1.8 INFORMATION RELATING TO PHARMACOVIGILANCE

1.8.2 RISK-MANAGEMENT PLAN

According to Article 8 (ia) of Directive 2001/83/EC, the risk management system which CuraTeQ Biologics s.r.o intends to implement post marketing authorisation is described in the risk management plan (RMP). RMP is enclosed herewith.

ZEFYLTI

RISK MANAGEMENT PLAN (RMP)

EU Risk Management Plan for ZEFYLTI

RMP version to be assessed as part of this application:

RMP Version number	0.1
Data lock point for this RMP	30-Aug-2023
Date of final sign off	04-Oct-2023
Rationale for submitting an updated RMP	Marketing Authorization Application
Summary of significant changes in this RMP	NA

Others RMP versions under evaluation:

RMP Version Number	NA
Submitted on	NA
Procedure number	NA

Details of the currently approved RMP:

Version Number	NA
Approved with procedure	NA
Date of approval (opinion date)	NA

QPPV Name	Dr. Martina Liskova
QPPV Signature with date	[redacted]
Contact person for this RMP	[redacted]
E-mail address or telephone number of contact person	[redacted]

List of abbreviations

ATC: Anatomical Therapeutic Chemical

G-CSF: Granulocyte Colony-Stimulating Factor

ICSR: Individual Case Safety Report

IV: Intravenous

ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IMP: Investigational Medicinal Product

MAH: Marketing Authorization Holder

PIL: Product Information Leaflet

PSUR: Periodic Safety Update Report

QPPV: Qualified Person for Pharmacovigilance

RMP: Risk Management Plan

SC: Subcutaneous

Table of Contents

Part I: Product(s) Overview

Table 1 Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Filgrastim
Pharmacotherapeutic group(s) **(ATC Code)**	Immunostimulants, colony stimulating factors (L03AA02)
Marketing Authorisation Holder	CuraTeQ Biologics s.r.o. Třtinová 260/1, Prague, 19600, Czech Republic
Medicinal products to which this RMP refers	01
Invented name(s).	Zefylti 30 MU/0.5 ml solution for injection/infusion in a pre-filled syringe Zefylti 48 MU/0.5 ml solution for injection/infusion in a pre-filled syringe
Marketing authorisation procedure	Centralised Procedure (H0006400)
Brief description of the product Chemical class	Filgrastim is a man-made protein that is similar to the naturally occurring protein, granulocyte-colony stimulating factor (G-CSF). Its chemical formula is $C_{845}H_{1343}N_{223}O_{243}S_9$ with a Molecular weight of 18.800 daltons.
Summary of mode of action:	Endogenous GCSF is a lineage-specific colony-stimulating factor with selectivity for the neutrophil lineage. It is produced by monocytes, fibroblasts and endothelial cells. Filgrastim (rGCSF) exerts its therapeutic effects by • Regulating the production of neutrophils within the bone marrow • Affects neutrophil progenitor proliferation, differentiation and selected end-cell functions (including enhanced phagocytic ability, priming of cellular metabolism

	associated with respiratory burst, antibody-dependent phagocytosis and the increased expression of some cell surface antigens).
Important information about its composition	Origin of active substance: *E. coli* (harbouring the transgene encoding rGCSF are grown in bioreactors, in growth medium and using culture conditions optimized for product yield and quality).
Hyperlink to the Product Information	Zefylti 30 MU/0.5 ml and 48 MU/0.5 ml solution for injection/infusion in a pre-filled syringe **(SmPC, PIL and Labelling)**
Indication(s) in the EEA Current	Zefylti 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 Zefylti are similar in adults and children receiving cytotoxic chemotherapy. Zefylti is indicated for the mobilisation of peripheral blood progenitor cells (PBPCs). In patients, children or adults, with severe congenital, cyclic, or idiopathic neutropenia with an ANC of ≤ 0.5 x 109 /L, and a history of severe or recurrent infections, long term administration of Zefylti is indicated to increase neutrophil counts and to reduce the incidence and duration of infection-related events. Zefylti is indicated for the treatment of persistent neutropenia (ANC less than or equal to 1.0 x 109 /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

Zefylti therapy should only be given in collaboration with an oncology centre which has experience in granulocyte-colony stimulating factors (G-CSFs) 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.

The syringe bears graduation marks (major graduations at 0.1 ml and minor graduations at 0.025 ml up to 1.0 ml) which are necessary to accurately measure doses of Zefylti equal to or less than 12MU, to meet to individual dosing requirements in paediatric patients.

Established cytotoxic chemotherapy

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/m2 /day (4.0 to 8.4 µg/kg/day) was used

In patients treated with myeloablative therapy followed by bone marrow transplantation

The recommended starting dose of filgrastim is 1.0 MU (10 µg)/kg/day. The first dose of Zefylti 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	Zefylti Dose Adjustment
> 1.0 x 109 /l for 3 consecutive days	Reduce to 0.5 MU (5 µg)/kg/day

Then, if ANC remains > 1.0 x 109 /l for 3 more consecutive days	Discontinue filgrastim
If the ANC decreases to < 1.0 x 109 /l during the treatment period the dose of Zefylti should be re-escalated according to the above steps	
ANC = absolute neutrophil count	

For the mobilisation of PBPC's in patients undergoing myelosuppressive or myeloablative therapy

followed by autologous PBPC transplantation

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 (5µg)/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 109 /L to > 5.0 x 109 /L. For patients who have not had extensive chemotherapy, one leukapheresis is often sufficient. In other circumstances, additional leukapheresis are recommended.

For the mobilisation of PBPCs in normal donors prior to allogeneic PBPC transplantation

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 106 CD34+ cells/kg recipient bodyweight. In patients with severe chronic neutropenia (SCN) 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. In patients with HIV infection 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 109 /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 109 /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 109 /L, with the median dose frequency being 3 days per week. Long term administration may be required to maintain the ANC > 2.0 x 109 /l. Patients with renal impairment

	Studies of filgrastim in patients with severe impairment of renal or hepatic function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances. Paediatric use in the SCN and cancer settings Sixty-five percent of the patients studied in the SCN trial program were under 18 years of age. The efficacy of treatment was clear for this age group, which included most patients with congenital neutropenia. There were no differences in the safety profiles for paediatric patients treated for SCN.
Pharmaceutical form(s) and strengths Current	Zefylti 30 MU/0.5 ml solution for injection or infusion in pre-filled syringe Zefylti 48 MU/0.5 ml solution for injection or infusion in pre-filled syringe
Is/will the product be subject to additional monitoring?	No

Part II: Safety specification

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

Not applicable

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

Key safety findings from non-clinical studies and relevance to human usage:

In view of the EMA draft Guideline EMEA/CHMP/BMWP/31329/2005 Rev 1, no animal studies have been performed with Zefylti and the results of Neupogen® are described in this section.

Toxicity

Single and repeat dose toxicity: A full set of conventional toxicity tests were performed for filgrastim. Single and repeat dose toxicity tests were conducted in monkeys, dogs, hamsters, rats and monkeys.

Key issues identified from acute or Repeat-dose toxicity studies

Single-dose administration of rGCSF by oral, intravenous (IV), subcutaneous (SC) or intraperitoneal (IP) route resulted in no significant toxicity in mice, rats or hamsters at doses up to 115 µg/kg/animal (862.5 µg/kg based on group mean pre-study body weights). An increase in leukocyte counts was observed in monkeys on day 7 and returned to the control values by day 14.

Consequently, the single-dose LD50 of r-metHuGCSF in monkeys is in excess of 3,450 µg/kg, which is at least 50- to 600-fold greater than the highest anticipated human clinical dose.

In repeat-dose studies in rats, hamsters, dogs, and monkeys, the following effects were observed:

- A dose-dependent increase in granulopoiesis
- An increase in total white blood cell counts (WBC)
- An increase in the proportion of segmented neutrophils in the circulation and
- An increase in myeloid to the erythroid ratio in the bone marrow

In two studies, 14-day monkey study and 13-week rat study, reduction in platelet counts were observed in two high dose groups. In all species, histopathologic examination of liver and spleen revealed evidence of ongoing extramedullary granulopoiesis. Dose-related increase in spleen weights was noted in all species. However, normal levels were achieved after the discontinuation of filgrastim treatment

Reproductive /developmental toxicity

Filgrastim had no observed effect on the fertility of male or female rats at doses up to 500 mcg/kg. The effects of filgrastim on prenatal development have been studied in rats and rabbits. No

malformations were observed in either species. Filgrastim has been shown to have adverse effects in pregnant rabbits at doses, 2 to 10 times higher than the human doses.

Offspring of rats administered with filgrastim during peri-natal and lactation periods depicts a delay in external differentiation, growth retardation (≥ 20 mcg/kg/day) and reduced survival rates (100 mcg/kg/day).

Results from the reproductive and developmental toxicity studies are depicted in the table below:

Table 2: Reproductive and Developmental Toxicity Studies of Filgrastim in Animals

Animal Model	Dosage (mcg/kg/day)	Adverse effct in animals
Pregnant rabbits	20	• Maternal toxicity • Reduction in embryo-fetal survival
	80	• Increased abortions
Pregnant rats	Up to 575	• No maternal or fetal anomalies

The above results in pregnant rabbits show signs of maternal toxicity, reduction in embryo-fetal survival (at 20 and 80 mcg/kg/day) and increased abortions (at 80 mcg/kg/day) were observed. In pregnant rats, no maternal or fetal effects were observed at doses up to 575 mcg/kg/day, which is approximately 58 times higher than the human dose of 10 mcg/kg/day.

Genotoxicity

No experimental evaluation of the genotoxic potential has been conducted. It has to be noted that filgrastim failed to induce bacterial gene mutations in either the presence or absence of a drug-metabolizing enzyme system.

Carcinogenicity

No experimental evaluation of the carcinogenic potential has been conducted.

Safety pharmacology

Specific tests on acute effects on vital organ systems functions were not performed.

Drug Interactions

No studies on drug interaction were performed.

Other toxicity – related information or data

No other toxicity studies were performed.

Part II: Module SIII - Clinical trial exposure

A Pivotal Phase I study has been completed for this product. The study details are as follow.

Comparison of BP13 (filgrastim) with EU-approved Neupogen® in Healthy Male Adult Subjects (Protocol Number: BP13-101).

Study Phase: Phase I

Title:

A Double-Blind, Randomized, Parallel, Controlled Study to Compare Pharmacokinetics and Pharmacodynamics of BP13 (Filgrastim) with EU-approved Neupogen® in Healthy Male Adult Subjects.

Objectives:

Primary

- To compare the PK and PD of BP13 (filgrastim) with EU-approved Neupogen®

Secondary

- To compare the PK of BP13 (filgrastim) with EU-approved Neupogen®
- To compare the PD of BP13 (filgrastim) with EU-approved Neupogen®
- To compare CD34+ cell response between BP13 and EU-approved Neupogen®
- To explore the potential immunogenicity of BP13 and EU-approved Neupogen®
- To assess and compare the safety and tolerability of BP13 with EU-approved Neupogen®

Study Design:

This was a single-center, double-blind, randomized, parallel, controlled study to compare PK and PD of the test medicinal product BP13 with reference medicinal product (EU-approved Neupogen®) in healthy male subjects.

A first group of 6 sentinel subjects (3 subjects receiving the test product BP13; and 3 subjects receiving EU-approved Neupogen®) were dosed first to establish the safety profile (example: AEs, TEAEs, SAEs, onset of serious allergic reactions, including anaphylaxis) prior to dosing the rest of the study population. Dosing of the remaining subjects was commenced after a minimum of 24 hours after dosing the sentinel subjects.

A total of 144 subjects was randomized in a 1:1 ratio to one of the treatment arms and received either BP13 (N=72) or Neupogen® (N=72). Subject received 5 mcg/kg/day subcutaneous (SC) injection of either BP13 or Neupogen® from Day 1 to Day 5.

The test product or the reference product was administered subcutaneously via 1 graduated pre-filled syringe (PFS) on the subject's abdomen, rotating quadrants for each dose. The graduated PFS was used on intact, non-irritated skin.

The study was conducted at one site in Australia.

The study comprised of

- Screening period (Day -28 to Day -2): Approximately 28 days, up to 2 days before first dose of IMP administration.
- Inpatient period (Day -1 to Day 10): The subject was admitted to the study center on Day -1 and received IMP on Days 1 to 5. The subject continued to reside at the study center until completion of 120 hour PD sample collection on Day 10.
- Follow-up/return visits: The subject returned to the study center for 4 follow-up visits (Day 11, Day 12, Day 14 and Day 15).

The total study duration for each subject was approximately 15 days (excluding the 28-day screening period). If the subjects tested positive for anti-drug antibodies (ADA), he was followed every 3 months until 12 months or until he tested negative for ADA.

Immunogenicity Results:

To assess the immunogenicity potential of the biosimilar, a systematic Immunogenicity evaluation was performed by using multi-tiered approach as per EMA & FDA guidelines. This includes a screening assay for identification of anti-Filgrastim positive samples (screen positive), a confirmatory assay which contained an immunodepletion step to confirm the presence of anti-Filgrastim antibody (confirmed positive) and followed by functional assay for the assessment of the neutralizing capacity of the antibodies. All the assays used for immunogenicity assessment were sensitive and validated prior to its intended use.

During the study sample analysis, a total number of 855 study samples (belonging to both BP13 and Neupogen® treatment arms) were analysed for the determination of anti-Filgrastim antibodies in screening assay. In screening assays, total 103 samples out of 855 samples showed potential positive response for the presence of anti-Filgrastim antibodies. Among these 55 samples belonged to BP13 treatment arm and 48 samples belonged to Neupogen® treatment arm.

All the 103 potential positive samples belonging to both BP13 and Neupogen® arms (screen positive) were subsequently tested in the confirmatory assay, where all samples were found to be negative for the presence of anti-Filgrastim antibodies (confirmed negative). Since none of the samples turned to be confirmed positive for the presence of anti-Filgrastim antibodies, there was no requirement for the assessment of neutralizing capacity of the antibodies.

This confirmed the result that all 855 samples belonging to both BP13 arm and Neupogen® arm analyzed are negative for the presence of anti-Filgrastim antibodies in immunogenicity assay. BP13 and Neupogen® were found to be similar to each other with respect to the ADA incidence / immunogenicity profiles.

Table SIII.1: Duration of exposure

Subject exposure to IMP (Zefylti or Neupogen®) is summarized in Table 3.

Table 3: Exposure of subjects to Investigational Products

Categories	BP13 (N=72)	Neupogen® (N=72)	Overall (N=144)
Total Dose received (mcg)			
n	72	72	144
Mean	1893.72	1905.00	1899.36
SD	259.497	213.951	237.051
Median	1878.75	1880.00	1878.75
Min, Max	798.0,2345.0	1365.0,2350.0	798.0,2350.0
Duration of Exposure (days)			
n	72	72	144
Mean	4.96	5.00	4.98
SD	0.354	0.000	0.250
Median	5.00	5.00	5.00
Min, Max	2.0, 5.0	5.0, 5.0	2.0, 5.0
Compliance (%)			
n	72	72	144
Mean	99.17	100.00	99.58
SD	7.071	0.000	5.000
Median	100.00	100.00	100.00
Min, Max	40.0, 100.0	100.0, 100.0	40.0, 100.0

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation.

Percentages are calculated based on the number of patients in the respective treatment group under Safety analysis set.

Duration of exposure is defined as the duration of time from the start of Zefylti or Neupogen® administration to the stop of administration.

The overall drug compliance is defined as percentage of total dose administered in mg during the study divided by the expected total dose in mg.

Table SIII.2: Age group and gender

Subject were 18 to 55 years of age inclusive and male.

Table SIII.3: Dose

Subjects received 5 mcg/kg/day subcutaneous (SC) injection of either BP13 or Neupogen® from Day 1 to Day 5. The test product or the reference product was administered subcutaneously via 1 mL graduated pre-filled syringe (PFS) on the subject's abdomen, rotating quadrants for each dose. The graduated PFS was used on intact, non-irritated skin.

Table SIII.4: Ethnic origin

Table 4: Ethnicity and race of enrolled subjects

Characteristics	**BP13 (N–72)**	**Neupogen® (N=72)**	**Overall (N=144)**
Race [n (%)]			
American Indian or Alaska Native	0	0	0
Asian	8 (11.1)	9 (12.5)	17 (11.8)
Black or African American	0	1 (1.4)	1 (0.7)
Native Hawaiian or Other Pacific Islander	1 (1.4)	0	1 (0.7)
White	59 (81.9)	57 (79.2)	116 (80.6)
Other	4 (5.6)	5 (6.9)	9 (6.3)
Ethnicity [n (%)]			
Hispanic or Latino	13 (18.1)	10 (13.9)	23 (16.0)
Not Hispanic or Latino	52 (72.2)	53 (73.6)	105 (72.9)
Not Stated	5 (6.9)	5 (6.9)	10 (6.9)
Unknown	2 (2.8)	4 (5.6)	6 (4.2)

Part II: Module SIV Populations not studied in clinical trials

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

Table 5: Exclusion criteria in clinical trials and discussion

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication
Current or previous cancer, diabetes, or any clinically significant cardiovascular, metabolic, renal, hepatic, gastrointestinal, hematologic, respiratory, dermatological, neurological, psychiatric, or any other disorder clinically relevant as judged by the Investigator. History of chronic cough, fever or acute respiratory illness within 4 weeks prior to the day of IMP administration. As judged by the Investigator, any past or concurrent medical conditions, which in the opinion of the Investigator would potentially increase subject's risk or affect the evaluation of study results. Any history of major surgery that in the opinion of the Investigator would interfere with the study or place the subject at risk. Hereditary fructose and/or sorbitol intolerance. Any history of previous exposure to pegfilgrastim or filgrastim, GCSF, or any analogue of these. Hypersensitivity to the constituents of Neupogen®, filgrastim (acetate, polysorbate 20, sodium and sorbitol) or hypersensitivity to	To assure a homogenous subject population without accompanying diseases interfering with the conduct and scientific evaluation of the results, and to minimize risk to the subjects' welfare.	According to the indications of Filgrastim, the population suitable for treatment in practice will include patients with a clinically significant laboratory abnormality or other clinical findings indicative of a clinically significant disease.

Escherichia. Coli derived proteins. Treatment with non-topical medications within 5 days prior to admission to the study center (Day -1), with the exception of hormonal contraceptives, multivitamins, vitamin C, food supplements and a limited amount of paracetamol (acetaminophen), which may be used throughout the study. Participation in a drug study involving hemopoietic growth factors, monoclonal antibodies, or immunoglobulins in the last three months prior to first administration of IMP or currently is on a follow-up visit for any other drug studies. Unable to follow protocol instructions in the opinion of the Investigator. Donation or loss of 470 mL or more of blood over a period of 90 days prior to first IMP administration. Positive screen for alcohol breath test and/or positive screen for drugs of abuse (opiates, methadone, methamphetamines, phencyclidine, tetrahydrocannabinol, cocaine, amphetamines [including ecstasy], cannabinoids, barbiturates, benzodiazepines, tricyclic		

antidepressants) at screening and admission (Day -1), unless a positive result is attributable to a documented use of a concomitant medication and is approved by the Investigator. (In case of a positive urine drug screen at screening or on Day -1, at the Investigator's discretion, the drug screen test may be repeated in the possible instance of a false positive due to i.e. poppy seed consumption. History of alcohol abuse or excessive intake of alcohol in the past 2 years as judged by the investigator. Positive screen on hepatitis B surface antigen (HbsAg), hepatitis B core antibody, anti-hepatitis C virus (HCV) antibodies, or anti-huma immunodeficiency virus (HIV) ½ antibodies at screening. Family history of acute myeloid leukemia or subjects with splenomegaly (spleen size > 13 cm in the craniocaudal dimension by ultrasound) at baseline, or with sickle cell disease.		

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions and adverse reactions with a long latency.

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

Table: 6: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Clinical data is inadequate on the use of filgrastim in pregnancy. However, there are cases in the literature where the transplacental passage of Filgrastim has been demonstrated. Few reports indicate trans placental passage of filgrastim in pregnant women by < 30 hours prior to preterm delivery (≤ 30 weeks gestation). Hence, filgrastim is not recommended in pregnancy. Reproductive toxicity studies in rabbits have shown maternal toxicity, reduction in embryo-fetal survival and increase in abortions when filgrastim was administered at doses 2 to 10 times the human dose. Studies in pregnant rats have shown no maternal or foetal anomalies.
Breastfeeding women	There is insufficient information on the excretion of filgrastim/metabolites in human breast 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 with relevant comorbidities: • Patients with hepatic impairment	Studies of Filgrastim in patients with severe impairment of hepatic function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances.

• Patients with renal impairment	Studies of Filgrastim in patients with severe impairment of renal function demonstrate that it exhibits a similar pharmacokinetic and pharmacodynamic profile to that seen in normal individuals. Dose adjustment is not required in these circumstances.
• Patients with cardiovascular impairment	Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) has been reported rarely in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. In most cases it resolved after withdrawal of GCSF.
• Immunocompromised patients	Not applicable
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable
Population with relevant different ethnic origin	Not applicable
Subpopulations carrying relevant genetic polymorphisms	Pharmacogenomics or genetics are not evaluated in this study
Other	Not applicable

Part II: Module SV Post-authorisation experience

Not applicable

Part II: Module SVI –additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Based on the nature of the product and its purpose of treatment, it is unlikely to have any potential for misuse.

Part II: 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

Not applicable

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

Not applicable

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

Information on Important identified risks

There are no important identified risks for filgrastim.

Information on Important potential risks

There are no important potential risks for filgrastim.

SVII.3.2. Presentation of the missing information

There is no missing information for filgrastim.

Part II: Module SVIII - Summary of the safety concerns

Table 28: SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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

III.1 Routine pharmacovigilance activities

Maintaining the Global Pharmacovigilance System according to EU regulations and the Company's procedures. Also collection, processing, assessment and reporting of Individual case safety report (ICSR), routine literature screening of EU journals for ICSRs and worldwide indexed journals, production of a Periodic Safety Update Report (PSUR) for all products that the MAH markets in EU and Signal detection to monitor, detect and evaluate any new safety concerns and Other requirements, as defined by local regulations.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:
None

Other forms of routine pharmacovigilance activities:
Traceability:
The MAH shall ensure product dispensed to a patient will have a specific lot number to facilitate product-level identification and have a unique brand name. These Product-specific identifiers shall be included in adverse drug reaction reports to facilitate the traceability of an adverse reaction to a specific suspect drug product.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities are recommended.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable

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

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Since no safety concerns are identified in Module SVIII, no routine minimisation measures are applicable for Part V.

V.2. Additional Risk Minimisation Measures

Not applicable

V.3. Summary of risk minimisation measures

Since no safety concerns are identified in Module SVIII, no summary of risk minimisation measures is applicable for Part V.

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Part VI: Summary of the risk management plan

Summary of risk management plan for Zefylti 30 MU/0.5 ml and 48 MU/0.5 ml, solution for injection or infusion in a pre-filled syringe (Filgrastim)

This is a summary of the risk management plan (RMP) Zefylti 30 MU/0.5 ml and 48 MU/0.5 ml, solution for injection or infusion in a pre-filled syringe (hereinafter referred to as Zefylti). The RMP details important risks of Zefylti, how these risks can be minimised, and how more information will be obtained about Zefylti's risks and uncertainties (missing information).

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

This summary of the RMP for Zefylti should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European

Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Zefylti's RMP.

I. The medicine and what it is used for

Zefylti works by increasing the production of white blood cells and it is indicated for:

- The reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy (with exception of chronic myeloid leukaemia and myelodysplastic syndrome).
- 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 • Mobilisation of peripheral blood progenitor cells (PBPCs)
- Increase of neutrophil counts and reduce the incidence and duration of infection-related events in patients with severe congenital, cyclic or idiopathic neutropenia and a history of severe or recurrent infections
- The treatment of persistent neutropenia in patients with advanced HIV infection

The active substance is filgrastim and it is given intravenously.

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

Important risks of Zefylti, together with measures to minimise such risks and the proposed studies for learning more about Zefylti'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 Product Monograph addressed to patients and healthcare professionals,
- Important advice on the medicine's packaging;

- The authorised pack size-the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about the adverse reactions is collected continuously and regularly analysed including ASR 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 Zefylti are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by the patient. 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 Zefylti. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

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

II.C Post-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 Zefylti.

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

There are no studies required for Zefylti as post-authorisation development plan.

Part VII: Annexes

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Part VII: Annexes

Annex 1 – EudraVigilance Interface

Not Applicable

Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Not applicable

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

Not applicable

Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable

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

Not Applicable

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 – Other supporting data (including referenced material)

Not applicable.

Annex 8 – Summary of changes to the risk management plan over time

Not applicable