, 1998), and interferon (Yamamoto et al, 2002). Capillary leak syndrome has also been reported in relation to miscellaneous conditions such as carbon monoxide poisoning, postpartum state, and pustular psoriasis (Kai-Feng et al, 2011).
Preventability	Close monitoring for CLS symptoms in patients receiving Pegylated Apo-Filgrastim. Immediate standard symptomatic treatment if symptoms occur.
Impact on the risk-benefit balance of the product	CLS is a serious, potentially life-threatening event that requires immediate treatment (might include intensive care), and it might have significant adverse impact on individual patient.

Important identified risk: Capillary leak syndrome (CLS)	
Public health impact	Not expected to have a significant public health impact

Table 10: Details of important potential risks

Important potential risk: Cytokine release syndrome (CRS)	
MedDRA terms (Preferred Terms)	Cytokine release syndrome, cytokine storm, infusion related reaction.
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 proinflammatory cytokine production (Boneberg et al, 2000; Pajkrt et al, 1997; Hartung et al, 1995a; Hartung et al, 1995b). 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 a study by Gorgen et al (1992), which demonstrated that G-CSF treatment was protective in both rat and mouse models of septic shock. In this study, increased G-CSF dose was associated with increased suppression of the proinflammatory cytokine, tumor necrosis factor-a and decreased mortality (mortality: 83% in control animals, 33% in animals treated with 50µg/kg G-CSF, 0% in animals treated with 250µg/kg G-CSF) (Gorgen et al, 1992). In a separate study by Fink et al (1993), lung injury was reduced by GCSF pretreatment in lipopolysaccharide-challenged pigs.
Evidence source(s) and strength of evidence	PRAC review of case reports in EudraVigilance and the scientific literature.
Characterisation of the risk	Cytokine release syndrome is a rapid, uncontrolled hypercytokinemia that results in a range of clinical

Important potential risk: Cytokine release syndrome (CRS)	
	effects from pyrexia and fatigue to multiple organ failure in association with therapeutic infusion of antibodies (eg, rituximab, trastuzumab). Mechanism of action for cytokine release syndrome involves targeted activation of immune cells and elevation of both pro-inflammatory (eg, tumor necrosis factor-α) and anti-inflammatory (eg, interleukin-10) cytokines (O'Neil and Bert, 2010; Chung, 2008; Dillman, 1999; Winkler et al, 1999). Clinical manifestation may include nonspecific 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 IgE mediated anaphylactic or non-lgE mediated anaphylactoid reaction (O'Neil and Bert, 2010; Kang and Saif, 2007). 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 lysis syndrome, that involve cytokine release from malignant cells targeted by these monoclonal antibodies (Howard et ai, 2011; Kang and Saif, 2007). Pegfilgrastim is not a monoclonal antibody and has no receptors to T-cells or B-cells.
Background incidence/prevalence	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 et al, 2007).
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

Important potential risk: Cytokine release syndrome (CRS)	
	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 lymphoma, patients with lymphocyte counts >50 x 109/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 et al, 2007).
Preventability	Monitoring for CRS symptoms and immediate treatment if symptoms occur.
Impact on the risk-benefit balance of the product	Most patients experience a mild to moderate reaction; however, the reaction may be severe and life-threatening.
Public health impact	Not expected to have a significant public health impact

SVII.3.2. Presentation of the missing information

Not Applicable

Part II: SVIII - Summary of the safety concerns

Table 11: Summary of safety concerns

Important identified risks	• Acute Respiratory Distress Syndrome (ARDS) • Capillary leak syndrome
Important potential risks	• Cytokine release syndrome
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for 'Capillary leak syndrome' and 'Cytokine release syndrome'.

Purpose: For collection and reporting of relevant safety information while use of Pelgraz. These questionnaires are appended in Annex 4 and include a question for switching between G-CSF biosimilars.

III.2 Additional pharmacovigilance activities

Not applicable

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

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

V.1. Routine Risk Minimisation Measures

Table 12: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risks	
Acute Respiratory Distress Syndrome (ARDS)	Routine risk communication: • SmPC Sections: 4.4 and 4.8. • PIL Sections: 2 amd 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Suggestion to discontinue pegfilgrastim at the discretion of the physician and the appropriate treatment given on the onset of preliminary signs of acute respiratory distress syndrome (ARDS) is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: • Prescription only status of the product. • Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.
Capillary leak syndrome	Routine risk communication: • SmPC Sections: 4.4 and 4.8. • PIL Sections: 2 and 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Instructions to closely monitor the patients who develop symptoms of capillary leak syndrome and should

Safety concern	Routine risk minimisation activities
	receive standard symptomatic treatment, which may include a need for intensive care is included in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: • Prescription only status of the product • Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.
Important Potential Risks	
Cytokine release syndrome	Routine risk communication: • None Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Prescription only status of the product • Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 13: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Acute Respiratory Distress Syndrome (ARDS)	Routine risk minimisation measures: • SmPC Sections: 4.4 and 4.8. • PIL Sections: 2 and 4. • Suggestion to discontinue pegfilgrastim at the discretion of the physician and the appropriate treatment given on the onset of preliminary signs of acute respiratory distress syndrome (ARDS) is included in SmPC section 4.4. • Prescription only status of the product. • Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activity: None
Capillary leak syndrome	Routine risk minimisation measures: • SmPC Sections: 4.4 and 4.8. • PIL Sections: 2 and 4. • Instructions to closely monitor the patients who develop symptoms of capillary leak syndrome and should receive standard symptomatic treatment, which may include a need for intensive care is included in SmPC section 4.4. • Prescription only status of the product.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targetted follow-up form for Capillary leak syndrome Additional pharmacovigilance activity:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. Additional risk minimisation measures: • None	None
Important Potential Risks		
Cytokine release syndrome	Routine risk minimisation measures: • Prescription only status of the product • Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targetted follow-up form for Cytokine release syndrome Additional pharmacovigilance activity: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector (Pegfilgrastim)

This is a summary of the risk management plan (RMP) for Pelgraz 6 mg solution for injection in pre-filled syringe and Pelgraz 6 mg solution for injection in pre-filled injector (*hereinafter to be referred as Pelgraz throughout the summary*). The RMP details important risks of Pelgraz, how these risks can be minimised, and how more information will be obtained about Pelgraz's risks and uncertainties (missing information).

Pelgraz's Summary of Product Characteristics (SmPC) and Package Leaflet give essential information to Healthcare Professionals and patients on how Pelgraz should be used.

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

I. The medicine and what it is used for

Pelgraz is authorised 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 is given by subcutaneous route.

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

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

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

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

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

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

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

II.A List of important risks and missing information

Important risks of Pelgraz are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Pelgraz. 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).

Important identified risks	• Acute Respiratory Distress Syndrome (ARDS) • Capillary leak syndrome

[redacted]

Important potential risks	• Cytokine release syndrome
Missing information	• None

II.B Summary of important risks

Important Identified Risks: Acute Respiratory Distress Syndrome (ARDS)	
Evidence for linking the risk to the medicine	This safety concern was identified in the post-marketing setting with Neulasta.
Risk factors and risk groups	Risk factors include concurrent chemotherapy and infections. A number of studies have showed that elevated risk of interstitial pneumonia is associated with use of rituximab in NHL. Interstitial pneumonitis and other interstitial lung diseases have been seen with other chemotherapy agents in the setting of lung cancer, particularly in Japan.
Risk minimisation measures	<u>Routine risk minimisation measures</u>: • SmPC Sections: 4.4 and 4.8. • PIL Sections: 2 and 4. • Suggestion to discontinue pegfilgrastim at the discretion of the physician and the appropriate treatment given on the onset of preliminary signs of acute respiratory distress syndrome (ARDS) is included in SmPC section 4.4. • Prescription only status of the product. • Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. <u>Additional risk minimisation measures</u>: • None
Important Identified Risks: Capillary leak syndrome	
Evidence for linking the risk to the medicine	Postmarketing adverse event reporting for Neulasta.

Risk factors and risk groups	Cancer patients undergoing chemotherapy (patients with advanced malignant diseases, sepsis, taking multiple chemotherapy medications). High white cell count might be contributory. Capillary leak syndrome has been reported after administration of multiple drugs, some of which include interleukins, gemcitabine, doxorubicin, granulocyte-macrophage colony-stimulating, and interferon. Capillary leak syndrome has also been reported in relation to miscellaneous conditions such as carbon monoxide poisoning, postpartum state, and pustular psoriasis.
Risk minimisation measures	Routine risk minimisation measures: • SmPC Sections: 4.4 and 4.8. • PIL Sections: 2 and 4. • Instructions to closely monitor the patients who develop symptoms of capillary leak syndrome and should receive standard symptomatic treatment, which may include a need for intensive care is included in SmPC section 4.4. • Prescription only status of the product. • Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. Additional risk minimisation measures: • None
Important Potential Risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	PRAC review of 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 minimisation measures	Routine risk minimisation measures: • Prescription only status of the product • Pelgraz therapy should be initiated and supervised by physicians experienced in oncology and/or haematology. Additional risk minimisation measures: • None

II.C Post-authorisation development plan

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

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

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

There are no studies required for Pelgraz.

Annex 4 - Specific adverse drug reaction follow-up forms

The MAH has proposed targeted follow up questionnaires for following safety concerns concerning the use of Pelgraz and they are appended below:

1. Capillary leak syndrome
2. Cytokine release syndrome

Targetted Follow-up Questionnaire for Capillary leak syndrome

ADVERSE DRUG REACTION (ADR) REPORT 1. **Name and Address of Reporter** _____ _____ _____ _____ _____ ☐ Health Authority ☐ Health Professional: ☐ MD ☐ Pharmacist Other ☐ Patient ☐ Literature citation Sign:_____ Date: __/___/_____	Accord Healthcare Limited Sage House, 319 Pinner Road North Harrow, Middlesex, HA1 4HF United Kingdom

I. REACTION INFORMATION

2. Reference #	3. **Patient Initials**	**4. Sex** M ☐ F ☐	**5. Date ADR Reported** (dd/mmm/yy)	**6. Initial Report** ☐ **Follow-up Report** ☐	**7. Weight**
8. Country	**9. Date of Birth** (dd/mmm/yy) __/___/__	**10. Age**	**11. Date of ADR Onset** (dd/mmm/yy)	**12. Pregnant at Time of Event(s)?** Yes	**13. Height**

At a minimum, the following mandatory sections should be completed:

4 (sex), 7 (weight), 9 (date of birth), (10) age, 11 (onset date), 19 (dechallenge/rechallenge) 25 (indication), 26 (treatment dates), 27 (duration of treatment), 29 (medical history), 30 (concomitant medication)

14a. Please provide a summary of the observed clinical signs and symptoms –eg presence, and sites of edema, recorded blood pressure

_____

_____

14b. Please provide results of all relevant tests/lab data- at the minimum the following is required

- Full Blood Count and differentials- highlighting hematocrit concentration: _____
- Blood albumin levels: _____
- (Please attach all relevant documents)

14c. Did the patient receive any ADR treatment?

☐ No ☐ Yes

[redacted]

If yes, please provide details

(e.g. medication name, dose, treatment dates and outcome).

_____

_____

14d. Was the patient administered any other G-CSF class of drug (e.g, Neulasta®, Ristempa®, Neupogen®, Grastofil®, Accofil®, Granix®, Zarxio®, etc.) before initiating treatment or after stopping treatment with Pelgraz®?

15. Check all Appropriate to event	16. **Outcome**	17. **Duration**
☐ Patient died. Date of death (dd/mmm/yy):__/__/____ ☐ Death attributed to event(s) ☐ Emergency Room stay only ☐ Hospitalization (initial or prolonged) From (dd/mmm/yy):__/__/__ To:__/__/__ ☐ Involved significant disability or incapacity ☐ Life-threatening ☐ Required intervention to prevent permanent damage Congenital anomaly ☐ Other. Specify other: _____ ☐ None of the Above	☐ Recovered. Date: __/__/____ ☐ Recovered with sequelae ☐ Recovering ☐ Ongoing ☐ Unknown	18. **N.A.**

19. **Dechallenge/Rechallenge**	**Yes**	**NO**	**NA**
Pelgraz discontinued?	☐	☐	☐
Reaction abated after stopping drug?	☐	☐	☐
Pelgraz restarted?	☐	☐	☐
Reaction reappeared after rechallenge?	☐	☐	☐

II. SUSPECT DRUG INFORMATION

20. **Suspect Medication** (incl. strength)		21. **Dose & Frequency**	22. **Route of Administration**	23. **Formulation**
24. **Lot # & Exp. Date**	25. **Indications**	26. **Treatment Dates** (dd/mmm/yy) From: __/__/__ To:__/__/__	27. **Duration of Treatment**	28. **Discontinued Treatment?** ☐ YES ☐ NO ☐ N/A

III. CONCOMITANT DRUG (S) AND HISTORY

29**. Patient History** (including allergies, concomitant medical conditions and other risk factors)						
30. **Concomitant Medications** (excluding those used to treat ADR)	31.**Co-suspect ADR Drug?** (Y / N)	32. **Dose & Frequency**	33. **Route of Administration**	34. **Date of Administration** (dd/mmm/yy)		35**. Indication**
				From	To	

[redacted]

Targetted Follow-up Questionnaire for Cytokine release syndrome

ADVERSE DRUG REACTION (ADR) REPORT 1. **Name and Address of Reporter** _____ _____ _____ _____ _____ ☐ Health Authority ☐ Health Professional: ☐ MD ☐ Pharmacist Other ☐ Patient ☐ Literature citation Sign:_____ Date: __/___/_____	Accord Healthcare Limited Sage House, 319 Pinner Road North Harrow, Middlesex, HA1 4HF United Kingdom

I. REACTION INFORMATION

2. Reference #	3. **Patient Initials**	**4. Sex** M ☐ F ☐	**5. Date ADR Reported** (dd/mmm/yy)	**6. Initial Report** ☐ **Follow-up Report** ☐	**7. Weight**
8. Country	**9. Date of Birth** (dd/mmm/yy) __/___/__	**10. Age**	**11. Date of ADR Onset** (dd/mmm/yy)	**12. Pregnant at Time of Event(s)?** Yes	**13. Height**

At a minimum, the following mandatory sections should be completed:

4 (sex), 7 (weight), 9 (date of birth), (10) age, 11 (onset date), 19 (dechallenge/rechallenge) 22 (route of administration) 25 (indication), 26 (treatment dates), 27 (duration of treatment), 29 (medical history), 30 (concomitant medication)

14a. Please provide a summary of the observed clinical signs and symptoms –(including but not limited to nausea, chills, fever, dyspnea, hypotension, tachycardia)

_____

_____

14b. Please provide results of all relevant tests/lab data- at the minimum the following is required

- blood uric acid: _____
- potassium: _____
- calcium: _____
- phosphate: _____

[redacted]

- lactate dehydrogenase: _____
- Chest X-ray
- Please attach all relevant documents

14c. Did the patient receive any ADR treatment?

☐ No ☐ Yes

If yes, please provide details

(e.g. medication name, dose, treatment dates and outcome).

_____

_____

14d. Was the patient administered any other G-CSF class of drug (e.g, Neulasta®, Ristempa®, Neupogen®, Grastofil®, Accofil®, Granix®, Zarxio®, etc.) before initiating treatment or after stopping treatment with Pelgraz®?

15. Check all Appropriate to event	16. **Outcome**	17. **Duration**
☐ Patient died. Date of death (dd/mmm/yy):__/__/____ ☐ Death attributed to event(s) ☐ Emergency Room stay only ☐ Hospitalization (initial or prolonged) From (dd/mmm/yy):__/__/__ To:__/__/__ ☐ Involved significant disability or incapacity ☐ Life-threatening ☐ Required intervention to prevent permanent damage Congenital anomaly ☐ Other. Specify other: _____ ☐ None of the Above	☐ Recovered. Date: __/__/____ ☐ Recovered with sequelae ☐ Recovering ☐ Ongoing ☐ Unknown	18. **N.A.**

19. **Dechallenge/Rechallenge**	**Yes**	**NO**	**NA**
Pelgraz discontinued?	☐	☐	☐
Reaction abated after stopping drug?	☐	☐	☐
Pelgraz restarted?	☐	☐	☐
Reaction reappeared after rechallenge?	☐	☐	☐

II. SUSPECT DRUG INFORMATION

20. **Suspect Medication** (incl. strength)	21. **Dose & Frequency**	22. **Route of Administration**	23. **Formulation**

[redacted]

24. **Lot # & Exp. Date**	25. **Indications**	26. **Treatment Dates** (dd/mmm/yy) From: __/__/__ To:__/__/__	27. **Duration of Treatment**	28. **Discontinued Treatment?** ☐ YES ☐ NO ☐ N/A

III. CONCOMITANT DRUG (S) AND HISTORY

29**. Patient History** (including allergies, concomitant medical conditions and other risk factors)

30. **Concomitant Medications** (excluding those used to treat ADR)	31.**Co-suspect ADR Drug?** (Y / N)	32. **Dose & Frequency**	33. **Route of Administration**	34. **Date of Administration** (dd/mmm/yy)		35**. Indication**
				From	To	