Medicines Adverse Reactions Committee

Meeting date	**13 September 2018**	Agenda item	3.2.2
Title	**Granulocyte-Colony Stimulating Factors (G-CSFs) and Pulmonary Haemorrhage/Haemoptysis**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active constituent	**Medicines**	**Sponsors**
Filgrastim	*Neupogen* 300mcg/mL	Amgen New Zealand Limited
	Zarzio 300mcg/0.5mL	Novartis New Zealand Limited
	Zarzio 480mcg/0.5mL	Novartis New Zealand Limited
Pegfilgrastim	*Neulastim* 6mg/0.6mL	Amgen New Zealand Limited
Lipegfilgrastim	*Lonquex* 6mg/0.6mL	Teva Pharma New Zealand Limited

Funding	**<u>Filgrastim</u>** *Zarzio* 300mcg/0.5mL and 480mcg/0.5mL – Special Authority *Neupogen* 300mcg/mL – Not funded **<u>Pegfilgrastim</u>** *Neulastim* 6mg/0.6mL – Special Authority **<u>Lipegfilgrastim</u>** *Lonquex* 6mg/0.6mL – Not funded
Previous MARC meetings	Not previously discussed
International action	European Medicines Agency: 14-17 May 2018 (Annex 1) – The Pharmacovigilance Risk Assessment Committee (PRAC) recommended that the Summary of Product Characteristics' (SmPCs) for lenograstim, lipegfilgrastim and pegfilgrastim containing products should be updated to include haemoptysis and pulmonary haemorrhage as undesirable effects (section 4.8 of the SmPC).
Prescriber Update	Nil
Schedule	Prescription medicine
Usage data	DataPharm (beta) shows the following usage data for 2016 (the most recent year for which data is available). The data presented is limited to medicines which are funded by PHARMAC and dispensed from a community pharmacy. Medicine — Number of people Filgrastim 300mcg/0.5mL — 523 Filgrastim 480mcg/0.5mL — 199 Pegfilgrastim 6mg/0.6mL — 1838
Advice sought	**The Committee is asked to advise whether:** – A class effect is plausible? – Updates to the New Zealand Granulocyte-Colony Stimulating Factors (G-CSFs) data sheets are required at this time, based on the evidence presented and international regulatory action? – Any further communication on this topic is required besides MARC's Remarks?

Table of Contents

1.0 PURPOSE

At the 14-17 May 2018 Pharmacovigilance Risk Assessment Committee (PRAC) meeting the Committee recommended that the Marketing Authorisation Holders (MAHs) for lenograstim, pegfilgrastim and lipegfilgrastim products should update the Summary of Product Characteristics' (SmPCs) to list haemoptysis and pulmonary haemorrhage as potential adverse reactions.

After reviewing the New Zealand Granulocyte-Colony Stimulating Factors (G-CSFs) data sheets we found no mention of pulmonary haemorrhage. However, some of the data sheets list haemoptysis as a potential adverse reaction.

This paper highlights the recommendation related to this signal made by the PRAC. It also presents some evidence for an association between G-CSFs and pulmonary haemorrhage/haemoptysis.

The advice sought from the Committee is whether the New Zealand G-CSF data sheets require updating at this time.

2.0 BACKGROUND

2.1 Granulocyte-Colony Stimulating Factor (G-CSF)

Granulocyte-Colony Stimulating Factor (G-CSF) is a glycoprotein that stimulates the proliferation and supports the survival of neutrophil progenitors, as well as promoting their differentiation into mature neutrophils (1).

In addition to this, G-CSF stimulates the release of neutrophils from the bone marrow into the blood and enhances their phagocytic capacity, superoxide anion production and bactericidal capability (1, 2).

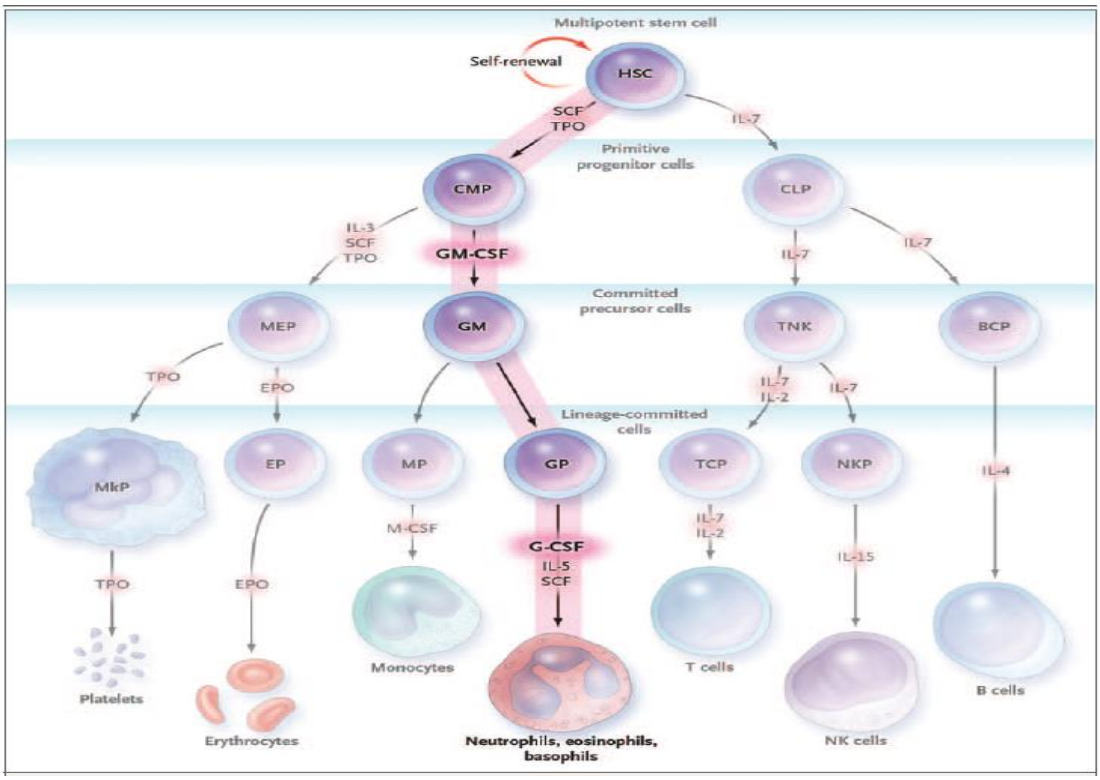


Figure 1: Use of Haemopoietic Growth Factors in the Survival and Differentiation of Haemopoietic Cells (1)

Granulocyte colony stimulating factor (G-CSF) supports the differentiation of committed granulocyte progenitors (GP) into mature granulocytes.

2.2 Recombinant Granulocyte-Colony Stimulating Factors (rG-CSFs) Available in New Zealand

2.2.1 Filgrastim

Filgrastim is the originator recombinant methionyl human G-CSF, produced from a genetically modified *Escherichia coli s*train (2-4). Filgrastim was first approved in the United States and subsequently approved in New Zealand in 1991 (2).

Currently, filgrastim has a number of indications in New Zealand which include (4, 5):

- Reduction in the duration of neutropenia and the incidence of febrile neutropenia in patients treated with established cytotoxic chemotherapy for malignancy (except for chronic myeloid leukaemia and myelodysplastic syndromes)
- Reduction in the duration of neutropenia and its clinical sequelae in patients undergoing myeloablative therapy followed by bone marrow transplantation considered to be at increased risk of prolonged severe neutropenia
- Mobilisation of autologous peripheral progenitor cells alone, or following myelosuppressive chemotherapy and the mobilisation of Peripheral Blood Progenitor Cells (PBPC) in normal donors (allogenic PBPC)
- Long term administration for patients, children or adults, with severe congenital, cyclic or idiopathic neutropenia with an Absolute Neutrophil Count (ANC) ≤ 0.5x 10^9/L, and a history of severe or recurrent infections, to increase neutrophil counts and to reduce the incidence and duration of infection-related events
- Treatment of persistent neutropenia (ANC ≤ 1.0x 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.

Filgrastim is administered daily. The dose, duration of treatment and route of administration (subcutaneous or intravenous) depend on the indication.

There is a positive linear correlation between the dose and the serum concentration of filgrastim, whether administered intravenously or subcutaneously.

Elimination half-life after intravenous and subcutaneous dosing is between two to four hours. Clearance and half-life are dependent on the dose and the neutrophil count. When neutrophil-mediated clearance is saturated by high filgrastim concentrations or diminished by neutropenia, the linear clearance pathway predominates and the pharmacokinetics appear linear (4, 5).

2.2.2 Pegfilgrastim

Pegfilgrastim was approved in New Zealand in 2007.

It is only indicated in New Zealand for the reduction in duration of neutropenia, the incidence of febrile neutropenia and the incidence of infection as manifested by febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy, except chronic myeloid leukaemia and myelodysplastic syndromes (6).

Pegfilgrastim is administered in adults as a single 6mg dose each chemotherapy cycle via subcutaneous injection, approximately 24 hours following cytotoxic chemotherapy (6).

Pegfilgrastim and filgrastim bind equally to the same G-CSF receptor and have the same mechanism of action (3).

Pegfilgrastim is composed of filgrastim with a 20kDa polyethylene glycol (PEG) molecule covalently bound to the N-terminal methionine residue (6). A diagram of the structure of pegfilgrastim is presented below in figure 2.

The addition of the PEG polymer increases mass and protects pegfilgrastim from enzymatic degradation and rapid renal clearance, making it a sustained duration form of filgrastim (3, 6). The main elimination pathway for pegfilgrastim appears to be neutrophil mediated clearance (>99%), which is saturable. The distribution of pegfilgrastim is limited to the plasma component (6).

Figure 2: Diagram of the structure of pegfilgrastim (3)

2.2.3 Lipegfilgrastim

Lipegfilgrastim was recently approved in New Zealand on 24 May 2018.

In New Zealand, it is only indicated for the reduction in the duration of neutropenia and the incidence of febrile neutropenia in adult patients treated with cytotoxic chemotherapy for malignancy, except for chronic myeloid leukaemia and myelodysplastic syndromes (7).

Lipegfilgrastim is administered in adults as a single 6mg dose each chemotherapy cycle via subcutaneous injection, approximately 24 hours after cytotoxic chemotherapy (7).

Lipegfilgrastim is a covalent conjugate of filgrastim and a 20kDa polyethylene glycol (PEG) moiety, enzymatically attached through a glycolinker to the amino acid threonine (7).

Lipegfilgrastim binds to the human G-CSF receptor like filgrastim and pegfilgrastim. Based on preclinical studies, G-CSF receptor binding was equivalent between lipegfilgrastim and pegfilgrastim. It is a sustained duration form of filgrastim due to its decreased renal clearance (3, 7).

Lipegfilgrastim has two distinct clearance pathways. The first pathway is linear and is likely comprised of degradation by proteolytic enzymes. The second pathway is non-linear neutrophil mediated clearance (intracellular) that is dependent on the Absolute Neutrophil Count (ANC) (7).

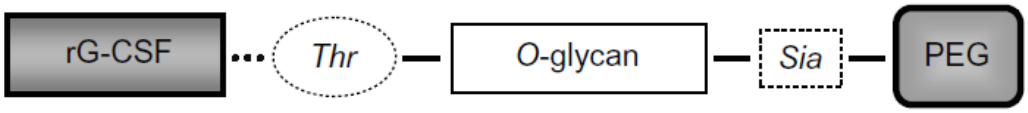


Figure 3: Diagram of the structure of lipegfilgrastim (3)

2.3 Pulmonary Haemorrhage and Haemoptysis

Pulmonary haemorrhage is any form of bleeding into the lung. Haemoptysis may be a symptom of pulmonary haemorrhage.

Haemoptysis, or the expectoration of blood, can range from blood-streaking of sputum to the presence of gross blood in the absence of any accompanying sputum. Haemoptysis has a broad differential, but the cause can be determined in the majority of patients.

Patients with mild-to-moderate haemoptysis and adequate gas exchange generally do not require hospitalization. Massive haemoptysis requires a prompt response to ensure adequate ventilation, protect the airway, and control bleeding (8).

2.4 International Regulatory Action

2.4.1 Europe

The recommendations made at the 14-17 May meeting of the Pharmacovigilance Risk Assessment Committee (PRAC) regarding this signal are documented below.

Recommendation

Having considered the evidence from the EudraVigilance database, the possibility of a class effect and the responses from MAHs, the PRAC recommended that the MAHs[1] of pegfilgrastim, lenograstim[2] and lipegfilgrastim should submit a variation within 60 days to update the product information as described below (new text underlined):

Summary of product characteristics

4.8. Undesirable effects

Respiratory, thoracic and mediastinal disorders

Haemoptysis (uncommon*)

Pulmonary haemorrhage (rare*)

Package leaflet

4. Possible side effects

(under corresponding frequencies):

Coughing up blood (haemoptysis) – uncommon*

Bleeding from the lung (pulmonary haemorrhage) – rare*

*Note: Stated frequencies are applicable for pegfilgrastim; for lipegfilgrastim and lenograstim the frequency is to be calculated by the MAHs.

[1]Applicants for products under evaluation should update their product information accordingly during evaluation.

[2]To include pulmonary haemorrhage and haemoptysis for both cancer patients and healthy donors.

Comment: Lenograstim is currently unavailable in New Zealand.

The recommendation seems to be related to chemotherapy patients and healthy PBPC donors.

The evidence behind the recommendation is based on case reports and company responses to the PRACs preliminary assessment report. Recommendation only suggests listing the adverse effects in section 4.8 of the SmPC.

In their response to the PRAC, Amgen, the MAH for pegfilgrastim stated that they were in agreement with the proposed additions to section 4.8 of the EU SmPC and that following the conclusion of this signal assessment procedure the SmPC would be updated. No evidence was presented in their response. A full copy is included as annex 1.

2.5 Current Information in the Data Sheets

2.5.1 New Zealand

The current safety information relating to pulmonary haemorrhage/haemoptysis in the G-CSF data sheets is presented below.

2.5.1.1 Filgrastim (*Neupogen*)

Section 4.8 Undesirable effects

Combined clinical trial data	**Frequency**
Haemoptysis	*Common (≥ 1/100 and < 1/10):*
Lung infiltration	*Uncommon (≥ 1/1,000 and < 1/100)*
For cancer patients	**Frequency**
Lung infiltration	*Very rare (<1/10,000)*
Normal donors undergoing Peripheral Blood Progenitor Cell Mobilisation (PBPC)	**Frequency**
Haemoptysis	*Very rare <1/10,000*
Lung infiltration	*Very rare <1/10,000*

2.5.1.2 Filgrastim (*Zarzio*)

Adverse Effects

In cancer patients	**Frequency**
Pulmonary infiltrates	*Very rare (<0.01%)*
In normal donors undergoing PBPC mobilisation	**Frequency**
Pulmonary infiltrates	*Very rare (<0.01%)*
Haemoptysis	*Very rare (<0.01%)*

2.5.1.3 Pegfilgrastim (*Neulastim*)

No safety information related to pulmonary haemorrhage/haemoptysis listed.

2.5.1.4 Lipegfilgrastim (*Lonquex*)

Section 4.8 Undesirable Effects

Tabulated Adverse Reactions	**Frequency**			
Pulmonary infiltrates	*Uncommon (≥ 1/1,000 to < 1/100)*			
Adverse Events with an incidence ≥2% of patients in either treatment group in Study XM22-04 (NSCLC patients)	**Frequency**			
	Placebo (N=125)		**Lonquex® 6mg (N=248)**	
	n	**%**	**n**	**%**
Haemoptysis	5	4.0	7	2.8

Comments: All data sheets except for pegfilgrastim list haemoptysis somewhere in section 4.8. However, no data sheet lists pulmonary haemorrhage as an adverse effect.

The term pulmonary/lung infiltrates/infiltration is listed in the New Zealand data sheets. Does the Committee think this term relates to bleeding? Or is it describing a cellular (neutrophilic) infiltrate?

2.5.2 Europe

The current safety information relating to pulmonary haemorrhage/haemoptysis in the G-CSF Summary of Product Characteristics (SmPCs) is presented below.

2.5.2.1 Filgrastim (*Neupogen*)

4.8 Undesirable effects

Tabulated summary of adverse reactions	**Frequency**
Haemoptysis	*Common (≥ 1/100 to < 1/10)*
Pulmonary Haemorrhage	*Uncommon (≥ 1/1000 to < 1/100)*
Lung Infiltration	*Uncommon (≥ 1/1000 to < 1/100)*

2.5.2.2 Filgrastim (*Zarzio*)

4.8 Undesirable effects

Tabulated summary of adverse reactions	**Frequency**
Haemoptysis	*Common (≥ 1/100 to < 1/10)*
Pulmonary Haemorrhage	*Uncommon (≥ 1/1,000 to < 1/100)*
Lung Infiltration	*Uncommon (≥ 1/1,000 to < 1/100)*

2.5.2.3 Pegfilgrastim (*Neulasta*)

No safety information related to pulmonary haemorrhage/haemoptysis listed.

Lists pulmonary infiltrates in section 4.8

2.5.2.4 Lipegfilgrastim (*Lonquex*)

No safety information related to pulmonary haemorrhage/haemoptysis listed.

Lists pulmonary infiltrates in section 4.8

Comments: Pulmonary haemorrhage and haemoptysis listed in the filgrastim SmPCs.

The submissions to include pulmonary haemorrhage/haemoptysis into the pegfilgrastim and lipegfilgrastim SmPCs may not have been processed as yet. MAHs were requested to submit their variations within 60 days of the meeting (14-17 May 2018).

In their response to the PRAC, Amgen, the MAH for pegfilgrastim agreed with their preliminary signal assessment.

3.0 SCIENTIFIC INFORMATION

3.1 Case Reports

3.1.1 Kopp HG, Horger M, Faul C, et.al. 2007 (9)

A 49-year-old man developed pulmonary haemorrhage during treatment with granulocyte colony-stimulating factors [G-CSF;specific drug not stated] prior to haematopoietic stem cell donation. The man, who was a cigarette smoker with a chronic nonproductive cough, started receiving SC G-CSF 10 µg/kg divided in two and, after 3 days, he developed retrosternal discomfort, cough and haemoptysis. A chest x-ray revealed thickening of his peribronchovascular lung interstitium associated with patchy infiltrates over both of his lower and middle pulmonary fields, consistent with pulmonary haemorrhage. A non-enhanced high-resolution CT scan showed patchy, ill-defined regions of ground-glass attenuation and even parenchymal consolidation and ill-defined centrilobular nodules. Arterial blood gas analyses revealed only minor changes. The man received high-dose prednisone and amoxicillin/clavulanic acid and, 3 days later, his haemoptysis and temperature abated. A repeat CT scan revealed marked improvement of his haemorrhage and he was discharged with antibacterials; G-CSF was discontinued.

Comment: This patient was reported to be a smoker which may be a confounding factor. The patient's chest x-ray showed signs consistent with pulmonary haemorrhage.

3.1.2 Negishi K, Lisa W, White A. 2018 (10)

A 60-year-old woman developed reactivation of pulmonary haemorrhage and anaemia following treatment with cyclophosphamide, dexamethasone, doxorubicin and pegfilgrastim [routes and dosages not stated]. The woman, who had a history of tuberculosis, presented with pulmonary haemorrhage which recovered completely. Biopsy of the breast mass revealed triple negative intra-ductal carcinoma with locally advanced disease. Blood loss was observed in her lungs. She started receiving treatment with cyclophosphamide, dexamethasone, doxorubicin and pegfilgrastim. After four days, she presented to the emergency room with mild shortness of breath and trace haemoptysis. Over the next 12 hours, she became hypoxic and required intubation and mechanical ventilation. Chest imaging demonstrated marked airspace disease and dense ground-glass opacities (GGO). Repeat bronchoscopy demonstrated evidence of pulmonary haemorrhage. Following pulmonary haemorrhage, she developed anaemia. ANA titre was positive at 1:40 and rheumatoid factor positive at 1:4. The woman started receiving treatment with steroids. Her infiltrates improved. She was discharged for outpatient follow-up. Three weeks later, chest imaging revealed nearly complete resolution of lung infiltrates with residual GGO.

Comments: The authors note her second presentation raises suspicion of a chemotherapy-induced reactivation of an underlying process.

3.1.3 Miura Y, Kami M, Yamada M, et al. 2008 (11)

A 65-year-old man developed fatal diffuse alveolar haemorrhage associated with retinoic acid syndrome (RAS) during treatment with tretinoin and filgrastim. The man was hospitalised and, following diagnosis of hypoplastic acute leukaemia, started receiving induction therapy with idarubicin and cytarabine. On day 2, he developed febrile neutropenia and received cefepime. However, his fever persisted and filgrastim 300mg [frequency not stated] was started on day 9. On day 12, his diagnosis was changed to acute promyelocytic leukaemia following karyotype analysis

and, on the same day, he started receiving tretinoin 45 mg/m^2 [frequency not stated]. On the same night, he developed rapid onset dyspnoea with hypoxia. A chest CT scan showed bilateral diffuse interstitial infiltrates. His peripheral leucocyte counts rapidly increased from day 14; differential peripheral leucocytes ranged from blasts to segmented neutrophils. He was diagnosed with RAS. Tretinoin and filgrastim were discontinued and the man started receiving dexamethasone. However, his respiratory status progressively deteriorated and he was intubated. Massive bloody secretions were suctioned from his endotracheal tube. He subsequently died of respiratory failure on day 15. Postmortem analysis showed massive alveolar haemorrhage. Matured neutrophil infiltration was observed in the man's lung parenchyma. The findings were suggestive of diffuse alveolar haemorrhage attributed to RAS. Matured neutrophils were observed in the marrow, liver and spleen.

Comments: The authors note the patient developed RAS two days after initiation of tretinoin. Administration of granulocyte colony-stimulating factor combined with tretinoin might be associated with the development of RAS and fatal diffuse alveolar haemorrhage in this patient.

3.1.4 Guenther C, Hahn U, Fertl A, et.al. 2007 (12)

A 38-year-old stem cell donor developed haemoptysis, dyspnoea and hypoxaemia during treatment with filgrastim prior to stem cell collection. The man, who was a smoker, received filgrastim 11 mg/kg, split in two doses, for 4 days. On treatment day 3, he developed a cough and massive haemoptysis. A chest x-ray revealed diffuse infiltrates in the middle and lower parts of the lung. The following day, he was hospitalised with continuing haemoptysis, dyspnoea and hypoxaemia (O_2 < 55mm Hg). Filgrastim was stopped and the man received oxygen and clarithromycin. He gradually improved and was discharged 4 days later with very mild haemoptysis and normal blood gas parameters. A pulmonary CT scan revealed diffuse opaque infiltrates with accentuation of the lower parts. Bronchoalveolar lavage showed diffuse haemorrhage. At 2-months' follow-up, he had recovered completely.

Comment: This patient was reported to be a smoker which may be a confounding factor. Diffuse haemorrhage was noted from bronchoalveolar lavage.

3.1.5 Wetzko K, Blechschmidt M, Holig K, et.al. 2013 (13)

A 20-year-old man received lenograstim 8.5 µg/kg/day. On day 3 he developed haemoptysis and dyspnoea; lenograstim was continued. Large volume apheresis was completed but subsequent diagnostic investigations indicated severe bronchitis. Bronchoscopy found diffuse haemorrhage. Nasal swab samples were positive for influenza B; lenograstim was suspected of having an impact on the severity of his illness. He received oseltamivir, as well as levofloxacin for suspected bacterial superinfection. He was discharged 2 days later, symptom free.

Comment: This patient had a respiratory tract infection which may have been aggravated by lenograstim. Lenograstim is not available in New Zealand.

3.1.6 Gokcebay DG, Fettah A, Kirbas I, et.al. 2015 (14)

A 16-year-old girl developed neutropenic fever, and haemoptysis due to invasive pulmonary aspergillosis, during chemotherapy with idarubicin, fludarabine, cytarabine and unspecified granulocyte colony-stimulating factors (IDA-FLAG) (durations of treatment to reaction onsets not all stated). The girl was diagnosed with acute lymphoblastic leukaemia, and received induction chemotherapy according to the ALL-IC BFM2009 regimen. However, follow-up revealed resistant disease. She started treatment with idarubicin 12 mg/m2/day on days 2, 3 and 4, fludarabine 30 mg/m2/day for 4 days, cytarabine 2 g/m2/day for 4 days, and granulocyte colony-stimulating factors 5 µg/kg/day. She subsequently developed prolonged neutropenic fever. Chest x-ray revealed lung infiltration; she received broad-spectrum antibacterials. Thoracic CT scanning due to persistent fever revealed 2 nodules in her right lung, with a halo of ground-glass attenuation; she was serum galactomannan antigen-positive. Invasive pulmonary aspergillosis was suspected; she started voriconazole treatment. Her neutropenia resolved, but aspergillosis persisted, although there was no evidence of vessel invasion. She was treated with fluconazole, cytarabine and granulocyte colony-stimulating factors. A week later, after 37 days of voriconazole treatment, she developed massive haemoptysis, with coughing, during a period of thrombocytopenia. Otolaryngological examination revealed subepiglottal bleeding. The girl received platelet and cryoprecipitate support; however, she experienced fresh bleeding within 90 minutes, and her haemoglobin level fell to 6.5 g/dL. Treatment with recombinant factor VIIa achieved haemostasis. Her right bronchial artery subsequently received coil embolisation. During 3 months of follow-up, there was no recurrence.

Comments: The authors state chemotherapy-induced severe neutropenia results in an immunodeficient state facilitating infection with filamentous mycosis. Following recovery of the bone marrow, the neutrophils are chemoattracted to the lung regions infected with fungi that enhance the local inflammatory response and release of proteolytic enzymes. These may play roles in the invasion of blood vessels by filamentous mycosis.

3.1.7 Liu H, Zhang J, Ren S, et.al. 2017 (15)

In a respective study, three patients (ages and sexes not stated) were described, who developed gastrointestinal bleeding, haemoptysis or urinary infection during treatment with omacetaxine mepesuccinate, cytarabine and unspecified granulocyte colony stimulating factors (G-CSF). The patients, who had a history of acute myeloid leukaemia, started receiving treatment with low-dose omacetaxine mepesuccinate, cytarabine and granulocyte colony stimulating factors. The patients received SC injection of granulocyte colony stimulating factors before the first injection of cytarabine. Subsequently, the patients developed non-hematological toxicities of gastrointestinal bleeding (n=1), haemoptysis (n=1) and urinary infection (n=1) (durations of treatments to reactions onset and outcomes not stated).

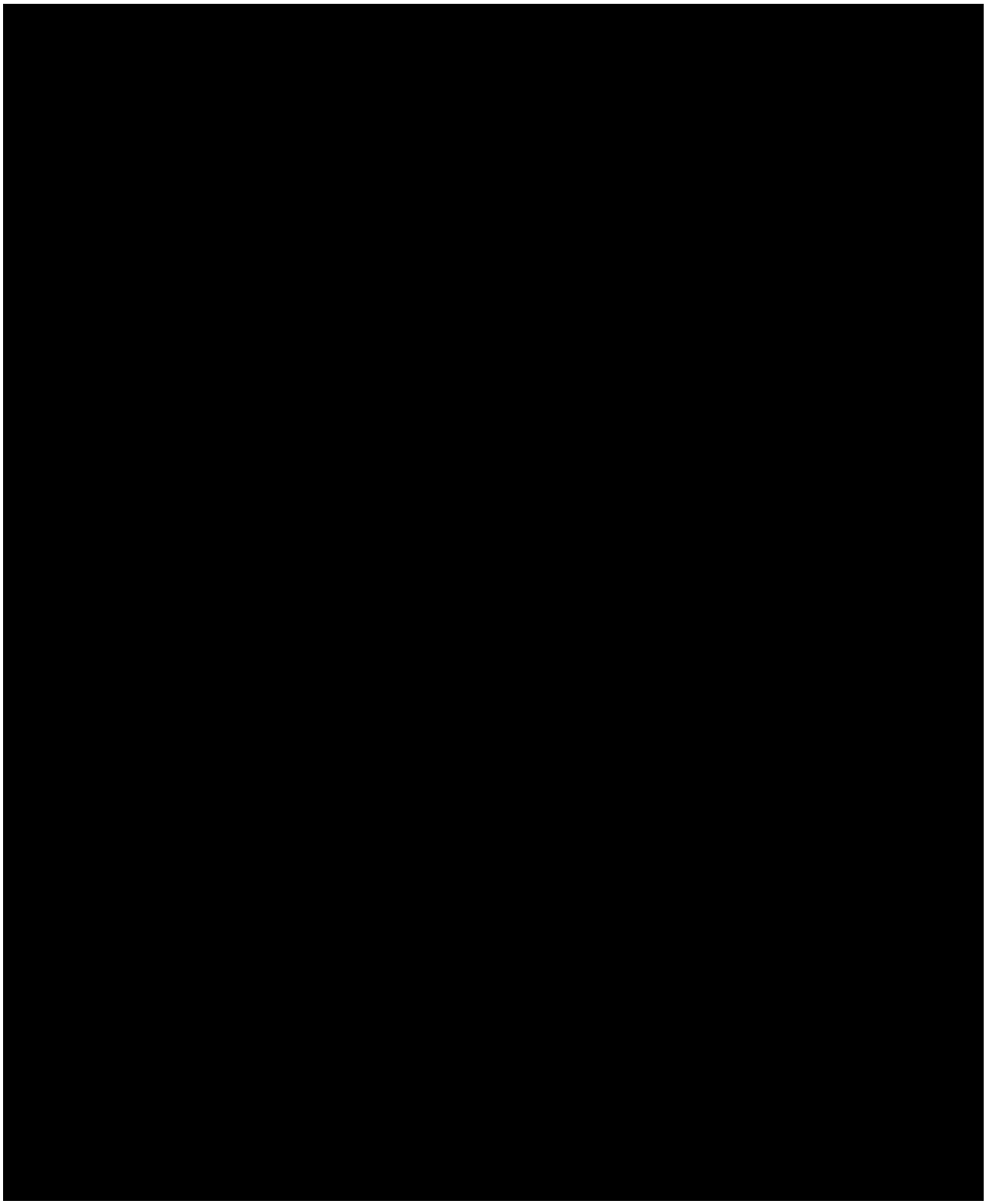
Comment: One patient developed haemoptysis. There is no mention of pulmonary haemorrhage.

3.2 Company data

3.2.1 [redacted]

[redacted]

[redacted]



[redacted]

3.3 CARM case reports

To date, CARM has not received any reports of pulmonary haemorrhage or haemoptysis associated with use of a Granulocyte-Colony Stimulating Factor (G-CSF).

3.4 Case reports in the WHO database

As at 26 August 2018 there are 88 individual ICSRs in the WHO database, Vigibase, relating to G-CSFs and the preferred terms (PTs) 'pulmonary haemorrhage' and/or 'haemoptysis'. However, six of these ICSRs are duplicate reports, which happen come from literature and are reported above in section 3.1 (9, 10). This means there are actually 82 ICSRs. An export of all reports is included as annex 3.

Out of the 82 ICSRs, 30 report a granulocyte-colony stimulating factor as the sole suspect medicine. An export of these reports is included as annex 4. The majority of the other reports list chemotherapy agents or antivirals as co-suspect medication.

Of the 30 reports where a G-CSF was the sole suspect 19 relate to filgrastim, six to pegfilgrastim, three to lenograstim and two to pegteograstim.

Of the 19 reports where filgrastim was the sole suspect five reports state there was a positive dechallenge and three state no effect when the medicine was withdrawn.

Of the six reports where pegfilgrastim was the sole suspect one report describes a positive dechallenge and one report states that the reaction abated with no change in dose.

Of the three reports where lenograstim was the sole suspect one report describes a positive dechallenge and one report states the reaction abated with no change in dose.

Both of the reports for pegteograstim state that the reaction was unlikely to have been caused by the medicine.

Tables 2 and 3 below show the disproportionality in reporting for G-CSFs and pulmonary haemorrhage and haemoptysis, respectively. However, these figures have not been adjusted to take into account the duplicate reports.

Table 2: Number of case reports received and the disproportionality values for the reporting rate of pulmonary haemorrhage with G-CSFs in the WHO database

Medicine	$N_{observed}$	IC_{025}
Filgrastim	25	2.21
Granulocyte- Colony Stimulating Factor	7	1.87
Pegfilgrastim	6	-1.60
Lenograstim	2	-1.20

Table 3: Number of case reports received and the disproportionality values for the reporting rate of haemoptysis with G-CSFs in the WHO database

Medicine	$N_{observed}$	IC_{025}
Filgrastim	24	0.34
Granulocyte-Colony Stimulating Factor	12	1.80
Pegfilgrastim	12	-2.10
Lenograstim	5	-0.25
Pegteograstim	2	-0.73

4.0 DISCUSSION AND CONCLUSIONS

There are three G-CSFs available in New Zealand (filgrastim, pegfilgrastim and lipegfilgrastim), which share the same mechanism of action (pegfilgrastim and lipegfilgrastim are longer-acting forms of filgrastim). However, filgrastim is indicated for more conditions than pegfilgrastim and lipegfilgrastim. It is unknown if the underlying condition could contribute to pulmonary haemorrhage and/or haemoptysis resulting in different reporting rates of these adverse reactions. Currently pulmonary haemorrhage is not listed in any of these data sheets. However, most list haemoptysis as an adverse reaction which is considered to be a symptom of pulmonary haemorrhage.

Although there have been no reports to CARM, there are a few cases reported internationally where G-CSFs have been associated with haemoptysis and pulmonary haemorrhage. The majority of cases reported in the literature include confounders such as a history of smoking and other concomitant medicines. Some reported signs of pulmonary haemorrhage that were seen on investigation (eg, x-ray, bronchalveolar lavage). [redacted]

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- A class effect is plausible?
- Updates to the New Zealand Granulocyte-Colony Stimulating Factors (G-CSFs) data sheets are required at this time, based on the evidence presented and international regulatory action?
- Any further communication on this topic is required besides MARC's Remarks?

6.0 ANNEXES

1. Amgen - Response to the PRAC
2. [redacted]
3. WHO database case reports for G-CSFs and pulmonary haemorrhage/haemoptysis (all ISCRs)
4. WHO database case reports for G-CSFs and pulmonary haemorrhage/haemoptysis (G-CSF sole suspect)

7.0 REFERENCES

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