EUROPEAN UNION RISK MANAGEMENT PLAN

Neulasta® (Pegfilgrastim)

Marketing Authorization Holder:	Amgen Europe B.V. Minervum 7061 4817 ZK Breda, Netherlands
Version:	11.0
Date:	20 May 2025
Supersedes:	Version 10.1 dated 18 September 2023

Risk Management Plan (RMP) version to be assessed as part of this application

Risk Management Plan (RMP) version number:	11.0
Data lock point of this RMP:	31 January 2025
Date of final sign-off:	20 May 2025
Rationale for submitting an updated RMP:	To remove the important identified risks of: • Sickle cell crisis in patients with sickle cell disease • Glomerulonephritis

Summary of significant changes in this RMP

Part/Module/Annex	Major Change(s)	Version Number and Date
Part II: Safety Specification		
SV: Postauthorization Experience	Postauthorization exposure information updated to a data lock point of 31 January 2025.	Version 11.0, 20 May 2025
SVII: Identified and Potential Risks	The following important identified risks were removed from the list of safety concerns: • Sickle cell crisis in patients with sickle cell disease • Glomerulonephritis	Version 11.0, 20 May 2025
SVIII: Summary of the Safety Concerns	List of safety concerns updated as stated above for Module SVII.	Version 11.0, 20 May 2025
Part V: Risk Minimization Measures (Including Evaluation of the Effectiveness of Risk Minimization Activities)	List of safety concerns updated as stated above for Module SVII.	Version 11.0, 20 May 2025
Part VI: Summary of the Risk Management Plan	Updated per changes listed above for Module SVII.	Version 11.0, 20 May 2025
Part VII: Annexes		
Annex 8: Summary of Changes to the Risk Management Plan Over Time	Summary of changes to the risk management plan over time updated.	Version 11.0, 20 May 2025

Other RMP versions under evaluation:	
RMP version number:	Not applicable
Submitted on:	Not applicable
Procedure number:	Not applicable
Details of the currently approved RMP:	
Version number:	10.1
Approved with procedure:	EMEA/H/C/000420/IB/0123
Date of approval (opinion date):	17 October 2023
Qualified Person for Pharmacovigilance (QPPV) Name:	Raphaël Van Eemeren, MSc Pharm and MSc Ind Pharm
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorization holder´s QPPV. The electronic signature is available on file.

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List of Abbreviations

Term/Abbreviation	Explanation
5-FU	fluorouracil
ADR	adverse drug reaction
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AMQ	Amgen MedDRA Query
ARDS	acute respiratory distress syndrome
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CAR-T	chimeric antigen receptor T-cell
CHMP	Committee for Medicinal Products for Human Use
CIN	chemotherapy-induced neutropenia
CLS	capillary leak syndrome
CSF	colony-stimulating factor
DLP	data lock point
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EORTC	European Organisation for Research and Treatment of Cancer
E coli	*Escherichia coli*
EU	European Union
FN	febrile neutropenia
G-CSF	granulocyte colony-stimulating factor

Term/Abbreviation	Explanation
INN	International Nonproprietary Name
KKC	Kyowa Kirin Co., Ltd
KKL	Kyowa Kirin Limited
MAH	marketing authorization holder
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	multi-gated acquisition scan
NCCN	National Comprehensive Cancer Network
NH	neutropenia hospitalization
NHL	non-Hodgkin's lymphoma
NSCLC	non-small cell lung cancer
OBI	on-body injector
PEG	polyethylene glycol
PFS	prefilled syringe
PI	Product Information
PIL	Patient Information Leaflet
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PV	pharmacovigilance
PT	preferred term
QPPV	Qualified Person for Pharmacovigilance
r-metHuG-CSF	recombinant methionyl human granulocyte colony-stimulating factor
RMP	risk management plan
SCLC	small-cell lung cancer
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Pegfilgrastim
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	L03AA13
Marketing authorization holder (MAH)	Amgen Europe B.V.
Medicinal products to which this Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	Neulasta®
Marketing authorization procedure	Centralized
Brief description of the product	
Chemical class	Pegfilgrastim is a covalent conjugate of recombinant methionyl human granulocyte colony-stimulating factor (r-metHuG-CSF) with a single 20 kDa polyethylene glycol (PEG) molecule.
Summary of mode of action	Pegfilgrastim regulates the production and release of neutrophils from the bone marrow. It is a sustained duration form of filgrastim due to decreased renal clearance.
Important information about its composition	Pegfilgrastim is composed of filgrastim (r-metHuG-CSF) with a 20 PEG molecule covalently bound to the N-terminal methionine residue. Filgrastim is produced by recombinant DNA technology in *Escherichia coli* (*E coli*).
Hyperlink to the Product Information (PI)	https://www.ema.europa.eu/en/documents/product-information/neulasta-epar-product-information_en.pdf
Indication(s) in the EEA	
Current	Reduction in 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 leukemia and myelodysplastic syndromes [MDS]).
Proposed (if applicable)	Not applicable.

PART I. PRODUCT(S) OVERVIEW

Table 1. Product(s) Overview

Dosage in the EEA	
Current	Neulasta therapy should be initiated and supervised by physicians experienced in oncology and/or hematology. One 6 mg dose (a single pre-filled syringe [PFS]) of Neulasta is recommended for each chemotherapy cycle, given at least 24 hours after cytotoxic chemotherapy. Paediatric population The safety and efficacy of Neulasta in children has not yet been established. Currently available data are described in Summary of Product Characteristic (SmPC) Sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made. Patients with renal impairment No dose change is recommended in patients with renal impairment, including those with end-stage renal disease.
Proposed (if applicable):	Not applicable.
Pharmaceutical form(s) and strength(s)	
Current (if applicable):	Neulasta is formulated as a clear, colorless solution for injection and is available in a PFS. Each PFS contains 6 mg of pegfilgrastim in 0.6 mL (10 mg/mL) solution for injection. The concentration is 10 mg/mL based on protein only. The concentration is 20 mg/mL if the PEG moiety is included.
Proposed (if applicable):	Not applicable.
Is/will 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)

Table 2. Summary of Epidemiology of Chemotherapy-induced Neutropenia

Incidence	The incidence of neutropenia hospitalization (NH) has been reported as 7.83 cases per 1000 patients with cancer (Caggiano et al, 2005). This incidence varies according to factors such as cancer type, therapy used, and cycle of chemotherapy. Neutropenia hospitalization is common in patients with hematologic (43.3 cases per 1000 patients) and pancreatic tumors (24.5 per 1000) (Caggiano et al, 2005). The incidence of grade 3 or 4 neutropenia (severe neutropenia) in patients with solid tumors treated with daily cyclophosphamide, rofecoxib and weekly vinblastine was 25.0% (Young et al, 2006), in patients with pancreatic cancer treated with gemcitabine was 26% (Burris et al, 1997), and in metastatic colorectal cancer patients treated with 5-fluorouracil (5-FU), irinotecan, leucovorin was 24.0% (Tournigand et al, 2004). In patients with non-small cell lung cancer (NSCLC) treated with combinations of vinorelbine, gemcitabine, and cisplatin, the incidence of severe neutropenia was 18.0% to 21.0% (Di Maio et al, 2005). A much higher incidence (85%) of severe neutropenia was observed in small-cell lung cancer (SCLC) patients treated with combination therapy of etoposide plus cisplatin (Pujol et al, 2001). Overall grade 4 neutropenia has been reported in 34.4% of breast cancer patients, with 43.8% of patients receiving taxane regimens experiencing grade 4 neutropenia (Schwenkglenks et al, 2011). Most events of grade 4 neutropenia appear to occur during the first cycle of chemotherapy (Schwenkglenks et al, 2011; Holmes et al, 2002) with the number of initial events decreasing in subsequent cycles. Thus, first cycle grade 4 neutropenia has been reported in 28.5% of patients treated with anthracycline-based therapy (Schwenkglenks et al, 2011) and 14.5% of those taking combinations of therapy with cyclophosphamide, methotrexate, 5-FU, doxorubicin, and docetaxel (Chia et al, 2013). In an observational study in England in patients with solid tumors, the observed incidence of FN was 19.4 per 1000 oncology admissions (Schelenz et al, 2012). A prospective United States registry described an overall FN incidence of 10.7% in the first 3 cycles of treatment with variations across tumor types: SCLC (17.9%), breast cancer (15.2%), non-Hodgkin's lymphoma (NHL) (14.0%), and Hodgkin disease (12.7%) and most patients experiencing their initial FN event in cycle 1 (Crawford et al, 2008).
Prevalence	No relevant literature is available.

Footnotes, including abbreviations, are defined on the last page of this table

Table 2. Summary of Epidemiology of Chemotherapy-induced Neutropenia

Demographics of population in the authorized indication and risk factors for the disease	Growth factor treatment guidelines (National Comprehensive Cancer Network [NCCN]/European Organisation for Research and Treatment of Cancer [EORTC]/American Society of Clinical Oncology [ASCO]) have identified populations at great risk of developing FN (Crawford et al, 2017; Smith et al, 2015; Aapro et al, 2011). As per the NCCN guidelines, patient risk factors that increase risk of FN include prior chemotherapy or radiation, persistent neutropenia, bone marrow involvement, recent surgery or open wound, liver or renal dysfunction, and age > 65 years. Older patients are at greater risk to develop FN and are overrepresented in many studies. In 1 study in patients with solid tumors, over 70.0% of those admitted with FN were ≥ 60 years old (range 25 to 80 years) (Schelenz et al, 2012). Female cancer patients are also recognized to be at greater risk of FN in most published studies (53% to 83%) (Schelenz et al, 2012; Lyman et al, 2010; Kuderer et al, 2006). The most common underlying cancer types were breast (28.1%to 61.6%), lung (13.1% to 15.6%), esophageal (15.6%), ovarian (12.5%), and colorectal (12.6%) (Schelenz et al, 2012; Lyman et al, 2010).
Main existing treatment options	Treatment options focus on either reducing the duration of neutropenia or altering the microbial risk. Treatment options include filgrastim, pegfilgrastim, or other white blood cell stimulating agents, selection of reduced myelosuppressive chemotherapy, use of dose reduction and/or dose delays, and addition of anti-infective prophylaxis (antibiotic, antiviral, antifungal) or stem cell support.
Natural history of the indicated condition in the population, including mortality and morbidity	An overall mortality of 6.12 per 1000 person-months (95% CI: 5.66, 6.61) and early mortality (12 months) of 8.59 per 1000 person-months (95% CI: 7.61, 9.71) have been reported among patients with FN in a retrospective cohort study using a large US healthcare claims database (Lyman et al, 2010). In a prospective study of solid tumor patients in the United Kingdom, the attributable mortality was 12.5% when adjusted for infection and/or sepsis as the main cause of death (Schelenz et al, 2012). In a systematic review of randomized clinical trials, the control group (receiving placebo or untreated) had an early mortality of 5.7% and infection-related mortality of 2.8% following chemotherapy for solid tumors or lymphoma (Kuderer et al, 2007). Mortality associated with chemotherapy-induced neutropenia (CIN) varies by cancer type, with the highest mortality reported for lung cancer (35.61 per 1000 person-month, 95% CI: 31.72, 39.98 [Lyman et al, 2010]; 13.4% [Kuderer et al, 2006]; 10.5% [Caggiano et al, 2005] and lowest for breast ((2.19; 95% CI: 1.88, 2.57) [Lyman et al, 2010]; 3.6% [Kuderer et al, 2006]; 3.4% [Caggiano et al, 2005]).

Footnotes, including abbreviations, are defined on the last page of this table

Table 2. Summary of Epidemiology of Chemotherapy-induced Neutropenia

Natural history of the indicated condition in the population including mortality and morbidity (continued)	A prospective observational study demonstrated that patients who died from FN were mostly ≥ 60 years old (83.3%) with an average neutrophil count of 0.27 x 10^9/L. Patients who died also tended to have more severe disease burden and presented more commonly with comorbidities compared with those patients who survived (Schelenz et al, 2012).
Important comorbidities	• Malignancy • Infection • Thrombocytopenia • Anemia • Cardiovascular disease Comedications include antibiotics or other anti-infective agents and antiemetic drugs.

5-FU = 5-fluorouracil; ASCO = American Society of Clinical Oncology; CIN = chemotherapy induced neutropenia; EORTC = European Organisation for Research and Treatment of Cancer; FN = febrile neutropenia; NCCN = National Comprehensive Cancer Network; NH = neutropenia hospitalization; NHL = non-Hodgkin's lymphoma; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; US = United States; WBC = white blood cell.

Part II: Module SII - Nonclinical Part of the Safety Specification

Table 3. Key Safety Findings From Nonclinical Studies and Relevance to Human Usage

Study Type	Important Nonclinical Safety Findings	Relevance to Human Usage
Toxicity		
Key issues identified from acute or repeat-dose toxicity studies	Preclinical data showed expected pharmacological effects including increase in leukocyte count, myeloid hyperplasia in bone marrow, extramedullary hematopoiesis, and splenic enlargement.	Generally asymptomatic cases of splenomegaly and cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim. This risk is minimized through the product labelling which details monitoring actions to take in the case of symptoms consistent with splenic abnormality.
Reproductive/developmental toxicity	In rabbit studies, pegfilgrastim caused embryo/fetal toxicity (embryo loss).	Studies in animals have shown reproductive toxicity; however, the potential risk to the human embryo or fetus is unknown. Data from the postmarket setting did not reveal any patterns suggestive of a safety concern and did not indicate any safety signals with the use of pegfilgrastim during pregnancy or lactation.

Part II: Module SIII - Clinical Trial Exposure

Table 4. Total Subject Exposure to Pegfilgrastim in Clinical Trials by Indication and Duration (Safety Analysis Set)

Indications	Exposure to Pegfilgrastim by Duration				
	< 1 Month n (subj-yrs)	≥ 1 Months n (subj-yrs)	≥ 4 Months n (subj-yrs)	≥ 7 Months n (subj-yrs)	Total n (subj-yrs)
Acute Myeloid Leukaemia	16 (2.2)	26 (6.2)	0 (0.0)	0 (0.0)	42 (8.4)
Chemotherapy-induced Neutropenia	911 (139.4)	5263 (2447.0)	276 (128.5)	3 (2.1)	6174 (2586.4)
Chemotherapy-induced Neutropenia (Pediatric)	3 (0.4)	34 (16.6)	0 (0.0)	0 (0.0)	37 (17.0)
Healthy Volunteers	327 (34.4)	0 (0.0)	0 (0.0)	0 (0.0)	327 (34.4)
Peripheral Blood Progenitor Cell	85 (18.0)	0 (0.0)	0 (0.0)	0 (0.0)	85 (18.0)
Pharmacokinetic Subjects with Renal Dysfunction	31 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	31 (3.7)
Total	1373 (198.2)	5323 (2469.8)	276 (128.5)	3 (2.1)	6696[a] (2668.0)

n = number of subjects exposed to pegfilgrastim; subj-yrs = total subject-yrs of follow-up.
[a] Subjects that received placebo and pegfilgrastim or filgrastim and pegfilgrastim (cross-over treatment groups) are summarized under the pegfilgrastim group.
Note: Data is from completed studies, ongoing open-label studies and unblinded interim analyses for ongoing blinded studies as of 31 January 2018. A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Source: t-07-ex-indic-dur.rtf

Table 5. Total Subject Exposure to Pegfilgrastim in Clinical Trials by Age Group and Gender (Safety Analysis Set)

	Infants and Toddlers (0 - <2 years) n (subj-yrs)	Children (2 to 11 years) n (subj-yrs)	Adolescents (12 to 17 years) n (subj-yrs)	Adults (18 to 64 years) n (subj-yrs)	Elderly (65 to 74 years) n (subj-yrs)	Elderly (75 to 84 years) n (subj-yrs)	Elderly (85+ years) n (subj-yrs)
Male							
Acute Myeloid Leukaemia	0 (0.0)	0 (0.0)	0 (0.0)	16 (2.9)	6 (1.4)	0 (0.0)	0 (0.0)
Chemotherapy-induced Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	673 (427.6)	522 (259.2)	253 (103.7)	28 (4.8)
Chemotherapy-induced Neutropenia (Pediatric)	3 (1.5)	15 (6.9)	5 (2.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Healthy Volunteers	0 (0.0)	0 (0.0)	0 (0.0)	209 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral Blood Progenitor Cell	0 (0.0)	0 (0.0)	0 (0.0)	43 (9.8)	6 (1.1)	0 (0.0)	0 (0.0)
Pharmacokinetic Subjects with Renal Dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	20 (2.4)	0 (0.0)	2 (0.2)	0 (0.0)
Total	3 (1.5)	15 (6.9)	5 (2.0)	963 (466.7)	534 (261.7)	255 (104.0)	28 (4.8)

n = number of subjects exposed to pegfilgrastim; subj-yrs = total subject-yrs of follow-up.
Note: Data is from completed studies, ongoing open-label studies and unblinded interim analyses for ongoing blinded studies as of 31 January 2018. A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/peggcsf/sd01/meta/RMP_2018/tables/t-ex-age-sex.sas
Output: t-08-ex-age-sex.rtf (Date generated: 24APR2018:07:39) Source data: crt.dm, crt.ex

Table 5. Total Subject Exposure to Pegfilgrastim in Clinical Trials by Age Group and Gender (Safety Analysis Set)

	Infants and Toddlers (0 - <2 years) n (subj-yrs)	Children (2 to 11 years) n (subj-yrs)	Adolescents (12 to 17 years) n (subj-yrs)	Adults (18 to 64 years) n (subj-yrs)	Elderly (65 to 74 years) n (subj-yrs)	Elderly (75 to 84 years) n (subj-yrs)	Elderly (85+ years) n (subj-yrs)
Female							
Acute Myeloid Leukaemia	0 (0.0)	0 (0.0)	0 (0.0)	16 (3.3)	4 (0.8)	0 (0.0)	0 (0.0)
Chemotherapy-induced Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	3249 (1285.0)	1050 (369.4)	378 (130.9)	21 (5.8)
Chemotherapy-induced Neutropenia (Pediatric)	1 (0.5)	3 (1.5)	6 (3.1)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Healthy Volunteers	0 (0.0)	0 (0.0)	0 (0.0)	118 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral Blood Progenitor Cell	0 (0.0)	0 (0.0)	0 (0.0)	29 (5.4)	7 (1.8)	0 (0.0)	0 (0.0)
Pharmacokinetic Subjects with Renal Dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.8)	0 (0.0)	3 (0.4)	0 (0.0)
Total	1 (0.5)	3 (1.5)	6 (3.1)	3420 (1306.3)	1061 (372.0)	381 (131.2)	21 (5.8)

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n = number of subjects exposed to pegfilgrastim; subj-yrs = total subject-yrs of follow-up
Note: Data is from completed studies, ongoing open-label studies and unblinded interim analyses for ongoing blinded studies as of 31 January 2018. A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Program: /userdata/stat/peggcsf/sd01/meta/RMP_2018/tables/t-ex-age-sex.sas
Output: t-08-ex-age-sex.rtf (Date generated: 24APR2018:07:39) Source data: crt.dm, crt.ex

Table 6. Exposure to Pegfilgrastim in Clinical Trials by Dose Level and Indication (Safety Analysis Set)

	Exposure to Pegfilgrastim in Days		Subject Exposure to Pegfilgrastim	
	Dosage 6 mg n (mean)	Dosage Other n (mean)	Dosage 6 mg n (subj-yrs)	Dosage Other[a] n (subj-yrs)
Acute Myeloid Leukaemia	42 (34.3)	0 (0.0)	42 (8.4)	0 (0.0)
Chemotherapy-induced Neutropenia	5727 (65.0)	447 (57.7)	5727 (2209.1)	447 (377.3)
Chemotherapy-induced Neutropenia (Pediatric)	0 (0.0)	37 (64.8)	0 (0.0)	37 (17.0)
Healthy Volunteers	262 (1.0)	65 (1.0)	262 (31.5)	65 (2.9)
Peripheral Blood Progenitor Cell	42 (12.3)	43 (11.2)	42 (8.5)	43 (9.5)
Pharmacokinetic Subjects with Renal Dysfunction	31 (1.0)	0 (0.0)	31 (3.7)	0 (0.0)
Total	6104 (61.3)	592 (48.6)	6104 (2261.3)	592 (406.8)

n = number of subjects exposed to pegfilgrastim; subj-yrs = total subject-yrs of follow-up
[a] Dosage Other: Weight-based and fixed doses (with the exception of the approved 6 mg dose) investigated during pegfilgrastim development.
Note: Data is from completed studies, ongoing open-label studies and unblinded interim analyses for ongoing blinded studies as of 31 January 2018. A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded.
Safety Analysis Set includes subjects who received at least 1 dose of investigational product.
Source: t-09-ex-doselev-indic.rtf

Table 7. Total Subject Exposure to Pegfilgrastim in Clinical Trials by Product and Race/Ethnic Group (Safety Analysis Set)

	White n (subj-yrs)	Black or African American n (subj-yrs)	Hispanic or Latino n (subj-yrs)	Asian n (subj-yrs)	Other n (subj-yrs)	Missing/ Unknown n (subj-yrs)	Total n (subj-yrs)
Acute Myeloid Leukaemia	38 (7.5)	1 (0.2)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	42 (8.4)
Chemotherapy-induced Neutropenia	5216 (2253.7)	471 (143.5)	327 (114.6)	88 (36.0)	72 (38.5)	0 (0.0)	6174 (2586.4)
Chemotherapy-induced Neutropenia (Pediatric)	29 (13.1)	3 (1.5)	4 (1.9)	0 (0.0)	1 (0.4)	0 (0.0)	37 (17.0)
Healthy Volunteers	233 (24.3)	70 (8.0)	9 (0.4)	6 (0.7)	5 (0.5)	4 (0.5)	327 (34.4)
Peripheral Blood Progenitor Cell	78 (17.0)	4 (0.2)	2 (0.4)	0 (0.0)	1 (0.5)	0 (0.0)	85 (18.0)
Pharmacokinetic Subjects with Renal Dysfunction	23 (2.7)	5 (0.6)	1 (0.1)	0 (0.0)	2 (0.3)	0 (0.0)	31 (3.7)
Total	5617 (2318.4)	554 (154.1)	343 (117.5)	97 (37.4)	81 (40.2)	4 (0.5)	6696[a] (2668.0)

n = number of subjects exposed to pegfilgrastim; subj-yrs = total subject-yrs of follow-up

[a] Subjects that received placebo and pegfilgrastim or filgrastim and pegfilgrastim (cross-over treatment groups) are summarized under the pegfilgrastim group.

Note: Data is from completed studies, ongoing open-label studies and unblinded interim analyses for ongoing blinded studies as of 31 January 2018. A study is considered "completed" if a final clinical study report is available or if the study has finished and data have been unblinded.

Safety Analysis Set includes subjects who received at least 1 dose of investigational product.

Source: t-10-ex-indic-race.rtf

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Pregnant or breastfeeding (for a subject of child-bearing potential)	There are no or limited data from the use of pegfilgrastim in pregnant and breastfeeding women.	No	Data from use of pegfilgrastim in the postmarketing setting did not reveal any patterns suggestive of a safety concern and did not indicate any safety signals with the use of pegfilgrastim during pregnancy or lactation. Appropriate warnings regarding pregnancy and lactation are provided in Section 4.6 of the SmPC.
Not using adequate contraception	There are no adequate data from the use of pegfilgrastim in pregnant and breastfeeding women.	No	Based on the available data, there is no scientific rationale for retaining as missing information; however, pegfilgrastim is not recommended during pregnancy and in women of childbearing potential not using contraception.
Hypersensitivity to the active substance or to any of the excipients	Pegfilgrastim is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.	No	It is not anticipated that pegfilgrastim will be utilized in patients with known hypersensitivity to the active substance or to any of the excipients.

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Any premalignant myeloid condition or malignancy with myeloid characteristics (eg, MDS or CML)	Granulocyte colony-stimulating factor (G-CSF) can promote growth of myeloid cells, including malignant cells.	No	While G-CSF can potentially promote growth of myeloid cells, no specific safety concerns have been observed for the use of pegfilgrastim in patients with premalignant myeloid condition or malignancy with myeloid characteristics (eg, MDS or CML) to date; thus, the safety and efficacy of pegfilgrastim is not expected to differ in subjects with premalignant myeloid conditions or malignancies with myeloid characteristics.
Active infection	Usually myelosuppressive chemotherapy should not be administered if active infection is present.	No	The safety and efficacy of pegfilgrastim is not expected to differ in subjects with active infection.
Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 x upper limit of normal (ULN) concomitant with alkaline phosphatase > 2.5 x ULN	Clinical chemistry values were required to be within near normal range to provide a homogeneous study population in terms of metabolic characteristics.	No	Liver cell damage is frequent in patients with liver metastases of cancer, who are treated with myelotoxic chemotherapy. As it is primarily cleared through receptor-mediated endocytosis, pegfilgrastim pharmacokinetics is unlikely to be affected by hepatic impairment; thus, the safety and efficacy of pegfilgrastim is not expected to differ in subjects with AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN.

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Bilirubin > ULN according to institutional standard	Clinical chemistry values were required to be within near normal range to provide a homogeneous study population in terms of metabolic characteristics.	No	Liver cell damage is frequent in patients with liver metastases, who are treated with myelotoxic chemotherapy. As it is primarily cleared through receptor-mediated endocytosis, pegfilgrastim pharmacokinetics is unlikely to be affected by hepatic impairment; thus, the safety and efficacy of pegfilgrastim is not expected to differ in subjects with bilirubin > ULN according to institutional standard.
Inadequate renal function (creatinine ≥ 1.5 x ULN)	Clinical chemistry values were required to be within near normal range to provide a homogeneous study population in terms of metabolic characteristics.	No	Pegfilgrastim is cleared primarily by neutrophils with minimal renal clearance; thus, the safety and efficacy of pegfilgrastim is not expected to differ in subjects with inadequate renal function.
Clinically significant cardiac disease that would preclude the use of doxorubicin or left ventricular ejection fraction < 50% at rest, measured by multi-gated acquisition scan (MUGA) or echocardiogram	Pegfilgrastim was studied with doxorubicin-containing chemotherapy. Clinically significant cardiac disease might have precluded use of doxorubicin in the clinical trial setting.	No	No effect of pegfilgrastim on cardiac function is known. The safety and efficacy of pegfilgrastim is not expected to differ in subjects with clinically significant cardiac disease.

Table 8. Important Exclusion Criteria in Pivotal Studies Across the Development Program

Criterion	Reason for Exclusion	Included as Missing Information (Yes/No)	Rationale
Prior exposure to pegfilgrastim, filgrastim, or other colony-stimulating factors (CSFs) within 6 weeks of intended study administration of pegfilgrastim (ie, cycle 1 day 2), with exception of ≤ 2 injections of short-acting CSFs	In the clinical trial setting, previous exposure to G-CSF agents was avoided.	No	The safety and efficacy of pegfilgrastim is not expected to differ in subjects who have been exposed to other CSFs.

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SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as adverse reactions with a long latency, or those caused by prolonged or cumulative exposure. For rare adverse drug reactions (ADRs) (frequency ≥ 0.01% and < 0.1%), the probability of observing ≥ 1 event is ≥ 49% and < 100.0%.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programs

Table 9. Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Nine pregnancies were reported 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.
Patients with renal impairment	Thirty-one subjects with renal impairment, including end-stage renal disease, were included in the pegfilgrastim clinical development program.
Patients with cardiovascular impairment	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Approximately 83.9% of the subject population were white. Table 7 provides the race/ethnicity for the remaining subjects.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	
Pediatric patients	Thirty-seven pediatric subjects with sarcoma were included in the pegfilgrastim clinical development program.
Elderly patients > 65 years of age	Two thousand two hundred eighty (34.1%) subjects > 65 years of age were included in the pegfilgrastim clinical development program. Table 5 provides the age groups for the remaining subjects.

Part II: Module SV - Postauthorization Experience

SV.1 Postauthorization Exposure

SV.1.1 Method Used to Calculate Exposure

Amgen's estimates of postmarketing patient exposure are in part based on unit sales data (eg, vials or syringes), and in part on observed drug utilization parameters. Worldwide unit sales are reported monthly by country and are converted to estimates of person-time and when feasible, person-count, using region- and product-specific utilization parameters and algorithms. These parameters include the average number of mg per administration, average length of treatment, days between administrations, patient turnover rates, market penetration rates, and average revenue per patient. These drug utilization parameters can change over time to best represent the current patient and market experience.

SV.1.2 Exposure

The estimated cumulative number of patient-years of exposure to pegfilgrastim through commercial distribution is shown in Table 10 below. The estimated cumulative number of patients exposed to pegfilgrastim through commercial distribution is shown in Table 11 below.

Table 10. Estimated Number of Patient-years of Exposure to Pegfilgrastim, by Region and Demographic Characteristics, in the Postmarketing Setting Cumulatively From Launch to 31 January 2025

Demographic Characteristic	Cumulative Number of Patients-years of Exposure					
	AU	CA	EU	US	Other	Total
Overall	60 165	23 565	937 584	1 552 214	193 301	2 766 828
Sex						
Female	39 372	15 421	613 928	1 016 947	126 772	1 812 439
Male	20 793	8144	323 656	535 267	66 530	954 389
Age						
< 18	331	130	5242	8808	1126	15 637
18 - 34	1612	632	25 386	42 416	5371	75 418
35 - 49	9434	3695	147 280	244 228	30 506	435 143
50 - 64	29 691	11 628	461 540	762 364	94 541	1 359 765
65 - 74	11 618	4551	181 454	301 015	37 626	536 264
≥ 75	7478	2929	116 682	193 382	24 131	344 602
Sex by age						
Female						
< 18	144	57	2285	3835	489	6810
18 - 34	902	354	14 244	23 853	3033	42 386
35 - 49	7382	2892	115 324	191 350	23 927	340 875
50 - 64	20 625	8077	320 711	529 914	65 753	945 080
65 - 74	6606	2588	103 361	171 739	21 530	305 824
≥ 75	3712	1454	58 002	96 256	12 040	171 465
Male						
< 18	180	71	2865	4823	619	8558
18 - 34	710	278	11 142	18 563	2339	33 032
35 - 49	2052	804	31 955	52 878	6579	94 268
50 - 64	9067	3551	140 829	232 451	28 788	414 685
65 - 74	5018	1965	78 185	129 426	16 115	230 709
≥ 75	3766	1475	58 679	97 126	12 091	173 137

AU = Australia and New Zealand; CA = Canada; EU = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); Other = countries, not otherwise specified above, where Amgen is the marketing authorization holder; US = United States

Note: Numbers may not add to the total due to rounding.

Age and sex breakdowns are based on patient characteristics in MarketScan, a US health insurance claims database. Applying these distributions to regions outside the US requires strong assumptions that are not easily testable.

Table 11. Estimated Number of Patients Exposed to Pegfilgrastim, by Region and Demographic Characteristics, in the Postmarketing Setting Cumulatively From Launch to 31 January 2025

Demographic Characteristic	Cumulative Number of Patients Exposed					
	AU	CA	EU	US	Other	Total
Overall	180 494	70 695	2 847 329	6 413 497	579 904	10 091 920
Sex						
Female	118 115	46 264	1 864 412	4 202 189	380 315	6 611 296
Male	62 379	24 431	982 917	2 211 308	199 589	3 480 624
Age						
< 18	993	389	15 918	36 469	3379	57 147
18 - 34	4837	1896	77 085	175 486	16 114	275 418
35 - 49	28 301	11 086	447 260	1 009 345	91 518	1 587 511
50 - 64	89 074	34 884	1 401 685	3 148 947	283 623	4 958 212
65 - 74	34 853	13 653	551 038	1 244 104	112 878	1 956 527
≥ 75	22 435	8788	354 343	799 147	72 392	1 257 104
Sex by age						
Female						
< 18	433	170	6937	15 874	1468	24 883
18 - 34	2707	1061	43 252	98 717	9098	154 835
35 - 49	22 147	8675	350 216	790 876	71 780	1 243 694
50 - 64	61,873	24 232	973 988	2 188 908	197 260	3 446 260
65 - 74	19 818	7764	313 878	709 965	64 589	1 116 014
≥ 75	11 136	4362	176 141	397 850	36 120	625 609
Male						
< 18	541	212	8700	19 974	1856	31 284
18 - 34	2130	834	33 833	76 769	7016	120 582
35 - 49	6155	2411	97 044	218 470	19 738	343 818
50 - 64	27 200	10 652	427 697	960 039	86 363	1 511 952
65 - 74	15 053	5896	237 440	534 760	48 344	841 493
≥ 75	11 299	4425	178 202	401 296	36 272	631 495

AU = Australia and New Zealand; CA = Canada; EU = Europe (European Union, European Economic Area, Switzerland, and the United Kingdom); Other = countries, not otherwise specified above, where Amgen is the marketing authorization holder; US = United States

Note: Numbers may not add to the total due to rounding.

Age and sex breakdowns are based on patient characteristics in MarketScan, a US health insurance claims database. Applying these distributions to regions outside the US requires strong assumptions that are not easily testable.

Postauthorization Use From Business Partners

Kyowa Kirin Limited (KKL) is a subsidiary of Kyowa Kirin Co., Ltd (KKC).

Cumulatively through 31 January 2025, an estimated 744 743 patients (248 248 patient-years of exposure) were treated with pegfilgrastim in KKC territories.

Cumulatively through 31 January 2025, an estimated 24 620 patients (8207 patient-years of exposure) were treated with pegfilgrastim in KKL territories.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

SVI.1 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

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

Not applicable, as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as this is not the initial RMP for the product. Please refer to the full safety profile in the SmPC.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

Table 12. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP		
Important Identified Risk		
Sickle cell crisis in patients with sickle cell disease	Sickle cell crisis in patients with sickle cell disease, previously classified as an important identified risk, is removed from the list of safety concerns.	The available information on this risk (previous safety assessment and review of PBRERs/PSURs [available in PBRER/PSUR #17, reporting period 01 February 2013 to 31 January 2016, to PBRER/PSUR #26, reporting period 01 February 2022 to 31 January 2025], along with routine signal detection to date) supports the reclassification of sickle cell crisis in patients with sickle cell disease as an identified risk not categorized as important and removal from the pegfilgrastim EU RMP. The risk has been well characterized and additional safety information is unlikely to alter that characterization. The risk minimization activities in the SmPC recommending specific clinical measures to address the risk are generally considered to be standard medical practice. In addition, there are aRMMs or additional pharmacovigilance activities in place for the risk. Sickle cell crisis in patients with sickle cell disease will continue to be monitored through routine pharmacovigilance activities.

Footnotes, including abbreviations, are defined on the last page of this table.

Table 12. New or Reclassification of Safety Concerns in the RMP

Safety Concern	Action Taken	Justification
Removal of Safety Concerns from the RMP		
Important Identified Risk (continued)		
Glomerulonephritis	Glomerulonephritis, previously classified as an important identified risk, is removed from the list of safety concerns.	The available information on this risk (previous safety assessment and review of PBRERs/PSURs [available in PBRERs/PSURs #17 to #26] along with routine signal detection to date) supports the reclassification of glomerulonephritis as an identified risk not categorized as important and removal from the pegfilgrastim EU RMP. The risk has been well characterized and additional safety information is unlikely to alter that characterization. The risk minimization activities in the SmPC recommending specific clinical measures to address the risk are generally considered to be standard medical practice. In addition, there are no aRMMs or additional pharmacovigilance activities in place for the risk. Glomerulonephritis will continue to be monitored through routine pharmacovigilance activities.

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aRMM = additional risk minimization measure; EU = European Union; PBRER = Periodic Benefit-Risk Evaluation Report; PSUR = Periodic Safety Update Report; RMP = risk management plan; SmPC = summary of product characteristics

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 and potential risks with pegfilgrastim treatment are characterized in the tables below. To provide a comprehensive assessment of the incidence and severity of the risks, subjects that received at least one dose of pegfilgrastim in the Amgen clinical development program were included in the analysis. However, to assess the strength of evidence, the analyses were limited to subjects that received study drug in placebo-controlled trials.

Table 13. Important Identified Risk: Capillary Leak Syndrome

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 (de Vos et al, 2004; Rechner et al, 2003; De Pas et al, 2001).
Evidence source(s) and strength of evidence	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. There were no events of capillary leak syndrome (CLS) in pegfilgrastim placebo controlled clinical studies.
Characterization of the risk	
Frequency	In pooled pegfilgrastim clinical studies, 729 of 6696 subjects (10.9%) administered pegfilgrastim experienced an event with a PT in the Capillary leak syndrome Amgen Medical Dictionary for Regulatory Activities (MedDRA) Query (AMQ). None of these 729 subjects experienced an event with the PT capillary leak syndrome. Cases of CLS were reported in the postmarketing setting.
Severity	In pegfilgrastim studies, the majority of the events in the CLS AMQ were mild to moderate. Life threatening and fatal events occurred infrequently.
Reversibility	Capillary leak syndrome can be a life-threatening condition and discontinuation of pegfilgrastim in combination with appropriate medical management may reverse the risk.
Long-term outcomes	The prognosis of CLS is poor when supportive therapy is delayed or inadequately managed, especially during the post-capillary leak phase, due to cardiovascular overload secondary to the after effects of overzealous fluid resuscitation. Recurrences have been reported in some cases.
Impact on quality of life	Capillary leak syndrome can lead to sodium and water retention, which may result in edema, serous effusions, and acute kidney injury. More serious manifestations including hypovolemic shock, pleural effusion, and pulmonary edema occur less frequently (Siddall et al, 2017).

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 13. Important Identified Risk: Capillary Leak Syndrome

Risk factors and risk groups	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 (Krzesiński et al, 2010), granulocyte-macrophage colony-stimulating factor (Al-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	No data are currently available on potential measures to prevent CLS.
Impact on the risk-benefit balance of the product	The risk of CLS has been considered in the product benefit-risk assessment. In light of the product labeling in place to address this risk, the overall benefit-risk balance is expected to be positive.
Public health impact	Pegfilgrastim is indicated in a specific and limited population and as a result, the overall impact on public health is considered to be low.

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AMQ = Amgen MedDRA Query; CLS = capillary leak syndrome; G-CSF = granulocyte colony-stimulating factor; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

Table 14. Important Identified Risk: Acute Respiratory Distress Syndrome

<table>
<tr><td>Potential mechanisms</td><td>The pathogenesis of acute respiratory distress syndrome (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.</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. The placebo-controlled clinical study data show a higher rate of ARDS in subjects receiving pegfilgrastim compared to subjects receiving placebo.</td></tr>
<tr><td>Characterization of the risk</td><td></td></tr>
<tr><td>Frequency</td><td>In pooled pegfilgrastim clinical studies, 2099 of 6696 subjects (31.3%) administered pegfilgrastim experienced an event with a PT in the Respiratory, thoracic and mediastinal disorders SOC. From 2099 subjects, there were 67 reported events:
<table>
<tr><th>Preferred Term</th><th>No. of Subjects Reporting Events</th></tr>
<tr><td>Haemoptysis</td><td>44 (0.7%)</td></tr>
<tr><td>Pulmonary oedema</td><td>14 (0.2%)</td></tr>
<tr><td>Pneumonitis</td><td>4 (< 0.1%)</td></tr>
<tr><td>Interstitial lung disease</td><td>2 (< 0.1%)</td></tr>
<tr><td>Acute respiratory distress syndrome</td><td>1 (< 0.1%)</td></tr>
<tr><td>Pulmonary haemorrhage</td><td>1 (< 0.1%)</td></tr>
<tr><td>Acute respiratory failure</td><td>1 (< 0.1%)</td></tr>
</table>
Cases of ARDS were reported in the postmarketing setting.</td></tr>
<tr><td>Severity</td><td>In pegfilgrastim studies, the majority of events retrieved using Respiratory SOC were mild to moderate. However, life-threatening and fatal events were reported.</td></tr>
<tr><td>Reversibility</td><td>Data on reversibility are not available.</td></tr>
<tr><td>Long-term outcomes</td><td>Acute respiratory distress syndrome may require prolonged hospitalization and ventilation, and may be fatal.</td></tr>
<tr><td>Impact on quality of life</td><td>Acute respiratory distress syndrome is associated with significant mortality and survivors have reported increase in neurocognitive sequelae, moderate to severe depression, anxiety, and a decrease in health-related quality of life (Marti et al, 2016; Hodgson et al, 2012; Hopkins et al, 2005).</td></tr>
</table>

Footnotes, including abbreviations, are defined on the last page of this table.

Table 14. Important Identified Risk: Acute Respiratory Distress Syndrome

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 (Huang et al, 2011; Katsuya et al, 2009). Interstitial pneumonitis and other interstitial lung diseases have been seen with other chemotherapy agents in the setting of lung cancer (Zimmerman et al, 1984), particularly in Japan (Camus et al, 2004).
Preventability	The onset of pulmonary signs, such as cough, fever, and dyspnea in association with radiological signs of pulmonary infiltrates and deterioration in pulmonary function may be preliminary signs of ARDS. Neutropenic patients receiving pegfilgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS.
Impact on the risk-benefit balance of the product	The risk of ARDS has been considered in the product benefit-risk assessment. In light of the product labeling in place to address this risk, the overall benefit-risk balance is expected to be positive.
Public health impact	Pegfilgrastim is indicated in a specific and limited population and as a result, the overall impact on public health is considered to be low.

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ARDS = acute respiratory distress syndrome; NHL = non-Hodgkin's lymphoma; PT = preferred term; SOC = System Organ Class

Table 15. Important Potential Risk: Cytokine Release Syndrome

Potential mechanisms	Some monocyte/macrophages populations are reported to express granulocyte colony-stimulating factor receptor (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 Görgen 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-α and decreased mortality (mortality: 83% in control animals, 33% in animals treated with 50 μg/kg G-CSF, and 0% in animals treated with 250 μg/kg G-CSF) (Görgen et al, 1992). In a separate study by Fink et al (1993), lung injury was reduced by G-CSF pretreatment in lipopolysaccharide-challenged pigs.
Evidence source(s) and strength of evidence	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. There were no events of cytokine release syndrome in pegfilgrastim placebo controlled clinical studies.
Characterization of the risk	
Frequency	In pooled pegfilgrastim clinical studies, 3765 of 6696 subjects (56.2%) administered pegfilgrastim experienced an event with a PT in the Cytokine release syndrome AMQ. Two ($<$ 0.1%) of these 3765 subjects experienced an event with the PT cytokine release syndrome. Cases of cytokine release syndrome were reported in the postmarketing setting.
Severity	In pegfilgrastim studies, the majority of the events in the cytokine release syndrome AMQ were mild to moderate. Life threatening and fatal events occurred infrequently.
Reversibility	The reversibility of cytokine release syndrome depends on the grade of the disease as per Common Terminology Criteria for Adverse Events (CTCAE) (Lee et al, 2014). Patients experiencing milder grades 1 or 2 of cytokine release syndrome are more likely to have a reversible disease than those experiencing severe grades 3 or 4. Tocilizumab prevents the binding of IL-6 to both cell-associated and soluble IL-6 receptor and is recommended treatment for patients with severe grades of cytokine release syndrome (Lee et al, 2014).

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Footnotes, including abbreviations, are defined on the last page of this table.

Table 15. Important Potential Risk: Cytokine Release Syndrome

Characterization of the Risk (continued)	
Long-term outcomes	Among patients who received G-CSF-mobilized T cell-replete peripheral blood haplo-HCT, those with severe cytokine release syndrome experienced shorter median survival duration (2.6 vs 13.1 months) and higher transplant related mortality rates (hazard ratio: 4.6; 95% CI: 1.4, 14.7) than patients with mild cytokine release syndrome (Abboud et al, 2016).
Impact on quality of life	There are no reports in the published literature on the impact of cytokine release syndrome on quality of life.
Risk factors and risk groups	Patients receiving bi-specific antibodies and T cells engineered to express anti-CD19 chimeric antigen receptor are at particularly high risk for cytokine release syndrome (Frey, 2017). The severity of the cytokine release syndrome mediating infusion reaction might be related to the number of circulating lymphocytes (Chung, 2008). Among patients with B-cell malignancies, risk factors for developing cytokine release syndrome included higher bone marrow tumor burden, higher CAR-T cell dose, bulk CD8+ T-cell selection, lymphodepletion using fludarabine/cyclophosphamide, and presence of thrombocytopenia before lymphodepletion (Hay et al, 2017).
Preventability	Information on preventability is not available.
Impact on the risk-benefit balance of the product	The risk of cytokine release syndrome has been considered in the product benefit-risk assessment. In light of the product labeling in place to address this risk, the overall benefit-risk balance is expected to be positive.
Public health impact	Pegfilgrastim is indicated in a specific and limited population and as a result, the overall impact on public health is considered to be low.

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AMQ = Amgen MedDRA query; CAR-T = chimeric antigen receptor -cell; CTCAE = Common Terminology Criteria for Adverse Events; G-CSF = granulocyte colony-stimulating factor; G-CSF-R = granulocyte colony-stimulating factor receptor; IL-6 = interleukin-6; PT = preferred term

SVII.3.2 Presentation of the Missing Information

Not applicable.

Part II: Module SVIII - Summary of the Safety Concerns

Table 16. Summary of Safety Concerns

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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are presented in Table 17.

Table 17. Specific Adverse Reaction Follow-up Questionnaires

Follow-up Questionnaire (Annex 4)	Safety Concern(s)	Purpose
Neulasta (pegfilgrastim) capillary leak syndrome follow-up questionnaire	Capillary leak syndrome	To further characterize events of capillary leak syndrome reported in patients treated with pegfilgrastim in the postmarketing setting.
Neulasta (pegfilgrastim) cytokine release syndrome follow-up questionnaire	Cytokine release syndrome	To further characterize events of cytokine release syndrome reported in patients treated with pegfilgrastim in the postmarketing setting.

III.2 Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance activities.

III.3 Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned pegfilgrastim category 1 to 3 studies.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

Risk Minimization Plan

V.1 Routine Risk Minimization Measures

Table 18. (Table Part V.1) Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Capillary Leak Syndrome	Routine risk communication: • SmPC Section 4.4, Special warnings and precautions for use • SmPC Section 4.8, Undesirable effects • PL Section 2, What you need to know before you use Neulasta • PL Section 4, Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: • In Section 4.4 of SmPC: 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. Other routine risk minimization measures beyond the PI: • None
Acute Respiratory Distress Syndrome	Routine risk communication: • SmPC Section 4.4, Special warnings and precautions for use • SmPC Section 4.8, Undesirable effects • PL Section 2, What you need to know before you use Neulasta • PL Section 4, Possible side effects Routine risk minimization activities recommending specific clinical measures to address the risk: • In Section 4.4 of SmPC: Pegfilgrastim should be discontinued at the discretion of the physician and the appropriate treatment given. Other routine risk minimization measures beyond the PI: • None
Important Potential Risks	
Cytokine Release Syndrome	Routine risk communication: • None Routine risk minimization activities recommending specific clinical measures to address the risk: • None Other routine risk minimization measures beyond the PI: • None

PI = product information; PL = Package Leaflet; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimization Measures

Routine risk minimization measures as described in Part V.1 are considered sufficient to manage the safety concerns of Neulasta.

V.3 Summary of Risk Minimization Measures

Table 19. (Table Part V.3) Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Capillary Leak Syndrome	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Neulasta (pegfilgrastim) capillary leak syndrome follow-up questionnaire Additional pharmacovigilance activities: • None
Acute Respiratory Distress Syndrome	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risks		
Cytokine Release Syndrome	Routine risk communication: • None Other routine risk minimization measures beyond the PI: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Neulasta (pegfilgrastim) cytokine release syndrome follow-up questionnaire Additional pharmacovigilance activities: • None

PI = product information; PL = Package Leaflet; SmPC = Summary of Product Characteristics

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the RMP for pegfilgrastim is presented below.

Summary of Risk Management Plan for Neulasta® (Pegfilgrastim)

This is a summary of the RMP for Neulasta. The RMP details important risks of Neulasta, how these risks can be minimized, and how more information will be obtained about Neulasta's risks.

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

This summary of the RMP for Neulasta should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of 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 Neulasta's RMP.

I. The Medicine and What it is Used for

Neulasta is authorized for reduction in the duration of neutropenia and the incidence of febrile neutropenia (FN) in adult patients (see SmPC for the full indication). It contains pegfilgrastim as the active substance and it is given by subcutaneous injection.

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

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

Important risks of Neulasta, together with measures to minimize such risks and the proposed studies for learning more about Neulasta'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 authorized 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 public (eg, with or without prescription) can help to minimizes its risks.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (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 Neulasta 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 Neulasta. 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 (eg, 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

Important Identified risk: Capillary leak syndrome	
Evidence for linking the risk to the medicine	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. There were no events of capillary leak syndrome in pegfilgrastim placebo controlled clinical studies.
Risk factors and risk groups	Capillary leak syndrome has been reported after administration of multiple drugs, some of which include interleukins (Kai-Feng et al, *BMC Cancer*, 2011;11:204), gemcitabine (Baron et al, *Clin Oncol (R Coll Radiol)*, 2006;18:90-91), doxorubicin (Krzesiński et al, *Cardiol J*, 2010;17:88-91), granulocyte-macrophage colony-stimulating (Al-Homaidhi et al, *Bone Marrow Transpl*, 1998;21(2):209-214), and interferon (Yamamoto et al, *Arch Intern Med*, 2002;25:481-482). 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, *BMC Cancer*, 2011;11:204).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None

Important identified risk: Acute respiratory distress syndrome	
Evidence for linking the risk to the medicine	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. The placebo-controlled clinical study data show a higher rate of acute respiratory distress syndrome in subjects receiving pegfilgrastim compared to subjects receiving placebo.
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 non-Hodgkin's lymphoma (NHL) (Huang et al, *Ann Hematol*, 2011;90:1145-1151; Katsuya et al, *Leukemia & lymphoma*, 2009;50:1818-1823). Interstitial pneumonitis and other interstitial lung diseases have been seen with other chemotherapy agents in the setting of lung cancer (Zimmerman et al, *J Clin Onc*, 1984;2:396-405), particularly in Japan (Camus et al, *Br J Cancer,* 2004;91 Suppl 2:S18-23).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4 Additional risk minimization measures: • None

Important potential risk: Cytokine release syndrome	
Evidence for linking the risk to the medicine	Data to evaluate the safety concerns are derived from available data sources, including clinical studies and postmarketing adverse event reporting. There were no events of cytokine release syndrome in pegfilgrastim placebo controlled clinical studies.
Risk factors and risk groups	Patients receiving bi-specific antibodies and T cells engineered to express anti-CD19 chimeric antigen receptor are at particularly high risk for cytokine release syndrome (Frey, *Best Pract Res Clin Haematol*, 2017;30(4):336-340). The severity of the cytokine release syndrome mediating infusion reaction might be related to the number of circulating lymphocytes (Chung, *Oncologist*, 2008;13:725-732). Among patients with B-cell malignancies, risk factors for developing cytokine release syndrome included higher bone marrow tumor burden, higher chimeric antigen receptor T-cell (CAR-T) cell dose, bulk CD8+ T-cell selection, lymphodepletion using fludarabine/ cyclophosphamide, and presence of thrombocytopenia before lymphodepletion (Hay et al, *Blood*, 2017;130(21):2295-2306).
Risk minimization measures	Routine risk minimization measures: • None Additional risk minimization measures: • None

II.C. Postauthorization 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 Neulasta.

II.C.2. Other Studies in Postauthorization Development Plan

Not applicable.

PART VII: ANNEXES

Table of Contents

Annex 4. Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

Follow-up Form Title	Date of Follow-up Version
Neulasta (pegfilgrastim) capillary leak syndrome follow-up questionnaire	13 September 2023
Neulasta (pegfilgrastim) cytokine release syndrome follow-up questionnaire	13 September 2023

AMGEN®

Report of Suspected
NEULASTA (pegfilgrastim)
CAPILLARY LEAK SYNDROME

Date of this Report (dd/mm/yyyy)	AER #

This form is subject to applicable laws governing the protection of personal information. The information provided on this form may be transferred and processed outside of the country in which it is collected. Amgen does not wish to receive information through which a patient can be identified therefore please do not provide any information other than the specific information required by this form. This prohibition includes, for example, name, address, telephone number and government issued identifier.

1. PATIENT INFORMATION

Date of birth or Patient identifier: _____

Patient initials (confidential): _____

Patient age at time of event: _____

Gender: ☐ Male ☐ Female: Pregnant: ☐ Yes ☐ No

Weight: _____ lbs _____ kg

White cell count before event: _____ x 10^9/L Provide date: _____

2. NEULASTA (pegfilgrastim) THERAPY:

Start date (dd/mm/yyyy): _____ Stop date: _____

Last dose received (mg): _____ Batch/Lot# _____

Action taken: ☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug withdrawn ☐ Drug rechallenge

Indication: _____

Route of administration: ☐ SC ☐ Other (specify): _____

3. ADVERSE EVENT INFORMATION

Adverse event: _____

Event onset date (dd/mm/yyyy): _____ Resolved date (dd/mm/yyyy): _____ Outcome: ☐ Resolved ☐ Resolving ☐ Ongoing

Death; If patient died, please provide cause and date of death: _____

Was an autopsy performed? ☐ Yes ☐ No If yes, please provide autopsy results: _____

4. MEDICAL HISTORY/ADDITIONAL DETAILS (Please attach any relevant documents or reports.)

Relevant medical history (please provide dates); to include history of capillary leak syndrome, blood/bone marrow stem cell transplant, use of steroids/immunosuppressants, cytokine reaction after biologic agents, etc.: _____

Relevant concomitant medications:

Name: _____ Start date (dd/mm/yyyy): _____ Stop Date: _____ Dosage: _____ Indication: _____

Name: _____ Start date (dd/mm/yyyy): _____ Stop Date: _____ Dosage: _____ Indication: _____

Name: _____ Start date (dd/mm/yyyy): _____ Stop Date: _____ Dosage: _____ Indication: _____

Relevant laboratory/diagnostic tests (please attach available reports); e.g. chest x-ray, echocardiogram, chest CT, etc.:

Test name: _____ Date of test (dd/mm/yyyy): _____

Results (include units if applicable): _____

Test name: _____ Date of test (dd/mm/yyyy): _____

Results (include units if applicable): _____

Narrative (provide clinical presentation, e.g. hypovolemic shock, congestive heart failure, blood pressure, edema, dyspnea, tachypnea, ascites, etc., treatment provided and patient status at resolution of the event). If available/applicable, please provide the discharge summary:

_____

_____

_____

_____

_____

_____

RETURN TO AMGEN VIA SECURE EMAIL OR FAX AT:

Fax:

Email:

REPORTER Name: _____

State/Province: _____

Country/Postal Code: _____

Phone: (include country code) _____

Signature _____

Title _____ **Date** _____

AMGEN®

Report of Suspected
NEULASTA (pegfilgrastim)
CYTOKINE RELEASE SYNDROME

Date of this Report (dd/mm/yyyy)	AER #

1. PATIENT INFORMATION

Date of birth or Patient identifier: _____

Patient initials (confidential): _____

Patient age at time of event: _____

Gender: ☐ Male ☐ Female: Pregnant: ☐ Yes ☐ No

Weight: _____ lbs _____ kg

White cell count before event: _____ x 10^9/L Provide date: _____

2. NEULASTA (pegfilgrastim) THERAPY:

Start date (dd/mm/yyyy): _____ Stop date: _____

Last dose received (mg): _____ Batch/Lot# _____

Action taken: ☐ None ☐ Dose reduced ☐ Dose increased ☐ Drug withdrawn ☐ Drug rechallenge

Indication: _____

Route of administration: ☐ SC ☐ Other (specify): _____

3. ADVERSE EVENT INFORMATION

Adverse event: _____

Event onset date (dd/mm/yyyy): _____ Resolved date (dd/mm/yyyy): _____ Outcome: ☐ Resolved ☐ Resolving ☐ Ongoing

Death; If patient died, please provide cause and date of death: _____

Was an autopsy performed? ☐ Yes ☐ No If yes, please provide autopsy results: _____

4. MEDICAL HISTORY/ADDITIONAL DETAILS (Please attach any relevant documents or reports.)

Relevant medical history (please provide dates); to include history of capillary leak syndrome, blood/bone marrow stem cell transplant, use of steroids/immunosuppressants, cytokine reaction after biologic agents, etc.: _____

Relevant concomitant medications:

Name: _____ Start date (dd/mm/yyyy): _____ Stop Date: _____ Dosage: _____ Indication: _____

Name: _____ Start date (dd/mm/yyyy): _____ Stop Date: _____ Dosage: _____ Indication: _____

Name: _____ Start date (dd/mm/yyyy): _____ Stop Date: _____ Dosage: _____ Indication: _____

Relevant laboratory/diagnostic tests (please attach available reports); e.g. chest x-ray, echocardiogram, chest CT, etc.:

Test name: _____ Date of test (dd/mm/yyyy): _____

Results (include units if applicable): _____

Test name: _____ Date of test (dd/mm/yyyy): _____

Results (include units if applicable): _____

Narrative (Provide clinical presentation, e.g. multiple organ failure, fever/chills, headache, chest pain, blood pressure, dyspnea, tachypnea, edema, etc., treatment provided and patient status at resolution of the event. If available/applicable, please provide the discharge summary:

_____

_____

_____

_____

_____

_____

RETURN TO AMGEN VIA SECURE EMAIL OR FAX AT:

Fax:

Email:

REPORTER Name: _____

State/Province: _____

Country/Postal Code: _____

Phone: (include country code) _____

Signature _____

Title _____ **Date** _____

Annex 6. Details of Proposed Additional Risk Minimization Activities (if Applicable)

Not applicable.

Annex 7. Other Supporting Data (Including Referenced Material)

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