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Summary of the risk management plan (RMP) for Accofil (filgrastim)

This is a summary of the risk management plan (RMP) for Accofil, which details the measures to be taken in order to ensure that Accofil is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Accofil, which can be found on Accofil's EPAR page.

Overview of disease epidemiology

Accofil (filgrastim) is a biosimilar medicine (a biological medicine that is similar to another biological medicine, also known as the 'reference medicine', that is already authorised in the EU). The reference medicine for Accofil is Neupogen. Both are used to stimulate the production of white blood cells (neutrophils), which reduces the risk of infection. Accofil is approved for use in the following situations:

- to reduce the duration of neutropenia (low levels of neutrophils) and the occurrence of febrile neutropenia (neutropenia with fever) in patients receiving cytotoxic chemotherapy (a type of cancer medicine).

  Up to 70% of cancer patients experience neutropenia. Factors that increase the risk of developing febrile neutropenia include type of cancer and type and dose of medications used to treat it (for some, the risk is >20%). Older patients (≥65 years), females, patients with other health problems and previous history of febrile neutropenia or infection are more likely to develop febrile neutropenia. Nearly 10% of patients who are hospitalised with febrile neutropenia die, and the risk is roughly twice as great in patients who have additional health problems (e.g. heart, lung, liver, or kidney disease) or develop bacterial or fungal infections.

- to reduce the duration of neutropenia in patients at risk of long-term severe neutropenia from treatment to destroy the stem cells in the bone marrow (the cells that produce the blood cells) before having fresh stem cells transplanted;

  More than 50,000 patients per year receive a stem cell transplant. Approximately 55% of patients receive their own stem cells, and 45% receive stem cells from a donor.

- to help release stem cells from the bone marrow in people who are about to donate them for transplant;

- to increase levels of neutrophils and reduce the risk of infections in patients with neutropenia who have a history of severe, repeated infections. This includes patients with conditions such as congenital and cyclic neutropenia, which are inherited and start in childhood, and those with idiopathic neutropenia (neutropenia that starts at any point in life for unknown reasons).

  Approximately one in a million people have cyclic neutropenia, and one in 200,000 have congenital or idiopathic neutropenia.

- to treat persistent neutropenia in patients with advanced human-immunodeficiency-virus (HIV) infection, to reduce the risk of bacterial infections when other treatments are not appropriate.

  Approximately 10 to 50% of patients with HIV infection develop neutropenia.

Summary of treatment benefits

Because Accofil is a biosimilar medicine, studies in healthy participants were carried out to show that Accofil produces similar levels of the active substance in the body to Neupogen and increases the numbers of neutrophils in a comparable way.

Accofil was studied in one main study involving 120 women with breast cancer who had neutropenia due to chemotherapy. Patients were given the chemotherapy on day 1 of a three-week cycle, and then received one dose of filgrastim the next day and daily for up to 14 days. The main measure of effectiveness was the duration of severe neutropenia. Severe neutropenia lasted on average for 1.4 days. This is comparable with the 1.6 days and 1.8 days reported in other studies found in the literature using filgrastim. Data from published studies indicate that the benefits and safety of filgrastim are similar in both adults and children receiving chemotherapy.

Unknowns relating to treatment benefits

Because the studies with Accofil were designed to establish its similarity to Neupogen, any uncertainties regarding its benefits are considered to be the same as for the reference medicine.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions which may cause weakness, drop in blood pressure, difficulty breathing, and swelling of the face (Hypersensitivity including anaphylaxis or severe allergic reactions)	More than one in 100 patients with cancer will experience an allergic reaction to filgrastim. In most cases the symptoms rapidly resolved after treatment.	The product information contains warnings for patients and healthcare professionals on the possibility of allergic reactions and how to recognise them. Patients who are allergic to filgrastim or any of the other ingredients in the medicine must not receive it. Allergic reactions can be managed by immediate discontinuation of the medicine and treatment of the symptoms. Patients who develop a serious allergic reaction must not be given filgrastim again.
Increase in spleen size/rupture of the spleen (Splenomegaly/splenic rupture)	Pain in the left upper part of the belly, pain below the left ribcage or pain at the tip of the shoulder may relate to enlargement or rupture of the spleen, a small organ at the base of the ribcage that plays a role in filtering the	Regular evaluation of the spleen size and immediate treatment of a ruptured spleen is recommended in patients taking Accofil. A decrease in filgrastim dose can slow or stop the increase in spleen size.

Risk	What is known	Preventability
	blood. Increase in spleen size is very common in severe chronic neutropenia patients (more than 1 in 10 patients), common in patients who have HIV (more than one in 100) and uncommon (up to 1 in a 100) in normal stem cell donors. Spleen rupture is uncommon (up to 1 in 100). It is a medical emergency and can be fatal.	
Severe lung inflammation causing difficulty in breathing (dyspnoea) (Acute respiratory distress syndrome or ARDS)	ARDS is uncommon in patients with cancer and it may be fatal. The onset of signs of lung problems such as cough, fever, difficulty breathing and worsening of lung function may be preliminary signs of ARDS.	Accofil should be stopped and appropriate treatment given if the patient develops signs such as cough, fever and difficulty in breathing.
Reaction of the donor cells against the patient receiving the transplant following use of fligrastim (Graft versus host disease, GvHD)	The immune system of a recipient of a stem cell or bone marrow transplant may react against the donor cells and recognise them as 'foreign'. Signs and symptoms include rash on the palms and soles, and ulcers and sores in the mouth, gut, liver, skin, eyes, lungs, vagina and joints.	The product information for Accofil includes a mention to GvHD in sections 4.4 and 4.8.
Coughing up blood (Haemoptysis)	Coughing up blood has been seen in cancer patients and normal stem cell donors.	Accofil should be stopped if patients cough up blood.
Leukaemia in patients with severe chronic neutropenia	Patients with severe chronic neutropenia treated with filgrastim are at an increased risk of developing leukaemias (cancer of the white blood cells) and myelodysplastic syndromes (a group of diseases in which the body produces large numbers of one or more types of abnormal blood cells). This could also be a complication of the disease.	Regular blood tests should be carried out whilst being treated with Accofil to count the number of neutrophils and other white blood cells, and patients should have periodic bone marrow examinations. Treatment with Accofil should be discontinued if patients develop leukaemia or myelodysplastic syndromes.
Loss of calcium from the bones which leads to the bones becoming weak and	More than one in 100 severe chronic neutropenia patients receiving long-term treatment	Monitoring of bone density may be needed in some patients who undergo continuous therapy with filgrastim for

Risk	What is known	Preventability
fragile (osteoporosis) in patients with severe chronic neutropenia	with filgrastim will develop decreased bone density and osteoporosis. In some patients this might also be due to the already existing bone density problems.	more than 6 months.
Worsening of inherited blood disorder that affects red blood cells (Sickle cell anaemia with crises)	Patients with sickle cell disease given filgrastim may experience sickle cell crises which can be fatal. Symptoms may include severe pain in the bones, chest, gut or joints.	Doctors should carefully evaluate the benefits and risks when considering the use of filgrastim in patients with sickle cell disease.
Painful, raised, plum-coloured sores on the limbs and sometimes the face and neck with fever (Acute febrile neutrophilic dermatosis, Sweet's syndrome)	Sweet's syndrome has been uncommonly reported in cancer patients treated with filgrastim.	The product information for Accofil states that cases of Sweet syndrome have been reported post-marketing with filgrastim.
Worsening (exacerbation) of rheumatoid arthritis	Worsening of symptoms of arthritis has been uncommonly reported in cancer patients and stem cell donors treated with filgrastim.	The product information for Accofil states that exacerbation of rheumatoid arthritis has been uncommonly reported with filgrastim.
Abnormal x-rays of the lungs (Lung infiltration)	Adverse effects in the lungs, shown by abnormal x-rays, have been reported in patients treated with filgrastim. The condition may lead to respiratory failure or severe lung inflammation and breathing difficulty.	Doctors should evaluate the patient if any lung symptoms or changes in lung function develop.
Inflammation of the blood vessels in the skin (Cutaneous vasculitis)	Inflammation of the blood vessels of the skin is commonly seen (in more than 1 in 100 patients) in severe chronic neutropenia patients and uncommonly in cancer patients (in more than 1 in 1000 patients).	The product information for Accofil mentions that cutaneous vasculitis may occur.
Leakage of blood from the small blood vessels into nearby body cavities and muscles	Capillary leak syndrome is caused by a sudden and unexplained change in the capillary walls that allows fluid to leak out. It is an uncommon	Doctors should monitor for symptoms of capillary leak syndrome, which may include generalised swelling or puffiness, possibly associated with passing water less frequently,

Risk	What is known	Preventability
(Capillary leak syndrome)	effect (may affect up to 1 in 100 people treated with filgrastim). These symptoms generally develop rapidly. Unless urgently treated, the condition results in a sharp drop in blood pressure that can lead to organ failure and death.	difficulty breathing, stomach swelling and feeling of fullness, and a general feeling of tiredness. Patients and stem cell donors should contact their doctor immediately if they develop these symptoms, which should be treated immediately.
Inflammation and scarring of the lungs (Interstitial pneumonia)	Inflammation of the lungs is uncommonly seen in cancer patients treated with filgrastim.	Doctors should monitor for signs such as cough, fever and difficulty breathing and stop Accofil if they occur.
Bleeding in the lungs (Pulmonary haemorrhage)	Bleeding in the lungs is uncommonly seen in cancer patients and stem cell donors. It may lead to respiratory failure or severe lung inflammation and breathing difficulty.	Doctors should monitor for signs such as cough, fever and difficulty breathing and stop Accofil if they occur.

Important potential risks

Risk	What is known
Cancer of the blood in stem cell donors (Malignant cell growth - haematological malignancy and myelodysplastic syndrome in healthy stem cell donors)	Temporary changes in cellular components have been seen in stem cell donors following filgrastim use. It is unknown if donors who develop these changes are at higher risk of developing leukaemia later on. More information is needed to better describe these risks, therefore stem cell donors should be followed for a long time (at least 10 years) after donation.
Theoretical risk of interaction with lithium	Since lithium promotes the release of a type of white blood cell called neutrophils, and filgrastim helps the body to make more neutrophils, there is a theoretical possibility that combination of these two substances could cause an increase in the white blood cell count above the normal range (leukocytosis). This interaction has not been formally investigated, and so far there is no evidence that use of both medicines together is harmful.
Risk of antibody production (immunogenicity) which may result in a lack of effect or allergic reactions	As with all large therapeutic proteins, there is a theoretical risk that patients treated with filgrastim may develop antibodies against the medicine possibly resulting in the medicine being not effective, or in allergic reactions. It is not known if or how frequently patients receiving filgrastim develop antibodies against the medicine and more information needs to be collected to confirm this.
Cytokine release	Some patients treated with filgrastim might potentially experience release into

Risk	What is known
syndrome	the bloodstream of cytokines (proteins that cause inflammation) similar to those found in severe infection. This can lead to symptoms such as fever, nausea, chills, low blood pressure, increased heart rate, headache, rash, scratchy throat, and difficulty breathing. In most patients the symptoms are mild to moderate and are managed easily. However, some patients may experience severe, life-threatening reactions requiring urgent medical attention and permanent discontinuation of filgrastim treatment.
Risks due to long-term use	Some patients have to use filgrastim for long periods of time (e.g. in severe chronic neutropenia or in human immunodeficiency virus - HIV). Although some risks of long-term use are known (e.g. development of leukaemias, inflammation of the blood vessels in the skin, loss of calcium from the bones), more information is needed to better describe these risks.
Use in unapproved conditions (Off-label use)	Doctors can decide to use filgrastim for the treatment of conditions for which the use of filgrastim is not approved. Possible adverse effects related to its use in these conditions are not well known.

Missing information

Risk	What is known
Pregnancy and breastfeeding	Accofil has not been tested in pregnant women, and the potential risk for the unborn baby is unknown. Accofil has also not been tested in breastfeeding women and its use is not recommended. The package leaflet for patients instructs women to ask their doctor or pharmacist for advice before taking this medicine if they are pregnant or breastfeeding, think they may be pregnant or are planning to have a baby.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as ‘routine risk minimisation measures’.

The SmPC and the package leaflet are part of the medicine’s product information. The product information for Accofil can be found on Accofil’s EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Post-approval study	To monitor and assess the long term safety of filgrastim in severe chronic neutropenia patients. To study the incidence and outcome of identified and potential risks.	Osteoporosis, splenomegaly/splenic rupture, cutaneous vasculitis cytogenetic abnormalities, myelodysplastic syndrome and leukaemia.	To be initiated post launch.	Interim analysis every 12 months after start of the study; Completion of study 10 years after start of the study; Submission of study report 11 years after start of the study
Post approval EBMT study	To evaluate the short and long term safety of healthy stem cell donors treated with filgrastim for the mobilisation of peripheral blood progenitor cells or PBPCs (for releasing stem cells from the bone marrow in donors).	Development of malignancy (haematological, non haematological); Development of autoimmune disease; Occurrence of pulmonary disorders (haemoptysis, lung infiltration, pulmonary haemorrhage)	To be initiated post launch.	Interim analysis every 12 months after start of the study; Completion of study 10 years after start of the study; Submission of studay report 11 years after start of the study

Neither of the above studies are conditions of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 08-2014.