FILGRASTIM RISK MANAGEMENT PLAN

RMP Version number: 12.2

Data lock point for this RMP: 31 March 2023

Date of final sign off: 06 December 2023

Rationale for submitting an updated RMP: The MAH has updated this RMP and moved the category 3 NI PASS NEST ZOB-NIV-1513 (C1121008) to a completed additional pharmacovigilance study. Additionally, the MAH is proposing to remove the important potential risk of cytogenetic abnormalities and development of secondary haematologic malignancies from the list of safety concerns for the reasons that with the completion of the category 3 NI PASS there are no ongoing or planned additional PhV activities and there are no ongoing additional RMMs needed to manage the risk.

Summary of significant changes in this RMP are provided below:

- Part I: No updates.
- Part II: Module SI: No updates.
- Part II: Module SII: No updates.
- Part II: Module SIII: No updates.
- Part II: Module SIV: No updates.
- Part II: Module SV: Updated post-authorisation exposure through 31 March 2023.
- Part II: Module SVI: No updates.
- Part II: Module SVII: Updated to remove the important potential risk cytogenetic abnormalities and development of secondary haematologic malignancies from the list of safety concerns.
- Part II: Module SVIII: Updated according to changes made to the safety concerns for Nivestim.
- Part III: Updated to move the category 3 NI PASS NEST ZOB-NIV-1513 (C1121008) to a completed additional pharmacovigilance study.
- Part IV: No updates.
- Part V: Updated according to changes made to the safety concerns for Nivestim.

- Part VI: Updated summary of the RMP.
- Part VII: Updated the annexes to the RMP.
- Annex 2: Moved NEST study to completed.
- Annex 8: Summary of Changes

Other RMP versions under evaluation: Not applicable.

Details of the currently approved RMP:

Version number: 11.0

Approved with procedure: EMEA/H/C/001142/IB/0068

Date of approval (opinion date): 15 September 2022

QPPV name: Barbara De Bernardi, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukaemia
AMQ	Amgen MedDRA Query
ANC	Absolute Neutrophil Count
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BMT	Bone Marrow Transplant
CDS	Core Data Sheet
CEP	Customer Engagement Programme
CIN	Chemotherapy-Induced Neutropenia
cm	Centimeter
CML	Chronic Myeloid Leukemia
CMV	Cytomegalovirus
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
CT	Clinical Trial
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDD	Defined Daily Dose
DKMS	Deutsche Knochen Mark Spenderdatei (or German Bone Marrow Donor File)
DLP	Data-Lock Point
DNA	Deoxyribonucleic Acid
DSN	Duration of Severe Neutropenia
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	European Agency for the Evaluation of Medicinal Products
EPAR	European Public Assessment Report
ESRD	End Stage Renal Disease
EU	European Union
F	Female
FiO_2	Fraction of Inspired Oxygen
FN	Febrile Neutropenia

FSFV	First Subject First Visit
G-CSF	Granulocyte Colony Stimulating Factor
GGT	Gamma-Glutamyl Transferase
gHCD	Gamma Heavy Chain Disease
GSD	Glycogen Storage Disease
GvHD	Graft versus Host Disease
GVP	Good Pharmacovigilance Practices
H_2O	Water
HBsAg	Hepatitis B Virus Surface Antigen
HCP	Healthcare Professional
HELLP	Hemolysis, Elevated Liver Enzymes, and Low Platelets
HD	Healthy Donors
HIV	Human Immunodeficiency Virus
HSC	Haematopoietic Stem Cell
HSCT	Haematopoietic Stem Cell Transplant
IBCC	Inbound Call Center
Ig	Immunoglobulin
IL	Interleukin
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IMS	Intercontinental Marketing Services
INN	International Nonproprietary Name
IV	Intravenous
LDH	Lactate Dehydrogenase
LGL	Large Granular Lymphocytes
LSLV	Last Subject Last Visit
M	Male
MA	Marketing Authorsation
MAH	Marketing Authorisation Holder
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeter of Mercury
MRSA	Methicillin-Resistant Staphylococcus Aureus
MU	Million Units
N	Number
NHL	Non-Hodgkin’s Lymphoma
NonCT	Non-Clinical Trial
NY	New York
PaO_2	Partial Pressure of Oxygen
PASS	Post-Authorisation Safety Study
PBPC	Peripheral Blood Progenitor Cell
PBPCT	Peripheral Blood Progenitor Cell Transplant
PBSC	Peripheral Blood Stem Cells
PCR	Polymerase Chain Reaction

PDA	Patent Ductus Arteriosus
PhV	Pharmacovigilance
PL	Patient Leaflet
PLD	Pegylated Liposomal Doxorubicin
PM	Post-Marketing
PRAC	Pharmacovigilance Risk Assessment Committee
PRAC AR	Pharmacovigilance Risk Assessment Committee Assessment Report
PSUR	Periodic Safety Update Report
PT	Preferred Term
Q	Every
QPPV	Qualified Person for Pharmacovigilance
r-metHuG-CSF	Recombinant Methionyl Human Granulocyte Colony Stimulating Factor
RA	Rheumatoid Arthritis
RBD	Reference Biologic Drug
rhG-CSF	Recombinant Human Granulocyte Colony Stimulating Factor
RIP	Radioimmunoprecipitation Assay
RM	Risk Management
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
RP	Reference Product
RSI	Reference Safety Information
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous
SCN	Severe Chronic Neutropenia
SCNIR	Severe Chronic Neutropenia International Registry
SDB	Safety Database
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TK	Toxicokinetics
TUD	Technical University Dresden
US	United States
USPI	United States Prescribing Information
WBC	White Blood Cell Count
WHIM	Warts, Hypogammaglobulinemia, Immunodeficiency, and Myelokathexis
WHO	World Health Organization
Y	Years

TABLE OF CONTENTS

LIST OF TABLES

PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Filgrastim
Pharmacotherapeutic group(s) (ATC Code)	L03AA02
Marketing Authorisation Holder	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Nivestim
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class: Recombinant methionyl G-CSF produced in *Escherichia coli* (BL21) by recombinant DNA technology.
	Summary of mode of action: Human G-CSF is a glycoprotein which regulates the production and release of functional neutrophils from the bone marrow. Nivestim containing r-metHuG-CSF (filgrastim) causes marked increases in peripheral blood neutrophil counts within twenty-four hours, with minor increases in monocytes. In some SCN patients filgrastim can also induce a minor increase in the number of circulating eosinophils and basophils relative to baseline; some of these patients may present with eosinophilia or basophilia already prior to treatment. Elevations of neutrophil counts are dose dependent at recommended doses. Neutrophils produced in response to filgrastim show normal or enhanced function as demonstrated by tests of chemotactic and phagocytic function. Following termination of filgrastim therapy, circulating neutrophil counts decrease by 50% within 1 to 2 days, and to normal levels within 1 to 7 days.
	Important information about its composition: Nivestim is produced in Escherichia coli by recombinant DNA technology.
Hyperlink to the Product Information:	Module 1.3.1

Indication(s) in the EEA	Current: Filgrastim is indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy. Filgrastim is indicated for the mobilisation of PBPCs. In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an ANC of $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections, long term administration of filgrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events. Filgrastim is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0×10^9/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.
Dosage in the EEA	Current: Filgrastim therapy should only be given in collaboration with an oncology centre which has experience in G-CSF treatment and haematology and has the necessary diagnostic facilities. The mobilisation and apheresis procedures should be performed in collaboration with an oncology-haematology centre with acceptable experience in this field and where the monitoring of haematopoietic progenitor cells can be correctly performed. Established cytotoxic chemotherapy *Posology* The recommended dose of filgrastim is 0.5 MU (5 µg)/kg/day. The first dose of filgrastim should be administered at least 24 hours after cytotoxic chemotherapy. In randomised clinical trials, a subcutaneous dose of 230 µg/m^2/day (4.0 to 8.4 µg/kg/day) was used. Daily dosing with filgrastim should continue until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Following established chemotherapy for solid tumours, lymphomas, and lymphoid leukaemia, it is expected that the duration of treatment required to fulfil these criteria will be up to 14 days. Following induction and consolidation treatment for acute myeloid leukaemia the duration of treatment may be substantially longer (up to 38 days)

depending on the type, dose and schedule of cytotoxic chemotherapy used.

In patients receiving cytotoxic chemotherapy, a transient increase in neutrophil counts is typically seen 1 to 2 days after initiation of filgrastim therapy. However, for a sustained therapeutic response, filgrastim therapy should not be discontinued before the expected nadir has passed and the neutrophil count has recovered to the normal range. Premature discontinuation of filgrastim therapy, prior to the time of the expected neutrophil nadir, is not recommended.

Method of administration

Filgrastim may be given as a daily subcutaneous injection or as a daily intravenous infusion diluted in 5% glucose solution given over 30 minutes (see section 6.6 of the SmPC). The subcutaneous route is preferred in most cases. There is some evidence from a study of single dose administration that intravenous dosing may shorten the duration of effect. The clinical relevance of this finding to multiple dose administration is not clear. The choice of route should depend on the individual clinical circumstance.

<u>In patients treated with myeloablative therapy followed by bone marrow transplantation</u>

Posology

The recommended starting dose of filgrastim is 1.0 MU (10 µg)/kg/day. The first dose of filgrastim should be administered at least 24 hours following cytotoxic chemotherapy and at least 24 hours after bone marrow infusion.

Once the neutrophil nadir has been passed, the daily dose of filgrastim should be titrated against the neutrophil response as follows:

Neutrophil count	**Filgrastim dose adjustment**
> 1.0 x 10^9/L for 3 consecutive days	Reduce to 0.5 MU (5 µg)/kg/day
Then, if ANC remains > 1.0 x 10^9/L for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < 1.0 x 10^9/L during the treatment period, the dose of filgrastim should be re-escalated according to the above steps.	

Method of administration

Filgrastim may be given as a 30 minute or 24 hour intravenous infusion or given by continuous 24 hour subcutaneous infusion. Filgrastim should be diluted in 20 ml of 5% glucose solution (see section 6.6 of the SmPC).

	<u>For the mobilisation of PBPCs in patients undergoing myelosuppressive or myeloablative therapy followed by autologous PBPC transplantation</u> *Posology* The recommended dose of filgrastim for PBPC mobilisation when used alone is 1.0 MU (10 µg)/kg/day for 5 to 7 consecutive days. Timing of leukapheresis: one or two leukapheresis on days 5 and 6 are often sufficient. In other circumstances, additional leukapheresis may be necessary. Filgrastim dosing should be maintained until the last leukapheresis. The recommended dose of filgrastim for PBPC mobilisation after myelosuppressive chemotherapy is 0.5 MU (5 µg)/kg/day from the first day after completion of chemotherapy until the expected neutrophil nadir is passed and the neutrophil count has recovered to the normal range. Leukapheresis should be performed during the period when the ANC rises from < 0.5 x 10^9/L to > 5.0 x 10^9/L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukapheresis is recommended. *Method of administration* Filgrastim for PBPC mobilisation when used alone: Filgrastim may be given as a 24 hour subcutaneous continuous infusion or subcutaneous injection. For infusions filgrastim should be diluted in 20 ml of 5% glucose solution (see section 6.6 of SmPC). Filgrastim for PBPC mobilisation after myelosuppressive chemotherapy: Filgrastim should be given by subcutaneous injection. <u>For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation</u> *Posology* For PBPC mobilisation in normal donors, filgrastim should be administered at 1.0 MU (10 µg)/kg/day for 4 to 5 consecutive days. Leukapheresis should be started at day 5 and continued until day 6 if needed in order to collect 4 x 10^6 $CD34^+$ cells/kg recipient bodyweight. *Method of administration* Filgrastim should be given by subcutaneous injection.

	<u>In patients with severe chronic neutropenia (SCN)</u> *Posology* Congenital neutropenia: the recommended starting dose is 1.2 MU (12 µg)/kg/day as a single dose or in divided doses. Idiopathic or cyclic neutropenia: the recommended starting dose is 0.5 MU (5 µg)/kg/day as a single dose or in divided doses. Dose adjustment: Filgrastim should be administered daily by subcutaneous injection until the neutrophil count has reached and can be maintained at more than 1.5 x 10^9/L. When the response has been obtained the minimal effective dose to maintain this level should be established. Long term daily administration is required to maintain an adequate neutrophil count. After one to two weeks of therapy, the initial dose may be doubled or halved depending upon the patient's response. Subsequently the dose may be individually adjusted every 1 to 2 weeks to maintain the average neutrophil count between 1.5 x 10^9/L and 10 x 10^9/L. A faster schedule of dose escalation may be considered in patients presenting with severe infections. In clinical trials, 97% of patients who responded had a complete response at doses ≤ 24 µg/kg/day. The long-term safety of filgrastim administration above 24 µg/kg/day in patients with SCN has not been established. *Method of administration* Congenital, idiopathic or cyclic neutropenia: Filgrastim should be given by subcutaneous injection. <u>In patients with HIV infection</u> *Posology* For reversal of neutropenia: The recommended starting dose of filgrastim is 0.1 MU (1 µg)/kg/day with titration up to a maximum of 0.4 MU (4 µg)/kg/day until a normal neutrophil count is reached and can be maintained (ANC > 2.0 x 10^9/L). In clinical studies, > 90% of patients responded at these doses, achieving reversal of neutropenia in a median of 2 days. In a small number of patients (< 10%), doses up to 1.0 MU (10 µg)/kg/day were required to achieve reversal of neutropenia. For maintaining normal neutrophil counts: When reversal of neutropenia has been achieved, the minimal effective dose to maintain a normal neutrophil count should be established. Initial dose adjustment to alternate day dosing with 30 MU (300 µg)/day is recommended. Further dose adjustment may be necessary, as determined by the patient's ANC, to maintain the neutrophil count at > 2.0 x 10^9/L. In clinical

	studies, dosing with 30 MU (300 µg)/day on 1 to 7 days per week was required to maintain the ANC > 2.0 x 10^9/L, with the median dose frequency being 3 days per week. Long term administration may be required to maintain the ANC > 2.0 x 10^9/L. *Method of administration* Reversal of neutropenia or maintaining normal neutrophil counts: filgrastim should be given by subcutaneous injection.
Pharmaceutical form(s) and strengths	Current: <u>Nivestim 12 MU/0.2 ml solution for injection/infusion</u> Each ml of solution for injection or infusion contains 60 MU (600 µg) of filgrastim*. Each pre-filled syringe contains 12 MU (120 µg) of filgrastim in 0.2 ml (0.6 mg/ml). <u>Nivestim 30 MU/0.5 ml solution for injection/infusion</u> Each ml of solution for injection or infusion contains 60 MU (600 µg) of filgrastim*. Each pre-filled syringe contains 30 MU (300 µg) of filgrastim in 0.5 ml (0.6 mg/ml). <u>Nivestim 48 MU/0.5 ml solution for injection/infusion</u> Each ml of solution for injection or infusion contains 96 million units [MU] (960 µg) of filgrastim*. Each pre-filled syringe contains 48 MU (480 µg) of filgrastim in 0.5 ml (0.96 mg/ml). *recombinant methionyl G-CSF produced in *Escherichia coli* (BL21) by recombinant DNA technology.
Is/will the product be subject to additional monitoring in the EU?	No

PART II. SAFETY SPECIFICATION

Nivestim (filgrastim) is a biosimilar to the EU-licensed Neupogen® Reference Product (hereafter referred to as Neupogen in this document), which is considered representative of the EU approved Neupogen RBD, manufactured and licensed by Amgen. As such, this RMP is based on the Neupogen EU RMP developed by Amgen, dated 04 August 2017, and based on the PRAC PSUR AR (EMEA/H/C/PSUSA/00001391/201809) dated 16 May 2019, regarding updates to safety concerns according to the definitions of the GVP V Rev 2, with updates made as appropriate. Throughout this document, Nivestim will be used when discussing clinical trial information from the MAH clinical trial database, and filgrastim will be used as a collective term referring to any G-CSF product marketed worldwide when reviewing safety data, when not otherwise specified.

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Nivestim was developed as a biosimilar to the RP Neupogen; Module SI is not applicable for biosimilar products.

Module SII. Non-Clinical Part of the Safety Specification

Nivestim, which is licensed in the EU, is a filgrastim biosimilar to the reference product, Neupogen (EU-approved). Nivestim was demonstrated to be identical to Neupogen with respect to the amino acid sequence and similar to Neupogen with respect to physicochemical properties and response in a number of in vitro biological and functional assays. A comparative 4-week, repeat-dose toxicity study in rats demonstrated comparable toxicity, TK, pharmacodynamics, local tolerance and ADA (anti-filgrastim antibodies) profiles of Nivestim to Neupogen. These comparative data allow the nonclinical data generated by Amgen for Neupogen to be extrapolated to Nivestim. Nonclinical toxicity studies conducted by Amgen included single- and repeat-dose (up to 13 weeks duration) toxicity studies in mice, rats, hamsters, dogs, and/or cynomolgus monkeys, as well as reproductive and developmental toxicity studies in rats or rabbits.

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Reproductive/developmental toxicity • In pregnant rabbits, filgrastim caused increased abortion and embryolethality and was associated with increased fetal resorption. • In peri-postnatal studies in rats, delays in external differentiation and slight growth retardation were observed in offspring of dams treated with filgrastim.	There are no or limited amount of data from the use of filgrastim in pregnant women. Studies in animals have shown reproductive toxicity. An increased incidence of embryo-loss has been observed in rabbits at high multiples of the clinical exposure and in the presence of maternal toxicity. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated. Filgrastim is not recommended during pregnancy.

Module SIII. Clinical Trial Exposure

Nivestim is a recombinant human granulocyte colony-stimulating factor (rhG-CSF or G-CSF) that was developed by Pfizer as a biosimilar to the licensed filgrastim (reference product) approved in the European Union (EU) and marketed as Neupogen. The EU clinical development program for Nivestim consisted of the following clinical studies:

Two crossover PK/PD equivalence studies in healthy volunteers: a single-dose (GCF061, intravenous [IV] and subcutaneous [SC] administration) and a multiple-dose (GCF062, SC) study comparing PK, PD, and safety profile between Nivestim and the EU-Neupogen. Equivalence was demonstrated with no clinical meaningful differences in the safety profile compared with the EU-Neupogen.

One comparative safety and efficacy study (GCF071) in patients with breast cancer undergoing myelosuppressive chemotherapy assessed therapeutic equivalence in duration of severe neutropenia (DSN), PK/PD, immunogenicity and safety. Nivestim demonstrated comparable therapeutic response in the prophylaxis of neutropenia in subjects with comparable safety profile compared with the EU-Neupogen.

Table 2. Duration of Exposure (by study population)

Study group=Exposure in Phase I, healthy volunteers		
Duration of exposure (at least)	**Persons**	**Person-month**
≤1 month	98	19.29
Total person-months	19.29	
Study group=Exposure in Phase III, breast cancer patients		
Duration of exposure (at least)	**Persons**	**Person-month**
≤1 month	31	21.16
>1 – 2 months	245	358.18
>2 months	2	4.17
Total person-months	383.51	

Table 3. Duration of Exposure (totals)

Duration of exposure	**Persons**	**Person-month**
≤1 month	129	40.44
>1 – 2 months	245	358.18
>2 months	2	4.17
Total person-months	376	402.79

Table 4. By Dose (by indication)

Study group=Exposure in Phase I, healthy volunteers		
Dose of exposure	**Persons**	**Person-month**
5 mcg/kg	26	8.31
10 mcg/kg	72	10.97
Total	98	19.29
Study group=Exposure in Phase III, breast cancer patients		
Dose of exposure	**Persons**	**Person-month**
5 mcg/kg	278	383.51
Total	278	383.51

Table 5. By Dose (totals)

Total Population		
Dose of exposure	**Persons**	**Person-month**
5 mcg/kg	304	391.82
10 mcg/kg	72	10.97
Total	376	402.79

Table 6. By Age Group and Gender (by indication)

Study group=Exposure in Phase I, healthy volunteers				
Age group	**Persons**		**Person-month**	
	M	**F**	**M**	**F**
18-65y	51	47	11.33	7.95
Total	51	47	11.33	7.95
Study group=Exposure in Phase III, breast cancer patients				
Age group	**Persons**		**Person-month**	
	M	**F**	**M**	**F**
18-65y	0	272	0	374.11
>65-75y	0	6	0	9.40
Total	0	278	0	383.51

Table 7. By Age Group and Gender (totals)

Total population				
Age group	**Persons**		**Person-month**	
	M	**F**	**M**	**F**
18-65y	51	319	11.33	382.06
>65-75y	0	6	0	9.40
Total	51	325	11.33	391.46
Total	376		402.79	

Table 8. By Ethnic or Racial Origin (by indication)

Study group=Exposure in Phase I, healthy volunteers		
Ethnic/racial origin	**Persons**	**Person-month**
Caucasian	88	16.79
Black	6	1.97
Asian	2	0.13
Other	2	0.39
Total	98	19.29
Study group=Exposure in Phase III, breast cancer patients		
Ethnic/racial origin	**Persons**	**Person-month**
Caucasian	276	380.85
Asian	2	2.66
Total	278	383.51

Table 9. By Ethnic or Racial Origin (totals)

Total population		
Ethnic/racial origin	**Persons**	**Person-month**
Caucasian	364	397.63
Black	6	1.97
Asian	4	2.79
Other	2	0.39
Total	376	402.79

Table 10. By Route (by indication)

Study group=Exposure in Phase I, healthy volunteers		
Route	**Persons**	**Person-month**
Intravenous	22	1.38
Subcutaneous	76	17.91
Total	98	19.29
Study group=Exposure in Phase III, breast cancer patients		
Route	**Persons**	**Person-month**
Subcutaneous	278	383.51
Total	278	383.51

Table 11. By Route (totals)

Total population		
Route	**Persons**	**Person-month**
Intravenous	22	1.38
Subcutaneous	354	401.41
Total	376	402.79

Module SIV. Populations Not Studied in Clinical Trials

Nivestim is a biosimilar to Neupogen, the reference product in the EU, and information presented in this module were updated to present the reference product pivotal study information in the most current Neupogen EU RMP version 4.0, dated 04 August 2017 (DLP of 15 September 2016).

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

Table 12. Exclusion Criteria that Will Remain as Contraindications

Criterion	Implications for Target Population
All Indications	
Hypersensitivity to the active substance or to any of the excipients	Hypersensitivity, including anaphylactic reactions occurring on initial or subsequent treatment have been reported in patients treated with filgrastim.

Table 13. Exclusion Criteria That are Not Proposed to Remain as Contraindications

Criterion	Reasons for Inclusion as Exclusion Criterion	Justification for Not Being a Contraindication
All Indications		
Pregnant or lactating women	There are no adequate data from the use of filgrastim in pregnant women.	Appropriate warnings regarding pregnancy are provided in Section 4.6 of the SmPC. There are reports in the literature where the transplacental passage of filgrastim in pregnant women has been demonstrated. Filgrastim is not recommended during pregnancy. It is unknown whether filgrastim/metabolites are excreted 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 filgrastim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.
Patients currently receiving other investigational agent(s)	This requirement is specific to clinical trials.	Not applicable to the post-market setting.

Table 13. Exclusion Criteria That are Not Proposed to Remain as Contraindications

Criterion	Reasons for Inclusion as Exclusion Criterion	Justification for Not Being a Contraindication
Patients who have received corticosteroids or lithium within 4 weeks of study entry	Lithium may potentiate the release of neutrophils. Corticosteroids cause demargination of neutrophils from vasculature, resulting in an elevation of the neutrophil count.	These exclusion criteria were implemented due to the potential impact of these medicines on efficacy measurements, but this exclusion is not applicable in the post-market setting.
Medical or psychiatric conditions that compromise the patient's ability to give informed consent or complete the study.	This requirement is specific to clinical trials.	Not applicable to the post-market setting.
Patients considered by the Investigator to be inappropriate for participation in the study.	This requirement is specific to clinical trials.	Not applicable to the post-market setting.
Chemotherapy-induced Neutropenia		
Patients who have received antineoplastic agents other than cyclophosphamide/doxorubicin/ etoposide prior to the study	To avoid recruiting patients with previous damage to bone marrow	Filgrastim has a favorable benefit-risk profile in these higher risk patients.
Radiotherapy other than a single involved field (pelvis excluded) for superior vena cava syndrome, post obstructive pneumonias, epidural disease with impending spinal cord compression or cranial metastases. Patients with evidence of cranial metastases at the time of presentation may begin chemotherapy concurrently or within 3 to 5 days. Treatment with corticosteroids will not exclude the patient.	In the Neupogen clinical trial setting, subjects with inadequate bone marrow function were excluded to prevent the confounding of endpoints.	Not applicable to the post-market setting.
Within 2 weeks since major surgery	Chemotherapy might interfere with wound healing.	Exclusion criterion relevant for chemotherapy and not filgrastim. The decision of when to start chemotherapy after surgery is at the discretion of the prescribing physician. There is no evidence that filgrastim might negatively impact wound healing.
Carcinomatous meningitis	In the Neupogen clinical trial setting, this condition could interfere with adherence to the protocol.	Not applicable to the post-market setting.

Table 13. Exclusion Criteria That are Not Proposed to Remain as Contraindications

Criterion	Reasons for Inclusion as Exclusion Criterion	Justification for Not Being a Contraindication
Ongoing life-threatening infection	Usually myelosuppressive chemotherapy should not be administered if active infection is present.	Exclusion criterion relevant for chemotherapy and not filgrastim. Active infection might become clinically apparent after chemotherapy in which case filgrastim can be used to prevent further aggravation reducing the duration of neutropenia.
Patients receiving prophylactic antibiotics (ie, quinolones) for longer than 48 hours	In the Neupogen clinical trial setting, this is to prevent the confounding of endpoints.	Not applicable to the post-market setting. Although not recommended by guidelines,[1] G-CSF is sometimes combined with prophylactic use of antibiotics to prevent infection and infection-related complications in cancer patients at risk of neutropenia.
Patients concurrently enrolled in any antimicrobial protocol without Amgen approval	In the Neupogen clinical trial setting, this is to prevent the confounding of endpoints.	Not applicable to the post-market setting. Although not recommended by guidelines,[1] G-CSF is sometimes combined with prophylactic use of antibiotics to prevent infection and infection-related complications in cancer patients at risk of neutropenia.
Other serious medical or psychiatric illness which would prevent informed consent or intensive treatment	This requirement is specific to clinical trials.	Not applicable to the post-market setting.
Uncontrolled hypertension (diastolic blood pressure greater than 115 mmHg), evidence of clinically significant multifocal uncontrolled cardiac arrhythmias, or unstable angina	Neupogen was studied with doxorubicin-containing chemotherapy. Clinically significant cardiac disease might have precluded use of doxorubicin in the trial.	No interaction between filgrastim and cardiac function is known. Dosing of cytotoxic drugs is at the discretion of the prescribing physician.
Coronary heart failure New York Heart Association Class III-IV or abnormal baseline multiple-gated acquisition scan with left ventricular ejection fraction < 45%)	Neupogen was studied with doxorubicin-containing chemotherapy. Clinically significant cardiac disease might have precluded use of doxorubicin in the trial.	No interaction between filgrastim and cardiac function is known. Dosing of cytotoxic drugs is at the discretion of the prescribing physician.
Patients with prior cancer other than basal cell carcinoma	In the Neupogen clinical trial setting, previous damage to bone marrow was being avoided to prevent the confounding of endpoints.	Not applicable to the post-market setting.

Table 13. Exclusion Criteria That are Not Proposed to Remain as Contraindications

Criterion	Reasons for Inclusion as Exclusion Criterion	Justification for Not Being a Contraindication
Bone Marrow Transplant		
Serious cardiovascular, pulmonary, hepatic, or renal disease	Subjects with severe cardiac or respiratory dysfunction are excluded from BMT.	Determination of qualifying status of a subject for cytotoxic chemotherapy and BMT is at the discretion of the treating physician.
Serum total bilirubin greater than 3.0 mg/dL	To be able to safely administer chemotherapy	Exclusion criteria imposed due to risks of myelotoxic chemotherapy rather than filgrastim risks. Filgrastim pharmacokinetics is unlikely to be affected by hepatic impairment as it is primarily eliminated by neutrophils/neutrophil precursors and by the kidney.
Serum alanine or aspartate aminotransferase greater than 5 times normal	Clinical chemistry values were required to be within near normal range to provide a homogeneous study population in terms of metabolic characteristics.	Exclusion criteria imposed due to risks of myelotoxic chemotherapy rather than filgrastim risks. Filgrastim pharmacokinetics is unlikely to be affected by hepatic impairment as it is primarily eliminated by neutrophils/neutrophil precursors and by the kidney.
Serum creatinine greater than 2 times normal.	Clinical chemistry values were required to be within near normal range to provide a homogeneous study population in terms of metabolic characteristics.	Filgrastim is primarily eliminated by neutrophils/neutrophil precursors and by the kidney. Based on results from clinical studies, no dosage adjustment is recommended in patients with renal impairment.
Acute Myeloid Leukemia		
Patients in blast transformation of CML	G-CSF can support growth of myeloid cells in vitro, which leads to a theoretical risk that G-CSF might potentially be involved in the development of AML or MDS in normal donors who are exposed to G-CSF for PBPC mobilization.	Normal donor registry data do not suggest elevated risk of leukemia associated with G-CSF administration.
Previous treatment for AML	In the Neupogen clinical trial setting patients with inadequate bone marrow function or previous treatment of AML were excluded to prevent the confounding of endpoints.	Not applicable to the post-market setting. In the post-market setting, the choice of types and lines of therapy is at the discretion of the treating physician.

Table 13. Exclusion Criteria That are Not Proposed to Remain as Contraindications

Criterion	Reasons for Inclusion as Exclusion Criterion	Justification for Not Being a Contraindication
Patients with secondary AML (received previous chemotherapy or radiotherapy)	In the Neupogen clinical trial setting, patients with inadequate bone marrow function or previous treatment of AML were excluded to prevent the confounding of endpoints.	Not applicable to the post-market setting.
Patients with a prior diagnosis of MDS	In the Neupogen clinical trial setting, patients with inadequate bone marrow function were excluded to prevent the confounding of endpoints.	Not applicable to the post-market setting.
Previous treatment with colony-stimulating factors, ILs or interferons	In the Neupogen clinical trial setting, previous exposure to G-CSF agents was avoided to prevent the confounding of endpoints for efficacy.	Not applicable to the post-market setting.
Patients with a concurrent malignancy or history of malignancy (other than adequately treated basal cell carcinoma of the skin or cervical intra-epithelial neoplasia)	In the Neupogen clinical trial setting, patients with inadequate bone marrow function and patients concurrently treated for other malignancy were excluded to prevent the confounding of endpoints.	Not applicable to the post-market setting.
Severe Chronic Neutropenia		
Evidence of haematologic malignancy or myelodysplasia (such as excessive blasts in marrow or blood, chromosomal abnormalities, atypical cells other than LGLs)	Neupogen clinical trial subjects were limited to those with adequate bone marrow function to prevent the confounding of endpoints.	Not applicable to the post-market setting.
Idiopathic neutropenia with LGL with lymphocyte count > 5000	In the Neupogen clinical trial setting, patients with inadequate bone marrow function were excluded to prevent the confounding of endpoints.	Not applicable to the post-market setting.
Patients with Felty's Syndrome	Increased levels of neutrophils may worsen arthritis.	In the post-market setting, the decision to initiate therapy for SCN in the context of Felty's syndrome is at the discretion of the treating physician
Patients with drug-induced agranulocytosis	In the Neupogen clinical trial setting, patients with inadequate bone marrow function were excluded to prevent the confounding of endpoints.	Not applicable to the post-market setting.
Pancytopenia, eg, mild aplastic anemia or hypersplenism with a hematocrit consistently < 30 or platelet count consistently < 100000	In the Neupogen clinical trial setting, patients with inadequate bone marrow function were excluded to prevent the confounding of endpoints.	Not applicable to the post-market setting.

Table 13. Exclusion Criteria That are Not Proposed to Remain as Contraindications

Criterion	Reasons for Inclusion as Exclusion Criterion	Justification for Not Being a Contraindication
Clinically significant heart disease (NY Heart Classification III or IV)	In the Neupogen clinical trial setting, severe cardiac disease was excluded as subjects with these conditions may limit study participation and confound results.	Not applicable to the post-market setting.
Hemorrhagic diathesis or active bleeding	In the Neupogen clinical trial setting, patients with inadequate bone marrow function were excluded to prevent the confounding of endpoints.	In the post-market setting, diagnosis of and decision to initiate therapy for SCN is at the discretion of the treating physician.
PBPC After Myelosuppressive Chemotherapy		
Patients with AML	An aim of the Neupogen study (G-CSF-8815) was to demonstrate the applicability of PBPC collection in patients with diseases other than AML.	Other trials demonstrated the efficacy and safety of filgrastim in patients with AML.
Patients with malignant cells in the marrow assessed on morphologic examination	Presence of metastatic disease affecting the bone marrow were known to affect the primary endpoints of the Neupogen study, which were severe neutropenia and FN and the exclusion was included to prevent introduction of potential sources of bias.	Determination of the qualifying status of a patient as a donor is at the discretion of the treating physician.
Patients with significant non-malignant disease (eg, severe cardiac or respiratory dysfunction)	Neupogen subjects with severe cardiac or respiratory dysfunction are excluded as donors of bone marrow or PBPC.	Determination of qualifying status of a subject as donor is at the discretion of the treating physician.
Patients who have been previously treated with other cytokines	In the Neupogen clinical trial setting, previous exposure to G-CSF agents was avoided to prevent the confounding of endpoints for efficacy.	In the post-market setting, the choice of types of therapy is at the discretion of the treating physician.
PBPC in Normal Donors		
Inability to undergo general anesthesia and bone marrow harvest or to tolerate PBPC harvest	This was a Neupogen clinical trial specific requirement to be able to randomize donors to bone marrow harvest (in general anesthesia) or PBPC harvest.	Not applicable to the post-market setting. Determination of qualifying status of a subject as donor is at the discretion of the treating physician. General anesthesia is not required for the administration of filgrastim.
Peripheral venous access viewed as not possible on initial examination	This is a requirement for PBPC harvesting.	Determination of qualifying status of a subject as donor is at the discretion of the treating physician. Venous access is not a requirement for the administration of filgrastim.

Table 13. Exclusion Criteria That are Not Proposed to Remain as Contraindications

Criterion	Reasons for Inclusion as Exclusion Criterion	Justification for Not Being a Contraindication
Positive serology for hepatitis C and/or HBsAg, unless negative by PCR	Neupogen subjects with positive serology for hepatitis C and/or HBsAg, unless negative for antigen PCR, are excluded as donors of bone marrow or PBPC.	Determination of qualifying status of a subject as donor is at the discretion of the treating physician.
HIV positive	HIV-positive subjects are excluded as donors of bone marrow or PBPC	Determination of qualifying status of a subject as donor is at the discretion of the treating physician. Trials demonstrated the efficacy and safety of filgrastim in HIV-positive subjects.
History of malignant disease or current malignancy	Cancer patients are excluded as donors of bone marrow or PBPC.	Determination of qualifying status of a subject as donor is at the discretion of the treating physician. Trials demonstrated the efficacy and safety of filgrastim in patients receiving myelosuppressive chemotherapy for cancer.
HIV		
Presence of malignancy within 4 weeks of study entry with the exception of stable Kaposi's sarcoma not requiring treatment with myelosuppressive therapy (with the exception of interferon) and/or localized basal or squamous cell carcinoma.	Neupogen clinical trial-specific criterion to avoid the confounding of endpoints for efficacy.	Not applicable to the post-market setting.
Treatment with filgrastim, other hematopoietic growth factors (with the exception of erythropoietin alpha), within 14 days prior to randomization. Treatment with investigational agents within 14 days prior to randomization was also prohibited, unless approval had been granted by Amgen.	In the Neupogen clinical trial setting, previous exposure to G-CSF agents was avoided to prevent the confounding of endpoints for efficacy.	Not applicable to the post-market setting.
Patients with CMV retinitis receiving induction therapy with ganciclovir could not be enrolled for a minimum of 2 weeks after the completion of such therapy.	CMV and ganciclovir can induce bone marrow aplasia.	Relevant for ganciclovir therapy, however the prescription of G-CSF in the post-market setting is at the discretion of the treating physician.

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

Table 14. Limitations Common to All Clinical Trials

Ability to Detect Adverse Drug Reactions	Limitations of Trial Programme	Discussion of Implications for Target Population
Very rare ADRs	4906 Neupogen subjects were exposed to filgrastim in the clinical study programme across all indications.	For very rare ADRs (frequency < 0.01%), the probability of seeing at least 1 event was < 39%.
Rare ADRs	4906 Neupogen subjects were exposed to filgrastim in the clinical study programme across all indications.	For rare ADRs (frequency ≥ 0.01% and < 0.1%), the probability of observing at least 1 event was ≥ 39% to < 100%.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 15. Limitations With Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Patient Population	Representation in Clinical Trial Programme
Pregnant or lactating women	There are no or limited amount of data from the use of filgrastim in pregnant women. Filgrastim is not recommended during pregnancy. Cumulatively through 15 September 2016 (DLP of Neupogen RMP version 4.0 dated 04 August 2017) from Amgen-sponsored and non-Amgen sponsored study sources, there were 7 pregnancy cases reported in which patients were administered filgrastim during pregnancy. There was 1 case with a twin outcome; thus the total number of birth outcomes was 8. There were no cases with paternal exposure. Birth outcomes were 3 spontaneous abortions, 2 elective terminations (including 1 case with twin outcome), 1 elective termination with congenital anomaly, and 2 cases lost to follow-up. It is unknown whether filgrastim/metabolites are excreted 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 filgrastim therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. There have been no reports of lactation in women who received filgrastim in clinical trials.
Children	The pharmacokinetic properties of filgrastim in children with cancer were studied in 15 children (aged 1 to 9 years) with neuroblastoma[2] and 11 children (aged 6 to 18 years) after chemotherapy.[3] Pharmacokinetic properties of filgrastim have also been studied in 11 children with SCN.[4] The pharmacokinetics of filgrastim in pediatric patients after chemotherapy is similar to those in adults receiving the same weight-normalized doses, suggesting no age-related differences in the pharmacokinetics of filgrastim. As noted in the Neupogen RMP version 4.0 dated 04 August 2017, 65% of the patients studied in the SCN trial programme were under 18 years of age. The efficacy of treatment was clear for this age group, which included most

Table 15. Limitations With Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Patient Population	Representation in Clinical Trial Programme
	patients with congenital neutropenia. There were no differences in the safety profiles for pediatric patients treated for SCN. Data from Neupogen clinical studies in pediatric patients indicate that the safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy.
Geriatric patients	Among 855 subjects enrolled in 3 randomized, placebo-controlled Amgen trials of filgrastim use following myelosuppressive chemotherapy (Studies 8801, 8816, and 91134), there were 232 subjects 65 years of age or older, and 22 subjects 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other clinical experience has not identified differences in the responses between elderly and younger patients. As noted in the Neupogen RMP version 4.0 dated 04 August 2017, clinical studies of filgrastim in other approved indications did not include sufficient numbers of subjects aged 65 and older to determine whether elderly subjects respond differently from younger subjects. The safety and efficacy of filgrastim have not been assessed in normal donors > 60 years of age.
Patients with renal impairment	Clinical studies in cancer chemotherapy settings, including Neupogen studies, have generally excluded patients with significant renal compromise because renal compromise is a contraindication to chemotherapy. The pharmacokinetics and safety of filgrastim were evaluated in healthy subjects (n = 4), subjects with creatinine clearance of 30 to 60 mL/min (n = 4), and subjects with ESRD (n = 4) in an open-label clinical study (Study 940248). The results showed a trend towards higher mean peak serum concentration, higher mean AUC, and lower mean apparent clearance in the ESRD group compared with the other 2 groups; the trend was not reflected as higher mean ANC in the ESRD group. Similar results were obtained in a small clinical study (n = 9).[5] In another small clinical study, clearance of filgrastim appeared to be unaffected in subjects with chemotherapy-induced renal impairment (n = 5).[6] Since the mean ANC profiles were similar across varying degrees of renal function, including ESRD, filgrastim dose adjustment in patients with renal dysfunction is not necessary.
Patients with hepatic impairment	The pharmacokinetics of filgrastim is not expected to be affected by hepatic impairment. As noted in the Neupogen RMP version 4.0 dated 04 August 2017, in an open-label study of the pharmacokinetics and safety of filgrastim in subjects with normal (n = 12) versus impaired (n = 12) hepatic function (Study 940247), no differences in pharmacokinetic and pharmacodynamic parameters were observed between the 2 groups. In another small clinical study, clearance of filgrastim appeared to be unaffected in subjects with chemotherapy-induced hepatic impairment (n = 4).[6]
Patients with cardiac impairment	As noted in the Neupogen RMP version 4.0 dated 04 August 2017, clinical studies in chemotherapy settings, including filgrastim studies, have generally excluded patients with clinically significant cardiac disease because chemotherapy is known to worsen cardiac disease. No clinical studies of filgrastim have been conducted in subjects with cardiac impairment. No evidence of an adverse effect of filgrastim on cardiac function has been observed in clinical studies or in post-marketing reports.

Table 15. Limitations With Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Patient Population	Representation in Clinical Trial Programme
Patients with pulmonary impairment	As noted in the Neupogen RMP version 4.0 dated 04 August 2017, clinical studies in chemotherapy settings, including filgrastim studies, have generally excluded subjects with pulmonary impairment. Rare pulmonary adverse effects, in particular interstitial pneumonia, have been reported after G-CSF administration and in patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk.

SIV.4. Conclusions on the Populations Not-Studied and Other Limitations of the Clinical Trial Development Programme

Table 16. Missing Information: Conclusions Based on Populations Not Studied

Safety Concern	Comment	Missing Information?
Pregnant or lactating women	As noted in the Neupogen RMP, no adequate data are available concerning the use of filgrastim in pregnant women. Upon review of the Nivestim post-marketing data available as of 15 Feb 2021, there is no evidence of a significantly different safety profile when filgrastim is used in pregnant and lactating women when compared to the general target population within the approved indications.	No
Children (stem cell mobilization [patients < 16 years of age], post-transplant, HIV, and neonates)	The pharmacokinetics of filgrastim are similar in adults and children. Data from Neupogen clinical studies in pediatric patients indicate that the safety of filgrastim is similar in adults and children with CIN.	No
Geriatric patients	No overall differences in safety or effectiveness were observed between geriatric and younger subjects in Neupogen clinical trials in subjects receiving myelosuppressive therapy. Other clinical experience has not identified differences in the responses between elderly and younger patients.	No
Patients with renal impairment	Results of Neupogen clinical studies show no dose adjustment is required for patients with renal impairment.	No

Table 16. Missing Information: Conclusions Based on Populations Not Studied

Safety Concern	Comment	Missing Information?
Patients with hepatic impairment	The pharmacokinetics of filgrastim are not expected to be affected by hepatic impairment. In a small clinical trial, the pharmacokinetics of filgrastim did not appear to be affected by impaired hepatic function.	No
Patients with cardiac impairment	No evidence of an adverse effect of filgrastim on cardiac function has been observed in clinical studies or in post-marketing reports.	No

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

The estimated patient exposure to filgrastim as provided by IQVIA (formerly IMS Health Prescribing Insights Medical) database, is based on worldwide sales of 6,569,360 mg of filgrastim during the second quarter of 2011 through fourth quarter of 2022. The sales from 01 January 2023 to 31 March 2023 have been extrapolated by taking the average of sales of previous 4 quarters.

Previously an average dosage estimation of 25.2 mg was used for the purposes of calculating patient exposure. Following agency requests, within PSUR Assessment Reports, patient exposure estimations will be calculated using the WHO DDD. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The WHO DDD for parenteral Filgrastim is 0.35 mg/day.

The estimated total cumulative exposure to filgrastim, based on sales of finished product, is approximately 18,769,600 patient-days or 51,388 patient-years globally. Cumulative extrapolated sales for filgrastim are divided by WHO DDD 0.35 mg/day to obtain patient days, which are further divided by 365.25 to obtain patient years.

Cumulative estimated exposure by indication, gender, age group, dose, formulation, and region based on data provided by IQVIA Health Prescribing Insights Medical for the period second quarter of 2011 through fourth quarter of 2022 and extrapolated through 31 March 2023, are summarised in Table 17.

SV.1.2. Exposure

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

Nivestim does not have characteristics that would make it attractive for use for illegal purposes. There have been no cases of abuse or drug dependence with Nivestim.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Pursuant to the receipt of the Neupogen RMP v 6.3 dated 09 June 2022 from MEB (Netherlands), the MAH reviewed the "Summary of significant changes in this RMP" and noted that in Part II SVII the non-important identified risk of glomerulonephritis was upgraded and reclassified to an important identified risk in the reference drug RMP and the non-important identified risk of myelodysplastic syndrome/acute myeloid leukemia in breast and lung cancer patients receiving chemotherapy and/or radiotherapy was upgraded and reclassified to an important potential risk in the reference drug RMP.

An evaluation of these two risks for Nivestim included a review of pharmacovigilance activities, risk minimization measures, and the safety data to determine if each risk is fully characterised, well managed, and if the safety data received by the MAH since the DLP of the September 2021 PSUR provided new significant safety information for a known association that impacts the risk benefit balance of Nivestim.

In order to evaluate the safety data, the MAH compared the reporting frequency and seriousness of the adverse events received during the reporting period of the 2021 PSUR with the reporting frequency and seriousness of the adverse events received from the DLP of the 2021 PSUR through 31 March 2023. The search strategy for each risk was consistent with the search strategy used for each risk in the Neupogen RMP v 6.3 dated 09 June 2022.

<u>Glomerulonephritis</u>

In the Amgen Neupogen RMP v 6.3 dated 09 June 2022, glomerulonephritis, previously classified as a non-important identified risk, was reclassified as an important identified risk. The reference drug RMP notes that, "glomerulonephritis is reclassified as important because clinical action (urinalysis monitoring) is recommended to minimize the risk in Section 4.4 (Special Warnings and Precautions for Use) of the SmPC. The impact on the benefit-risk profile is anticipated to be low since glomerulonephritis generally resolves after dose reduction or withdrawal of filgrastim. Per the RMP, this risk will be monitored through routine pharmacovigilance and there are no non-routine risk minimization measures required for this risk."

The MAH proposes to not reclassify the risk of glomerulonephritis from a non-important identified risk to an important identified risk in the list of safety concerns of the Nivestim

RMP for the reasons that there are no ongoing or planned additional pharmacovigilance activities and no ongoing additional risk minimization measures needed to manage the risk as there is no expectation that additional pharmacovigilance activities would further characterise the risk and the risk is effectively managed through routine risk minimization measures, respectively. At this time, routine risk minimization measures recommending specific clinical measures (ie, urinalysis monitoring) to address the risk of glomerulonephritis are described in Sections 4.4 and 4.8 of the Nivestim SmPC and Sections 2 and 4 of the Nivestim Package Leaflet. Filgrastim has been marketed in the EU since 15 March 1991. These specific clinical measures (ie, urinalysis monitoring) are thought to be fully integrated into standard clinical practice and adhered to by prescribers. There is currently insufficient evidence presented in the innovator Neupogen RMP v6.3 - 9 Jun 2022 that the risk of glomerulonephritis is not fully characterised or appropriately managed.

Upon review of the PM safety data, the reporting frequency and seriousness of events of glomerulonephritis received since 2021 PSUR did not change the risk-benefit balance of Nivestim. There were 4 AEs (4 cases) received by the MAH through 15 September 2021 where the AE was coded to a PT in the MedDRA HLGT Nephropathies. This represents <0.1% of the total dataset (N=5116). All the events were serious. PTs included Renal tubular disorder (2), Glomerulonephritis (1), and Glomerulonephritis rapidly progressive (1). In comparison, there were 2 AEs received by the MAH during the reporting period 16 September 2021 through 31 March 2023. This represents 0.17% of the interval dataset (N= 1153). PTs included Glomerulonephritis proliferative (1) and Glomerulonephritis rapidly progressive (1). Both AEs were serious and reported in the same case as they occurred concurrently in the same patient.

In the one case received from medical literature, the authors report the clinical and pathologic findings of G-CSF induced exacerbation and crescentic transformation of pre-existing proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) with successful treatment and SCT. In this case, a 48-year-old male patient with recent diagnosis of monoclonal gammopathy of renal significance (MGRS) presenting as monoclonal PGNMID and monoclonal IgG Kappa with C3 deposits on biopsy, who had received bortezomib, cyclophosphamide and dexamethasone for an unspecified indication, was scheduled for an autologous stem cell transplantation. After receiving a G-CSF during stem cell mobilization, the patient was admitted to the hospital after an “acute” increase in creatinine from 2.87 mg/dl to 6.6 mg/dl with hematuria and proteinuria. A repeat kidney biopsy was significant for crescentic membranoproliferative (62% crescents) glomerulonephritis with monoclonal IgG/Kappa deposits. The patient received 5 sessions of plasmapheresis, one dose of renally adjusted IV Cytoxan, pulse steroids with a subsequent taper. After a month, the patient was able to receive the autologous SCT. His creatinine at pre-SCT baseline was 1.6 mg/dl. His kidney function continued to improve and after 16 months post-SCT his creatinine was 1.4 mg/dl. The authors noted that G-CSF enhances neutrophil activation in large counts and induces its endothelial activation. In the presence of pre-existing renal pathology, MGRS and MPGN with IgG kappa and C3 deposits in this case, the localized immunoglobin and complement deposits in the glomeruli can attract activated neutrophils leading to its infiltration and degranulation in the glomerular microenvironment and resulting in rupture of glomeruli basement membrane and formation of crescent.

Therefore, G-CSF induced kidney injury should be suspected due to its potential risk for exacerbating pre-existing glomerulonephritis.

Based on the information in this case, a possible contributory role of filgrastim in the reported serious events cannot be ruled out given the known safety profile of the drug and the implied temporal association. Of note, as specified in Section 4.4 of the SmPC, the events in this case were resolving after withdrawal of filgrastim as the patient's kidney function continued to improve after receiving filgrastim for stem cell mobilization.

The MAH will continue to collect and evaluate adverse events of glomerulonephritis and their impact on the risk-benefit balance of Nivestim through routine PhV activities.

Myelodysplastic Syndrome/Acute Myeloid Leukemia in Breast and Lung Cancer Patients Receiving Chemotherapy and/or Radiotherapy.

In the Amgen Neupogen RMP v 6.3 dated 09 June 2022, the non-important identified risk of myelodysplastic syndrome/acute myeloid leukemia in breast and lung cancer patients receiving chemotherapy and/or radiotherapy was reclassified as an important potential risk and included in the list of safety concerns. The Amgen Neupogen RMP notes the results of pegfilgrastim post authorization safety study 20160176 showed a statistically significant increase in the adjusted risk of MDS/AML in the breast cancer population treated with G-CSF compared to those not treated with G-CSF. However, while the evidence for this association was considered robust for pegfilgrastim, it was not considered equally robust for filgrastim. Therefore, at the request of the competent authorities, myelodysplastic syndrome/acute myeloid leukemia in breast and lung cancer patients receiving chemotherapy and/or radiotherapy was reclassified as an important potential risk. This risk was added to Section 4.4 of the Neupogen SmPC and, per the RMP, will be monitored through routine pharmacovigilance. No non-routine risk minimization measures are required for this risk.

The MAH proposes to not reclassify the risk of myelodysplastic syndrome/acute myeloid leukemia in breast and lung cancer patients receiving chemotherapy and/or radiotherapy from a non-important identified risk to an important potential risk in the list of safety concerns of the Nivestim RMP for the reasons that the robust evidence for the association for pegfilgrastim is applicable to filgrastim as, “Pegfilgrastim and filgrastim have been shown to have identical modes of action” whereby they both have the ability to recruit fresh neutrophils from the bone marrow and delay apoptosis of mature neutrophils which makes it biologically plausible for both G-CSFs to increase the risk of myeloid disorders such as secondary MDS and AML.

Additionally, evidence of the association between the anti-apoptotic effects of filgrastim and the risk of myeloid disorders such as secondary MDS and AML is documented in the published medical literature.

Hershman et al (2007)[7], demonstrated that the elevated risk of AML or MDS associated with adjuvant chemotherapy may be further increased by the concurrent use of growth factors because when patients were stratified by year of diagnosis, the risk of AML or MDS was twice as high among patients treated with G-CSF as among those not treated with G-CSF

(HR = 2.24; 95% CI 1.22, 4.10). Hershman et al (2007)[7] remarked that, "Chemotherapy given for a specific cancer may induce otherwise lethal mutations in a myeloid stem cell or progenitor cell, but the anti-apoptotic effect of G-CSF or GM-CSF saves the mutant cell from destruction, thereby permitting it to develop into a myeloid cancer."

Calip et al (2015)[8], estimated MDS/AML risk associated with specific breast cancer treatments in patients exposed to chemotherapy, radiotherapy, and/or filgrastim or pegfilgrastim. Among anthracycline/cyclophosphamide (AC)-containing regimens and G CSF, MDS/AML risk was differentially associated with filgrastim (HR = 1.47, 95% CI 1.05–2.06), but not pegfilgrastim (HR = 1.10, 95% CI 0.73–1.66). In additional analyses of the AC-containing regimens with filgrastim treatment by dose (1-5 doses/6+ doses), the risk increased for both categories but only significantly for the 6+ filgrastim dose-category (1-5 doses: HR = 1.82, 95% CI 0.94-3.39; 6+ doses: HR = 2.70, 95% CI 1.33–5.28, p trend = 0.036). No increased risk was observed among any of the other chemotherapy regimens with G-CSF treatment or with filgrastim or pegfilgrastim individually. Calip et al (2015)[8], remarked that, "While G-CSF reduces the need for treatment delays or dose reductions, the anti-apoptotic effects of G-CSF could potentially spare some lineage specific mutant stem cells resulting from cytotoxic therapy and permit survival in subsets of mature myeloid cells with chromosomal alterations."

Jabagi et al (2021)[9], analyzed the risk of hematologic malignancies associated with the use of G-CSF (filgrastim, lenograstim, pegfilgrastim) with chemotherapy for breast cancer. They observed a nonsignificant increase in the risk of AML (aHR, 1.3; 95% CI, 1.0-1.7), of MDS (aHR, 1.3; 95% CI, 0.9-1.8), and of ALL/LL (aHR, 2.0; 95% Cl, 1.0-4.4) among patients treated by chemotherapy plus G-CSF compared to chemotherapy only. In analyses by dose, they observed a slight increase in the risk of AML and of MDS and a significant increase in the risk of ALL with increasing cycles of G-CSF. Jabagi et al (2021)[9] remarked that, "Chemotherapy is thought to induce mutations in a progenitor cell and an anti-apoptotic effect of G-CSF might save the mutant cell from destruction."

Danese et al (2022)[10] evaluated the risk for MDS or AML in patients with breast cancer (Stage I-III), lung cancer (Stage I-III) or prostate (Stage I-IV) cancer receiving chemotherapy concurrently with a G-CSF versus not with a G-CSF. The use of filgrastim was found to be associated with a HR of 1.01 (95% CI 1.00-1.03) per administration in breast cancer and a HR of 1.02 (95% CI 0.99-1.05) per administration in lung cancer for MDS/AML. The authors concluded that the use of G-CSF in patients diagnosed with breast and lung cancer is associated with an increased risk of MDS-AML. Danese et al (2022)[10] remarked that, "Because G-CSF induces proliferation of myeloid progenitor cells, which are especially sensitive to myelosuppressive systemic therapy drugs, it is biologically plausible for G-CSF to increase the risk of myeloid disorders such as secondary MDS and AML."

In addition, the MAH proposes to not reclassify the risk of myelodysplastic syndrome/acute myeloid leukemia in breast and lung cancer patients receiving chemotherapy and/or radiotherapy from a non-important identified risk to an important potential risk in the list of safety concerns of the Nivestim RMP for the reasons that there are no ongoing or planned additional pharmacovigilance activities and no ongoing non-routine risk minimization measures needed to manage the risk as there is no expectation that additional

pharmacovigilance activities would further characterise the risk and the risk is effectively managed through routine risk minimization measures, respectively. The risk is communicated to HCPs in Section 4.4 of the Nivestim SmPC where it warns that, “In the post-marketing observational study setting, myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) have been associated with the use of pegfilgrastim, an alternative G-CSF medicine, in conjunction with chemotherapy and/or radiotherapy in breast and lung cancer patients. A similar association between filgrastim and MDS/AML has not been observed. Nonetheless, patients with breast cancer and patients with lung cancer should be monitored for signs and symptoms of MDS/AML.” Additionally, the risk is managed through routine risk minimization measures as filgrastim is prescribed by a specialist who is required to provide close supervision of patients throughout treatment.

Upon review of the PM safety data, there were no relevant cases received during the reporting period of the 2021 PSUR or during the reporting period 16 September 2021 through 31 March 2023; therefore, a cumulative search was performed through 31 March 2023. Upon review of the cumulative data, 25 cases were received by Pfizer where a patient with breast or lung cancer experienced an adverse event coded to a PT in the HLGT (All Paths) Leukaemias after receiving filgrastim in conjunction with chemotherapy and/or radiotherapy. Of note, all 25 cases were received between February 1996 and May 2004, which is prior to 08 June 2010 when Pfizer’s biosimilar filgrastim drug received first regulatory approval. Eighteen (18) of the total 25 cases originated from a non-Pfizer study and 7 cases were spontaneously reported. Of the 18 cases that originated from a non-Pfizer study and the 7 cases spontaneously reported, 15 were reported from an Amgen study and 6 were spontaneously received from Amgen, respectively. In all 25 cases, the patient received a DNA topoisomerase inhibitor (e.g., doxorubicin, etoposide epirubicin, irinotecan) and an alkylating agent (e.g., cyclophosphamide; thiotepa, cisplatin) for either breast cancer (23) or lung cancer (2); and in 16 cases, the patient received radiotherapy in addition to their chemotherapy. Finally, 24 patients experienced AML (14) and MDS (10) while one patient experienced AML followed by MDS after receiving filgrastim in conjunction with chemotherapy and/or radiotherapy. In many of the cases, Amgen added a case comment that, “Cases of this type have been attributed in the literature to an interaction between doxorubicin (DNA topoisomerase inhibitor) and cyclophosphamide (alkylating agent).” Therefore, in many cases, the AML or MDS were assessed as related to the DNA topoisomerase inhibitor and alkylating agent. However, in some cases, AML or MDS were also assessed as related to filgrastim. In those cases, the reporter noted, for example, that the event could be a result of “the patient's intensive previous treatment with chemotherapy and G-CSF”; “probably related to irinotecan with filgrastim” or because “an association between MDS and filgrastim has been described in several literature reports.”

The MAH will continue to collect and evaluate adverse events of MDS and AML in breast and lung cancer patients receiving chemotherapy and/or radiotherapy and their impact on the risk-benefit balance of Nivestim through routine PhV activities.

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

Not applicable.

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

The Non-Interventional (NI) Post-Authorisation Safety Study (PASS) C1121008 (ZOB-NIV-1513) is an additional pharmacovigilance activity in Part III of the currently CHMP endorsed Nivestim Oct 2022 RMP v 11.0. It was undertaken to further characterize the safety concern cytogenetic abnormalities and development of secondary haematologic malignancies. Pursuant to the completion of this post-authorisation safety study where healthy donors were exposed to Nivestim for haematopoietic stem cell mobilisation, the MAH performed an evaluation of the clinical safety data to assess "the long-term effects of Nivestim G-CSF in healthy donors undergoing PBSC mobilisation in terms of the emergence of myelodysplasia and other haematological malignancies."

The evaluation of this safety concern for Nivestim included a review of pharmacovigilance activities, risk minimization measures, and the clinical and post-marketing safety data to determine if the risk is fully characterised, well managed, and if the safety data provided new significant safety information for a known association that impacts the risk benefit balance of Nivestim. In order to evaluate the safety data, the MAH compared the reporting frequency and seriousness of the adverse events received during the reporting period of the 2021 PSUR with the reporting frequency and seriousness of the adverse events received from the DLP of the 2021 PSUR through 31 March 2023. The post-marketing search strategy for the safety concern was consistent with the search strategy used in the Nivestim 2022 RMP and September 2021 PSUR.

Important Identified Risks

There are no important identified risks for this product.

Important Potential Risks

In accordance with GVP Module V (Rev. 2) and after an evaluation of the safety concern, the MAH proposes to remove the safety concern cytogenetic abnormalities and development of secondary haematologic malignancies previously classified as an 'important potential risk.'

The MAH proposes to remove the risk as it is not considered important for inclusion in the list of safety concerns of the Nivestim RMP for the reasons that with the completion of the category 3 NI PASS C1121008 (ZOB-NIV-1513) designed to evaluate the safety of using Nivestim to mobilise stem cells in HDs due to theoretic concerns raised about filgrastim contributing to an increased risk of myeloid leukaemia or myelodysplasia in HDs, there are no ongoing or planned additional PhV activities as there is no expectation that additional PhV activities would further characterise the risk. In addition, there are no ongoing additional RMMs needed to manage the risk. At this time, the risk is managed through routine RMMs as filgrastim is prescribed to healthy donor undergoing a filgrastim-mobilized peripheral

blood stem cell collection by a specialist who is required to provide close supervision throughout treatment.

Upon review of the clinical safety data from the NI PASS C1121008 (ZOB-NIV-1513) using the final safety cut-off date 02 Mar 2023, no new malignancies were reported during the 5-year follow-up study. The safety results were consistent with the known safety profiles of the biosimilar Nivestim and the reference product Neupogen. Additionally, in the innovator Amgen Study 20130209, with the primary objective to describe the long-term incidence of malignant myeloid haematologic disorders in HDs who received and in HDs who did not receive filgrastim, the incidence and incidence rate ratio of malignant disorders in filgrastim-mobilized PBSC donors were not significantly different than in unstimulated BM donors. As a result, the innovator concluded that the current benefit/risk profile continues to support the use of filgrastim in the approved indications and the risk of transient cytogenetic abnormalities in normal donors following G-CSF use was removed from the Special warnings and precautions for use of the reference product Amgen Neupogen SmPC.

Upon review of the cumulative PM data through 31 March 2021, there have been no cases of a cytogenetic abnormalities and hematologic malignancies in Nivestim-mobilized PBSC donors.

The MAH will continue to collect and evaluate adverse events of cytogenetic abnormalities and hematologic malignancies in filgrastim-mobilized PBSC donors and their impact on the risk-benefit balance of Nivestim through routine PhV activities.

Missing Information

There is no missing information for this product.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

As previously stated, the important potential risk cytogenetic abnormalities and development of secondary haematologic malignancies does not meet the criteria for inclusion in the updated RMP when reviewed against the GVP Module V (rev 2) and the Guidance on the format of the RMP in the EU – in integrated format (Rev. 2.0.1 accompanying GVP Module V Rev. 2).

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

There are no important identified risks and important potential risks associated with the use of filgrastim.

SVII.3.2. Presentation of the Missing Information

There is no missing information associated with the use of filgrastim.

Module SVIII. Summary of the Safety Concerns

A summary of the important identified and potential risks and missing information is provided in Table 18. Strikethrough text indicates the safety concerns that the MAH

proposes to remove The MAH proposes to remove the important potential risk of Cytogenetic-abnormalities and development of secondary haematologic malignancies with this update. Therefore, there will be no important identified or potential risks, and no missing information for filgrastim. Strikethrough text indicates the safety concerns that the MAH proposes to remove.

Table 18. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None ~~Cytogenetic abnormalities and development of secondary haematologic malignancies~~
Missing information	None

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

  Not applicable.

- **Other forms of routine pharmacovigilance activities for safety concerns:**

  Not applicable.

General information for routine pharmacovigilance activities:

Nivestim will be administered under the supervision of a physician experienced in Oncology and/or Haematology. Additionally, the need to document the trade name and batch number is reinforced in the SmPC, which contains recommendations for health professionals to record the brand name and batch/lot number to help ensure traceability. These mechanisms will aid in the appropriate identification of the product at the time of AE reporting.

With regards to methods of distinguishing adverse event reports for the biosimilar from those of other licensed products (including the reference product), the Sponsor has established policies and procedures to trigger follow-up on adverse event reports where information on trade name and batch/lot numbers are not reported for biologics and biosimilars. Search criteria within the Sponsor global safety database enable adverse events reports to be distinguished by trade and generic name as well as by batch and lot numbers.

III.2. Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures in place.

The NIS PASS NEST ZOB-NIV-1513 (C1121008) was designed to evaluate the safety of using Nivestim to mobilise stem cells in HDs due to theoretic concerns raised about filgrastim contributing to an increased risk of myeloid leukaemia or myelodysplasia in HDs. The last participant last visit (LPLV) occurred on 02 March 2023.Upon review of the clinical safety data from the NI PASS C1121008 using the final safety cut-off date 02 Mar 2023, no new malignancies were reported during the 5-year study. The safety results were consistent with the known safety profiles of the biosimilar Nivestim and the reference product Neupogen. Therefore, due to the completion of the study, the MAH proposes to move the NIS PASS NEST ZOB-NIV-1513 (C1121008)to a completed additional pharmacovigilance. Please see the completed NIS PASS NEST ZOB-NIV-1513 (C1121008)information in Annex 2.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

Table 19. On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
None				

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

There are no planned post-authorisation efficacy studies that are conditions of the MA or that are a specific obligation at this time.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

The safety information in the proposed product information is aligned to the reference medicinal product. There are no important identified risks or missing information for filgrastim.

V.1. Routine Risk Minimisation Measures

The MAH has proposed to remove the important potential risk Cytogenetic abnormalities and development of secondary haematologic malignancies.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3. Summary of Risk Minimisation Measures

Not applicable**.**

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Nivestim

This is a summary of the RMP for Nivestim. There are no important identified risks, important potential risks, and uncertainties (missing information) associated with the use of filgrastim.

Nivestim's SmPC and its PL give essential information to healthcare professionals and patients on how Nivestim should be used.

This summary of the RMP for Nivestim 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 EPAR.

Important new concerns or changes to the current ones will be included in updates of Nivestim's RMP.

I. The Medicine and What It Is Used For

Nivestim is authorised for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) and for the reduction in the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia. The safety and efficacy of filgrastim are similar in adults and children receiving cytotoxic chemotherapy. Filgrastim is indicated for the mobilisation of PBPCs. In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an ANC of $\leq 0.5 \times 10^9$/L, and a history of severe or recurrent infections, long term administration of filgrastim is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events. Filgrastim is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0×10^9/L) in patients with advanced HIV infection, in order to reduce the risk of bacterial infections when other options to manage neutropenia are inappropriate.

It contains filgrastim as the active substance and it is given by IV or SC routes of administration.

Further information about the evaluation of Nivestim’s benefits can be found in Nivestim’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: link to the EPAR summary landing page.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Nivestim, together with measures to minimise such risks and the proposed studies for learning more about Nivestim'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 (eg 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 events 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 Nivestim 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 Nivestim. 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).

Table 20. List of important risks and missing information

Important identified risks	None
Important potential risks	None ~~Cytogenetic abnormalities and development of secondary haematologic malignancies~~
Missing information	None

II.B Summary of Important Risks

Not Applicable

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 Nivestim.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no other studies in Post-Authorisation Development Plan.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

REFERENCES

1 Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer*. 2011;47:8-32.

2 Stute N, Satana VM, Rodman JH, Schell MJ, Ihle JN, Evans WE. Pharmacokinetics of Subcutaneous Recombinant Human Granulocyte Colony-Stimulating Factor in Children. *Blood*. 1992;79:2849-2854.

3 Sturgill MG, Huhn RD, Drachtman RA, Ettinger AG, Ettinger LJ. Pharmacokinetics of intravenous recombinant human granulocyte colony-stimulating factor (rhG-CSF) in children receiving myelosuppressive cancer chemotherapy: clearance increases in relation to absolute neutrophil count with repeated dosing. *American Journal of Hematology*. 1997;54:124-130.

4 Kearns CM, Wang WC, Sttue N, Ihle JN, Evans WE. Disposition of recombinant human granulocyte colony-stimulating factor in children with severe chronic neutropenia. *J Pediatr*. 1993;123:471-479.

5 Shishido K, Nikura K, Akizawa T, Koshikawa S. The effects and pharmacokinetics of rhG-CSF on the treatment of neutropenia in patients with renal failure. *Nippon Jinzo Gakkai Shi*. 1991;33:973-981.

6 Petros WP, Rabinowitz J, Stuart A, Peters WP. Comparative pharmacokinetics of granulocyte colony-stimulating factor (rHuG-CSF) and granulocyte-macrophage colonystimulating factor (rHuGM-CSF) in patients receiving high-dose chemotherapy and autologous bone marrow support [abstract]. *Proc Am Soc Clin Oncol.* 1991;10:97. Abstract 256.

7 Hershman D, Neugut AI, Jacobson JS, et al. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. *J Natl Cancer Inst.* 2007;99(3):196-205.

8 Calip GS, Malmgren JA, Lee WJ, et al. Myelodysplastic syndrome and acute myeloid leukemia following adjuvant chemotherapy with and without granulocyte colony-stimulating factors for breast cancer. *Breast Cancer Res Treat.* 2015;154(1):133-43.

9 Jabagi MJ, Vey N, Goncalves A, et al. Risk of secondary hematologic malignancies associated with breast cancer chemotherapy and G-CSF support: A nationwide population-based cohort. *Int J Cancer.* 2021;148(2):375-84.

[10] Danese MD, Schenfeld J, Shaw J, et al. Association Between Granulocyte Colony-Stimulating Factor (G-CSF) Use and Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) Among Elderly Patients with Breast, Lung, or Prostate Cancer. *Adv Ther*. 2022;39(6):2778-95.

ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Follow-up forms: Not applicable.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.