EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 February 2015
EMA/187414/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ristempa

International non-proprietary name: pegfilgrastim

Procedure No. EMEA/H/C/003910/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Events
ANC	Absolute neutrophil counts
CHMP	Committee for Medicinal products for Human use
DSN	Duration of severe neutropenia
FN	Febrile Neutropenia
EC	European Commission
E.coli	Escherichia coli
EURD	EU reference dates
EMA	European Medicines Agency
EU	European Union
G-CSF	granulocyte- colony stimulating factor
NHL	Non-Hodgkin Lymphoma
PEG	polyethylene glycol
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SmPC	Summary of product characteristics

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Amgen Europe B.V. submitted on 5 September 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Ristempa, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 December 2013

The applicant applied for the following indication:

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

The legal basis for this application refers to:

Article 10(c) of Directive 2001/83/EC – relating to informed consent from a marketing authorisation holder for an authorised medicinal product.

The application submitted is composed of administrative information, quality, non-clinical and clinical data with a letter from a MAH Amgen Europe B.V. allowing the cross reference to relevant quality, non-clinical and/or clinical data.

This application is submitted as a multiple of Neulasta authorised on 22 August 2002 in accordance with Article 82.1 of Regulation (EC) No 726/2004.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Licensing status

Neulasta has been given a Marketing Authorisation in the EU on 22 August 2002.

1.2. Manufacturers

Manufacturers of the biological active substance

Amgen Inc
One Amgen Center Drive
Thousand Oaks
CA 91320
USA

Amgen Manufacturing Ltd.
PO Box 4060
State Road 31, Km 24.6
Juncos, PR 00777
Puerto Rico
USA

Manufacturers responsible for batch release

Amgen Europe B.V.
Minervum 7061
4817ZK BREDA
NETHERLANDS

Amgen Technology Ireland (ADL)
Pottery Road
Dun Laoghaire, Co Dublin
Ireland

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings

Co-Rapporteur: Johann Lodewijk Hillege

- The application was received by the EMA on 5 September 2014.
- The procedure started on 21 September 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 20 October 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 October 2014.
- PRAC RMP advice and assessment overview adopted by PRAC on 6 November 2014.
- During the meeting on 20 November 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 January 2015.
- PRAC RMP advice and assessment overview adopted by PRAC on 12 February 2015.
- Joint Rapporteur's assessment report on the MAH's responses circulated on 20 February 2015.
- During the meeting on 26 February 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing

Authorisation to Ristempa.

2. Scientific discussion

2.1. Introduction

This application has been submitted by Amgen Europe B.V. as an informed consent application in accordance with Article 10c of Directive 2001/83/EC as amended.

Ristempa is a solution for injection containing pegfilgrastim (ATC code; L03AA13; pharmacotherapeutic group: immunostimulants, colony stimulating factor). Pegfilgrastim is a covalent conjugate of recombinant human Granulocyte-Colony Stimulating Factor (r-met-HuG-CSF, filgrastim) with a single 20 kDa polyethylene glycol (PEG). Filgrastim is produced by recombinant-DNA technology in E. coli.

Pegfilgrastim and filgrastim belong to the class of haematopoietic growth factors (granulocyte-colony stimulating factor; G-CSF). Pegfilgrastim is a sustained duration form of filgrastim because of its decreased renal clearance. Pegfilgrastim and filgrastim have been shown to have identical modes of actions, causing a marked increase in peripheral blood neutrophil counts within 24 hours, with minor increases in monocytes and/or lymphocytes.

The proposed indication for Ristempa is:

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

Following the granting of a marketing authorisation for Neulasta, the authorisation holder (Amgen Europe B.V) has allowed use to be made of the pharmaceutical, preclinical and clinical documentation contained in the file on the medicinal product, with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

2.2. Quality aspects

Since this application is an informed consent of the Neulasta application, the quality data in support of the Ristempa application are identical to the up-to-date quality data of the Neulasta dossier, which has been assessed and approved (including all post-marketing procedures).

2.3. Non-clinical aspects

The applicant has made reference to module 4 of the Neulasta marketing authorisation application.

The primary pharmacodynamic studies provided adequate evidence that Neulasta has been shown to have the same granulopoietic properties as filgrastim in *in vitro* studies and *in vivo* in a variety of animal species, with the advantage of a prolonged duration of action after a single dose.

In single-dose toxicity studies, Neulasta was well-tolerated and caused the expected pharmacological effects as observed for filgrastim. In repeated-dose toxicity studies in two species, Neulasta produced a range of changes that reflected an exaggerated pharmacological response, or a reaction to the primary response, such as extramedullary haematopoiesis in the spleen and liver. All of the treatment-related

changes were reversible in both species. Immunogenicity was determined in pharmacodynamic and repeat toxicity studies. No genotoxicity or carcinogenicity studies have been undertaken which is acceptable given the biotechnological origin of the product and the reassuring clinical data on filgrastim. There were no adverse effects observed in offspring from pregnant rats given Neulasta subcutaneously, but in rabbits Neulasta has been shown to cause embryo/foetal toxicity (embryo loss) at higher doses. In rat studies, it was shown that Neulasta may cross the placenta. This information is adequately reported in the SmPC.

2.3.1. Ecotoxicity / environmental risk assessment

For the environmental risk assessment, proteins are exempt from the need for such an assessment in accordance with the CHMP Guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00), and therefore the filgrastim component of Ristempa is exempt on this basis. For the PEG component, the applicant notes that studies in animals have shown that PEGs of differing molecular sizes are excreted in bile and urine and then subject to aerobic microbial degradation. The applicant's environmental risk assessment for Ristempa is considered to be acceptable.

2.3.2. Discussion on non-clinical aspects

The dossier of Neulasta provided sufficient evidence that the pharmacological and toxicological profiles of pegfilgrastim and filgrastim are very similar.

No additional non-clinical studies have been provided as this application has been submitted under the legal basis Article 10(c) of Directive 2001/83/EC. For this reason, the proposed sections 4.6 and 5.3 of the SmPC are in agreement with the proposed and approved wording for Neulasta.

2.3.3. Conclusion on the non-clinical aspects

The CHMP considers the non-clinical data are acceptable to support the marketing authorisation.

2.4. Clinical aspects

The applicant makes reference to module 5 of the marketing authorisation application of Neulasta.

The application for Neulasta (pegfilgrastim) was based on the results of six clinical studies (2 pivotal phase III studies and 4 supportive phase II studies) and two studies in healthy volunteers. The individual studies were designed according to regulatory guidelines and the CPMP Scientific Advice.

Both pivotal studies were powered to demonstrate non-inferiority of single administration of Neulasta compared to daily filgrastim. The primary endpoint in these studies was a pharmacodynamic endpoint, namely Duration of Severe Neutropenia in cycle 1. The choice for DSN as primary endpoint was accepted by the CPMP in a scientific advice procedure. The analyses of the primary pharmacodynamics endpoint, supported by the analyses of the secondary pharmacodynamics endpoints (DSN in subsequent cycles, time to ANC recovery, and ANC-time profile) and clinical endpoints (cumulative incidence of FN, incidence of infections and use of anti-infectives) demonstrated the non-inferiority of Neulasta compared to filgrastim.

The conclusion of comparability between Neulasta and filgrastim was confirmed by the efficacy data of two relatively small, randomised, open-label phase II studies in patients receiving multiple cycles of chemotherapy for NHL.

2.4.1. Discussion on clinical efficacy

No additional clinical studies to evaluate the efficacy of Ristempa have been provided by the applicant. This is acceptable for submissions under the legal basis Article 10(c) of Directive 2001/83/EC.

2.4.2. Conclusions on the clinical efficacy

The CHMP considers that the clinical data are acceptable to support the marketing authorisation.

2.5. Clinical safety

The applicant makes reference to module 5 of the marketing authorisation application of Neulasta.

The safety population for the marketing authorisation application of Neulasta consisted of 796 patients treated for a malignant disease; 465 patients received Neulasta, 331 patients were treated with filgrastim. The mean number of SC injections of Neulasta was 3.8 (SD 1.0) versus 38.9 (SD 11.9) in the filgrastim group.

The safety profile of Neulasta is similar to that of filgrastim. The incidences of all AEs, serious AEs, related (serious) AEs, withdrawals due to AEs, and deaths were comparable between Neulasta and the filgrastim groups. The most frequently occurring AEs were associated with the primary disease and/or the administration of chemotherapy, their incidence was comparable between the treatment groups. The nature and frequency of AEs in the fixed dose Neulasta group was similar to those reported in the by-weight Neulasta dose groups and the filgrastim group.

Bone pain was the most frequently reported study drug-related AE in both treatment groups (overall incidence: Neulasta 26% and filgrastim 33%). Bone pain was of mild to moderate severity in the majority of patients, with a comparable severity between the Neulasta and the filgrastim patients. No increased incidence of (related) bone pain was observed in the 21 patients weighing ≤ 62 kg in the fixed dose pivotal study.

2.5.1. Discussion on clinical safety

No additional clinical studies to evaluate the safety of Ristempa have been provided by the applicant. This is acceptable for submissions under the legal basis Article 10(c) of Directive 2001/83/EC.

2.5.2. Conclusions on the clinical safety

The CHMP considers that the safety data are acceptable to support the marketing authorisation.

2.6. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.0 is acceptable. The PRAC endorsed the

PRAC Rapporteur assessment report, which is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Table 1: Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Severe splenomegaly/splenic rupture • Cutaneous vasculitis • Sweet's syndrome • Anaphylactic reaction • Capillary leak syndrome • Serious pulmonary adverse events (including Interstitial pneumonia and ARDS) • Sickle cell crisis in patients with sickle cell disease • Musculoskeletal pain-related symptoms • Leukocytosis • Thrombocytopenia
Important potential risks	• AML/MDS • Cytokine release syndrome • Medication errors including overdose • Drug interaction with lithium • Off-label use • Immunogenicity (incidence and clinical • implications of anti-G-CSF antibodies) • Extramedullary haematopoiesis
Missing information	• Risks in children <18 years of age • Risks during pregnancy and lactation

Pharmacovigilance plan

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 2: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Severe splenomegaly/splenic rupture	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 4.4, Special warnings and precautions for	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	use: - Uncommon but generally asymptomatic cases of splenomegaly and uncommon cases of splenic rupture, including some fatal cases, have been reported following administration of pegfilgrastim (see Section 4.8). Therefore, spleen size should be carefully monitored (eg, clinical examination, ultrasound). A diagnosis of splenic rupture should be considered in patients reporting left upper abdominal pain or shoulder tip pain. • Section 4.8, Undesirable effects, Summary of the safety profile: - Splenomegaly, generally asymptomatic, is uncommon. - Splenic rupture including some fatal cases is uncommonly reported following administration of pegfilgrastim (see Section 4.4). • Section 4.8, Undesirable effects, Tabulated summary of adverse reactions: - Splenomegaly and splenic rupture are listed as uncommon adverse reactions identified through postmarketing surveillance. <u>Text in PIL</u> • Section 2, What you need to know before you use Ristempa, Warnings and precautions: - Talk to your doctor, pharmacist, or nurse before using Ristempa if you get left upper abdominal pain or pain at the tip of your shoulder. This may be a sign of a problem with your spleen (splenomegaly). <u>Text in PIL (continued)</u> • Section 4, Possible side effects: - Increased spleen size is listed as an uncommon side effect (may affect up to 1 in 100 people). - Spleen rupture is listed as an uncommon side effect. Some cases of splenic rupture were fatal. It is important that you contact your doctor immediately if you experience pain in the upper left side of the abdomen or left shoulder pain since this may relate to a problem with your spleen.	
Cutaneous vasculitis	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u>	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Section 4.8, Undesirable effects, Tabulated summary of adverse reactions: - Cutaneous vasculitis is listed as an uncommon (≥ 1/1000 to < 1/100) adverse reaction identified through postmarketing surveillance. • Section 4.8, Undesirable effects, Description of selected adverse reactions: - Uncommon events of cutaneous vasculitis have been reported in patients treated with Ristempa. The mechanism of vasculitis in patients receiving Ristempa is unknown. <u>Text in PIL</u> • Section 4, Possible side effects: Cutaneous vasculitis (inflammation of the blood vessels in the skin) is listed as an uncommon side effect (may affect up to 1 in 100 people).	
Sweet's syndrome	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 4.8, Undesirable effects, Tabulated summary of adverse reactions: - Sweet's syndrome (acute febrile dermatosis) is listed as an uncommon (≥ 1/1000 to < 1/100) adverse reaction identified through postmarketing surveillance. • Section 4.8, Undesirable effects, Description of selected adverse reactions: - Uncommon cases of Sweet's syndrome have been reported, although in some cases underlying hematological malignancies may play a role. <u>Text in PIL</u> • Section 4, Possible side effects: - Sweet's syndrome (plum-colored, raised, painful lesions on the limbs and sometimes on the face and neck with fever) has occurred but other factors may play a role (uncommon side effect [may affect up to 1 in 100 people]).	None
Anaphylactic reaction	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 4.3, Contraindictions:	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Hypersensitivity to the active substance or to any of the excipients. <u>Text in SmPC (continued)</u> • Section 4.4, Special warnings and precautions for use: - Hypersensitivity, including anaphylactic reactions, occurring on initial or subsequent treatment have been reported in patients treated with Ristempa. Permanently discontinue Ristempa in patients with clinically significant hypersensitivity. Do not administer Ristempa to patients with a history of hypersensitivity to pegfilgrastim or filgrastim. If a serious allergic reaction occurs, appropriate therapy should be administered, with close patient follow-up over several days. • Section 4.8, Undesirable effects, Summary of the safety profile: - Hypersensitivity-type reactions, including skin rash, urticaria, angioedema, dyspnea, erythema, flushing, and hypotension occurred on initial or subsequent treatment with Ristempa (uncommon [≥ 1/1000 to < 1/100]). Serious allergic reactions, including anaphylaxis can occur in patients receiving Ristempa (uncommon) (see Section 4.4). • Section 4.8, Undesirable effects, Tabulated summary of adverse reactions: Hypersensitivity reactions and anaphylaxis are listed as uncommon adverse reactions. <u>Text in PIL</u> • Section 2, What you need to know before you use Ristempa, Warnings and precautions: - Do not use Ristempa if you are allergic to pegfilgrastim, filgrastim, *E coli*-derived proteins, or any of the other ingredients of this medicine. - Talk to your doctor, pharmacist, or nurse before using Ristempa if you experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), redness and flushing, skin rash and areas of the skin that itch. - Talk to your doctor, pharmacist, or nurse before using Ristempa if you have sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	the body, shortness of breath, wheezing, or trouble breathing these could be signs of a severe allergic reaction. • Section 4, Possible side effects: - Allergic-type reactions, including redness and flushing, skin rash, and raised areas of the skin that itch are listed as uncommon side effects (may affect up to 1 in 100 people). Serious allergic reactions, including anaphylaxis (weakness, drop in blood pressure, difficulty breathing, swelling of the face) are listed as uncommon side effects.	
Capillary Leak Syndrome	Text in PIL • Section 2, What you need to know before you use Ristempa, Warnings and precautions: - Talk to your doctor, pharmacist, or nurse before using Ristempa if you have any of the following or combination of the following side effects: swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These could be symptoms of condition called "Capillary leak syndrome" which causes blood to leak from the small blood vessels into your body. See Section 4. • Section 4, Possible side effects: - Please tell your doctor immediately if you have any of the following or combination of the following side effects: swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion. These could be symptoms of a rare (may affect up to 1 in 1000 people) condition called "Capillary leak syndrome" which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.	None
Serious pulmonary adverse events (including interstitial pneumonia and ARDS)	Medicinal product subject to restricted medical prescription. Text in SmPC • Section 4.4, Special warnings and precautions for use: - Uncommon (≥ 1/1000 to < 1/100) pulmonary adverse reactions, in particular interstitial	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	pneumonia, have been reported after G-CSF administration. Patients with a recent history of pulmonary infiltrates or pneumonia may be at higher risk (see Section 4.8). - The onset of pulmonary signs such as cough, fever, and dyspnea in association with radiological signs of pulmonary infiltrates, and deterioration in pulmonary function along with increased neutrophil count may be preliminary signs of Adult Respiratory Distress Syndrome. In such circumstances, Ristempa should be discontinued at the discretion of the physician and the appropriate treatment given (see Section 4.8). • Section 4.8, Undesirable effects, Summary of safety profile: - Uncommon pulmonary adverse reactions including interstitial pneumonia, pulmonary edema, pulmonary infiltrates, and pulmonary fibrosis have been reported. Uncommonly, cases have resulted in respiratory failure or Adult Respiratory Distress Syndrome, which may be fatal (see Section 4.4). • Section 4.8, Undesirable Effects, Tabulated summary of adverse reactions: - Adult Respiratory Distress Syndrome is listed as an uncommon adverse reaction identified through postmarketing surveillance. Pulmonary adverse reactions (interstitial pneumonia, pulmonary edema, pulmonary infiltrates, and pulmonary fibrosis) are listed as uncommon adverse reactions. <u>Text in PIL</u> • Section 2, What you need to know before you use Ristempa, Warnings and precautions: - Talk to your doctor, pharmacist, or nurse before using Ristempa if you experience a cough, fever, and difficulty breathing. This can be a sign of Acute Respiratory Distress Syndrome. - Talk to your doctor, pharmacist, or nurse before using Ristempa if you have recently had a serious lung infection (pneumonia), fluid in the lungs (pulmonary edema), inflammation of the lungs (interstitial lung disease), or an abnormal chest x-ray (lung infiltration). • Section 4, Possible side effects: Breathing problems are listed as an uncommon side effect (may affect up to 1 in 100 people). If you have a	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	cough, fever, and difficulty breathing please tell your doctor.	
Sickle cell crisis in patients with sickle cell disease	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 4.4, Special warnings and precautions for use: Sickle cell crises have been associated with the use of pegfilgrastim in patients with sickle cell trait or sickle cell disease (see Section 4.8). Therefore, physicians should exercise caution when prescribing pegfilgrastim in patients with sickle cell trait or sickle cell disease, should monitor appropriate clinical parameters and laboratory status, and be attentive to the possible association of this medicine with splenic enlargement and vaso-occlusive crisis. <u>Text in SmPC (continued)</u> • Section 4.8, Undesirable effects, Summary of the safety profile: - Isolated cases of sickle cell crises have been reported in patients with sickle cell trait or sickle cell disease (uncommon in sickle cell patients) (see Section 4.4). • Section 4.8, Undesirable Effects, Tabulated summary of adverse reactions: - Sickle cell crisis is listed as uncommon adverse reaction identified through postmarketing surveillance. <u>Text in PIL</u> • Section 2, What you need to know before you use Ristempa, Warnings and precautions: - Talk to your doctor, pharmacist, or nurse before using Ristempa if you have sickle cell anemia. Your doctor may monitor your condition more closely. • Section 4, Possible side effects: -Bone pain, and general aches and pains in the joints and muscles are listed as very common side effects (may affect more than 1 in 10 people). Your doctor will tell you what you can take to ease the bone pain.	None
Musculoskeletal pain-related symptoms	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u>	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	• Section 4.8, Undesirable effects, Summary of the safety profile: - The most frequently reported adverse reactions were bone pain (very common [≥ 1/10]) and musculoskeletal pain (very common). Bone pain was generally of mild to moderate severity, transient, and could be controlled in most patients with standard analgesics. • Section 4.8, Undesirable effects, Tabulated summary of adverse reactions: - Bone pain and musculoskeletal pain (myalgia, arthralgia, pain in extremity, back pain, musculoskeletal pain, neck pain) are listed as very common adverse reactions. <u>Text in PIL</u> • Section 4, Possible side effects: Bone pain, and general aches and pains in the joints and muscles are listed as very common side effects (may affect more than 1 in 10 people). Your doctor will tell you what you can take to ease the bone pain.	
Leukocytosis	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 4.4, Special warnings and precautions for use: - White blood cell counts of 100 x 10^9/L or greater have been observed in less than 1% of patients receiving Ristempa. No adverse events directly attributable to this degree of leukocytosis have been reported. Such elevation in white blood cells is transient, typically seen 24 to 48 hours after administration and is consistent with the pharmacodynamic effects of this medicine. Consistent with the clinical effects and the potential for leukocytosis, a WBC count should be performed at regular intervals during therapy. If leukocyte counts exceed 50 x 10^9/L after the expected nadir, this medicine should be discontinued immediately. • Section 4.8, Undesirable effects, Tabulated summary of adverse reactions: - Leukocytosis is listed as an uncommon (≥ 1/1000 to < 1/100) adverse reaction. • Section 4.8, Undesirable effects, Description of selected adverse reactions:	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	- Uncommon cases of leukocytosis (white blood count > 100 x 10^9/L) have been reported (see Section 4.4). Text in PIL • Section 2, What you need to know before you use Ristempa, Warnings and precautions: -Talk to your doctor, pharmacist, or nurse before using Ristempa if you are aware of any altered blood cell counts (eg, increase in white blood cells or anemia) or decreased blood platelet counts, which reduces the ability of your blood to clot (thrombocytopenia). Your doctor may want to monitor you more closely. Text in PIL (continued) • Section 4, Possible side effects: -Uncommon side effects (may affect up to 1 in 100 people): Some changes may occur in your blood, but these will be detected by routine blood tests. Your white blood cell count may become high for a short period of time.	
Thrombocytopenia	Medicinal product subject to restricted medical prescription. Text in SmPC • Section 4.4, Special warnings and precautions for use: - Treatment with Ristempa alone does not preclude thrombocytopenia and anemia because full dose myelosuppressive chemotherapy is maintained on the prescribed schedule. Regular monitoring of platelet count and hematocrit is recommended. Special care should be taken when administering single or combination chemotherapeutic agents which are known to cause severe thrombocytopenia. • Section 4.8, Undesirable effects, Tabulated summary of adverse reactions: - Thrombocytopenia is listed as a common (≥ 1/100 to < 1/10) adverse reaction. • Section 4.8, Undesirable effects, Description of selected adverse reactions: Common cases of thrombocytopenia have been reported. Text in PIL • Section 2, What you need to know before you use	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Ristempa, Warnings and precautions: - Talk to your doctor, pharmacist or nurse before using Ristempa if you are aware of any altered blood cell counts (eg, increase in white blood cells or anemia) or decreased blood platelet counts, which reduces the ability of your blood to clot (thrombocytopenia). Your doctor may want to monitor you more closely. • Section 4, Possible side effects: -Uncommon side effects (may affect up to 1 in 100 people): Some changes may occur in your blood, but these will be detected by routine blood tests. Your platelet count may become low which might result in bruising.	
Important potential risks		
AML/MDS	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 4.4, Special warnings and precautions for use: -Limited clinical data suggest a comparable effect on time to recovery of severe neutropenia for pegfilgrastim to filgrastim in patients with *de novo* acute myeloid leukemia (see Section 5.1). However, the long-term effects of Ristempa have not been established in acute myeloid leukemia; therefore, it should be used with caution in this patient population. <u>Text in SmPC (continued)</u> • Section 4.4, Special warnings and precautions for use: - The safety and efficacy of Ristempa have not been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukemia, and in patients with secondary acute myeloid leukemia; therefore, it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukemia from acute myeloid leukemia. - The safety and efficacy of Ristempa administration in *de novo* AML patients aged < 55 years with cytogenetics t(15;17) have not been established. <u>Text in PIL</u> • Section 2, What you need to know before you use	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Ristempa, Warnings and precautions: -You should talk to your doctor about your risks of developing cancers of the blood. If you develop or are likely to develop cancers of the blood, you should not use Ristempa, unless instructed by your doctor.	
Cytokine release syndrome	None	None
Medication errors including overdose	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 1, Name of the medicinal product: Ristempa® 6 mg solution for injection. <u>Text in SmPC (continued)</u> • Section 2, Qualitative and quantitative composition: - Each pre-filled syringe contains 6 mg of pegfilgrastim* in 0.6 mL solution for injection. The concentration is 10 mg/mL based on protein only**. * Produced in *E coli* cells by recombinant DNA technology followed by conjugation with polyethylene glycol (PEG). ** The concentration is 20 mg/mL if the PEG moiety is included. • Section 4.2, Posology and method of administration: - Ristempa therapy should be initiated and supervised by physicians experienced in oncology and/or hematology. - One 6 mg dose (a single pre-filled syringe) of Ristempa is recommended for each chemotherapy cycle, administered as a subcutaneous injection approximately 24 hours after cytotoxic chemotherapy. • Section 4.5, Interaction with other medicinal products and other forms of interaction: -Due to the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, Ristempa should be administered approximately 24 hours after administration of cytotoxic chemotherapy. In clinical trials, Ristempa has been safely administered 14 days before chemotherapy. Concomitant use of Ristempa with any chemotherapy agent has not been evaluated in patients. In animal models concomitant administration of Ristempa and 5-fluorouracil or other	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	antimetabolites has been shown to potentiate myelosuppression. <u>Text in SmPC (continued)</u> • Section 4.9, Overdose: - Single doses of 300 µg/kg have been administered subcutaneously to a limited number of healthy volunteers and patients with non-small cell lung cancer without serious adverse reactions. The adverse events were similar to those in subjects receiving lower doses of pegfilgrastim. <u>Text in PIL</u> • Section 3, How to use Ristempa, If you use more Ristempa than you should: - If you use more Ristempa than you should contact your doctor, pharmacist, or nurse. • Section 3, How to use Ristempa, If you forget to inject Ristempa: -If you have forgotten a dose of Ristempa, you should contact your doctor to discuss when you should inject the next dose.	
Drug interaction with lithium	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 4.5, Interaction with other medicinal products and other forms of interaction: -The potential for interaction with lithium, which also promotes the release of neutrophils, has not been specifically investigated. There is no evidence that such an interaction would be harmful.	None
Off-label use	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 4.1, Therapeutic indications: - Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukemia and myelodysplastic syndromes). • Section 4.4, Special warnings and precautions for use: - The safety and efficacy of Ristempa have not	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	been investigated in patients with myelodysplastic syndrome, chronic myelogenous leukemia, and in patients with secondary acute myeloid leukemia; therefore, it should not be used in such patients. Particular care should be taken to distinguish the diagnosis of blast transformation of chronic myeloid leukemia from acute myeloid leukemia. - The safety and efficacy of Ristempa administration in *de novo* AML patients aged < 55 years with cytogenetics t(15;17) have not been established. -The safety and efficacy of Ristempa have not been investigated in patients receiving high dose chemotherapy. This medicinal product should not be used to increase the dose of cytotoxic chemotherapy beyond established dosage regimens.	
Immunogenicity (incidence and Clinical implications of anti-G-CSF antibodies)	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 4.4, Special warnings and precautions for use: - As with all therapeutic proteins, there is a potential for immunogenicity. Rates of generation of antibodies against pegfilgrastim is generally low. Binding antibodies do occur as expected with all biologics; however, they have not been associated with neutralising activity at present. <u>Text in PIL</u> • Section 2, What you need to know before you use Ristempa, Loss of response to pegfilgrastim: -If you experience a loss of response or failure to maintain a response with pegfilgrastim treatment, your doctor will investigate the reasons why including whether you have developed antibodies which neutralise pegfilgrastim's activity.	None
Extramedullary haematopoiesis	None	None
Missing information		
Risks in children <18 years of age	Medicinal product subject to restricted medical prescription. <u>Text in SmPC</u> • Section 4.2, Posology and method of administration - The safety and efficacy of Ristempa in children	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	has not yet been established. Text in SmPC (continued) • Section 4.8, Undesirable effects, Pediatric population: - The experience in children is limited. A higher frequency of serious adverse reactions in younger children aged 0-5 years (92%) has been observed compared to older children aged 6-11 and 12-21 years respectively (80% and 67%) and adults. The most common adverse reaction reported was bone pain.	
Risks during pregnancy and lactation	Medicinal product subject to restricted medical prescription. Text in SmPC • Section 4.6, Fertility, pregnancy and lactation, Pregnancy: - There are no or limited amount of data from the use of pegfilgrastim in pregnant women. Studies in animals have shown reproductive toxicity (see Section 5.3). Ristempa is not recommended during pregnancy and in women of childbearing potential not using contraception. - Women who become pregnant during treatment are encouraged to enroll in Amgen's Pregnancy Surveillance programme. Contact details are provided in Section 6 of the Package leaflet. • Section 4.6, Fertility, pregnancy and lactation, Breast-feeding: - There is insufficient information on the excretion of Ristempa/metabolites in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Ristempa therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Product information

Ristempa is a duplicate application and therefore the SmPC, labelling and package leaflet of this product is based on the approved SmPC, labelling and package leaflet of the reference product Neulasta. The PI is identical except for the name of the product.

2.8.1. User consultation

Since the package leaflet included in this application is a duplicate of the currently authorised leaflet for the product Neulasta, with only changes to the product name made throughout, a user testing has not been performed. This was considered acceptable by the CHMP.

In accordance with Article 56a of Directive 2001/83/EC, as amended, and the European Commission "Guidance concerning the Braille requirements for labelling and the package leaflet" (2005), the invented name and strength in Braille will be placed on the packaging for Ristempa. The applicant has stated that the text which will be printed on the outer carton in Braille is included in section 16 of the outer carton product information and is represented by dots on the mock ups.

3. Benefit-Risk Balance

This is an informed consent application in accordance with article 10c of Directive 2001/83/EC.

The product of this application is a duplicate with identical composition and documentation as Neulasta (EU/1/02/227/001, 002 and 004), authorized in the treatment of:

Reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes).

The CPMP considered the benefit/risk balance of Neulasta positive based on the established efficacy of Filgrastim in chemotherapy induced neutropenia (reduction of the duration of neutropenia and incidence of febrile neutropenia) and the comparable efficacy and safety profiles between Neulasta and Filgrastim. Based on the previous review of data on quality, safety and efficacy for Neulasta, the benefit/risk balance for Ristempa is considered favourable.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ristempa in the treatment of the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.