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Summary of the risk management plan (RMP) for Ristempa (pegfilgrastim)

This is a summary of the risk management plan (RMP) for Ristempa, which details the measures to be taken in order to ensure that Ristempa 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 Ristempa, which can be found on Ristempa's EPAR page.

Overview of disease epidemiology

Ristempa is used to reduce the duration of neutropenia (abnormally low levels of neutrophils, a type of white blood cell) and the occurrence of febrile neutropenia (neutropenia with fever) in cancer patients that are receiving cytotoxic chemotherapy (medicines that treat cancer by killing cells) in order to help prevent infections.

Chemotherapy causes neutropenia (low levels of white blood cells) which can result in infection and illness. The more severe the neutropenia is and the longer it lasts, the greater the risk of infection. By increasing white blood cell counts Ristempa reduces the duration of neutropenia and the occurrence of febrile neutropenia (neutropenia with fever).

Up to 70% of cancer patients experience neutropenia. Factors that increase the risk of developing febrile neutropenia include the type of cancer and the 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 patients with a 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 who develop bacterial or fungal infections.

Summary of treatment benefits

Ristempa is the same as Neulasta, a medicine already authorised in the EU.

Ristempa has been studied in two main studies involving 467 patients with breast cancer who were being treated with cytotoxic chemotherapy. In both studies, a single injection of Ristempa was compared with multiple daily injections of another medicine, filgrastim, during each of four chemotherapy cycles. The main measure of effectiveness was the duration of severe neutropenia during the first cycle of chemotherapy.

Ristempa was as effective as filgrastim in reducing the duration of severe neutropenia. In both studies, the duration of severe neutropenia was around 1.7 days during the first chemotherapy cycle with Ristempa and filgrastim, compared with around five to seven days when neither medicine is used.

Unknowns relating to treatment benefits

Safety data on the use of Ristempa in children are limited. Ristempa has not been studied in women who are pregnant or breastfeeding. Ristempa should not be used during pregnancy unless clearly necessary. Women who are breastfeeding should not take Ristempa.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Enlarged spleen or rupture of spleen (severe splenomegaly/splenic rupture)	Enlarged spleen occurs uncommonly (in less than 1 patient in 100) with Ristempa. Enlarged spleen can increase the risk of splenic rupture, which could result in a fatal outcome if not detected and treated in a timely manner.	Patients should contact their doctor if they experience left upper belly (abdominal) pain, pain below the left rib cage or pain at the tip of their shoulder, which could indicate an enlarged or ruptured spleen.
Inflammation of the blood vessels in the skin (cutaneous vasculitis)	Inflammation of the blood vessels in the skin is uncommon in patients receiving Ristempa. When limited to small blood vessels in the skin, recovery is generally good.	Patients should contact their doctor if they experience changes to their skin such as purple or red spots or bumps, clusters of small dots, splotches, bruises, or hives.
Plum-coloured, raised, painful sores on the limbs and sometimes the face and neck with a fever (Sweet's syndrome)	Sweet's syndrome is an uncommon side effect in patients treated with Ristempa.	Treatment of conditions that increase the risk of Sweet's syndrome, such as infection, can help prevent Sweet's syndrome.
Severe allergic reaction (anaphylactic reaction)	Allergic reactions, including severe allergic reaction (anaphylaxis), skin rash and/or hives (urticaria), have occurred uncommonly in patients receiving Ristempa.	Patients who are allergic to pegfilgrastim or any of the other ingredients in the medicine must not receive Ristempa. 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 Ristempa again. Ristempa should not be administered to patients with a history of hypersensitivity to pegfilgrastim or filgrastim. Patients should contact their doctor if they have serious allergic-type reactions, including redness and flushing, skin rash, and raised

Risk	What is known	Preventability
		areas of the skin that itch; and serious allergic reactions, including anaphylaxis (weakness, drop in blood pressure, difficulty breathing, swelling of the face).
Leakage of fluid from small blood vessels into nearby body cavities and muscles (capillary leak syndrome)	Leakage of fluids from small blood vessels can result in low blood pressure (hypotension), overly concentrated blood (hemoconcentration), and low levels of the protein albumin in the blood (hypoalbuminemia). This condition, which can be life-threatening if treatment is delayed, has been reported rarely (affecting less than 1 patient in 1000) with Ristempa treatment.	Patients should contact their doctor if they have 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. Patients should contact their doctor immediately if they develop these symptoms, which should be treated immediately.
Severe lung inflammation causing difficulty in breathing (serious pulmonary adverse events including interstitial pneumonia and acute respiratory distress syndrome [ARDS])	ARDS has occurred uncommonly (less than 1 patient in 100) with Ristempa.	Patients should contact their doctor if they have symptoms such as cough, fever and shortness of breath that could be preliminary signs of ARDS. Ristempa treatment may be discontinued and appropriate treatment given.
Worsening of inherited blood disorder that affects red blood cells (sickle cell crisis in patients with sickle cell disease)	Sickle cell crises with symptoms such as severe pain in the bones, chest, gut, or joints have occurred uncommonly (less than 1 patient in 100) in patients with sickle cell disease receiving Ristempa.	Patients with sickle cell disease should receive Ristempa only after careful evaluation of the risks and benefits of treatment. Patients should tell their doctor if they have sickle cell disease, anaemia (low red blood cell counts), or related conditions that cause red blood cells to form a sickle shape.
Pain in muscle and/or bone (musculoskeletal pain-related symptoms)	Musculoskeletal pain-related symptoms occur very commonly in patients receiving chemotherapy and Ristempa (in more than 1 patient in 10). Musculoskeletal pain-related symptoms are generally mild to moderate in severity and can be treated with a painkiller.	Patients should contact their doctor if they have musculoskeletal pain-related symptoms, and general aches and pains in the joints and muscles. No information is currently available on how to prevent this event.
Increase in white blood	Ristempa is given in order to increase the level of white blood cells; thus,	Regular monitoring of white blood cell count is recommended while

Risk	What is known	Preventability
cells (leukocytosis)	there is a potential for an excessive increase in white blood cells (leukocytosis). Leukocytosis has been reported uncommonly in patients receiving Ristempa (less than 1 patient in 100).	taking Ristempa. Dose reduction or interruption may correct leukocytosis.
Decrease in levels of blood cells (platelets) that help the blood to clot (thrombocytopenia)	Low platelet levels have been reported commonly (in more than 1 patient in 100) in clinical studies with Ristempa.	Patients' platelet count should be checked regularly during Ristempa treatment.

Important potential risks

Risk	What is known
Cancer of the blood (acute myelogenous leukaemia [AML])/disorders that occur when the blood-forming cells of the bone marrow are damaged (myelodysplastic syndrome [MDS])	Since Ristempa stimulates the production of white blood cells, there is a theoretical possibility that Ristempa could be associated with the development of cancer of the blood (AML) or disorders that occur when the blood-forming cells in the bone marrow are damaged (MDS). Although it is not known whether Ristempa is associated with this risk, Ristempa should be used with caution in patients with AML and not be used in patients with MDS.
Release of immune-stimulating substances (cytokines) (cytokine release syndrome)	There have been reports of cytokine release syndrome possibly be related to pegfilgrastim. Cytokine release syndrome is characterised by symptoms such as nausea (feeling sick), headache, rapid heart rate, low blood pressure, rash, and shortness of breath. Most reactions are mild-to-moderate; however, the reaction may be severe, life-threatening, or fatal. Some patients may experience severe, life-threatening reactions requiring urgent medical attention and permanent discontinuation of Ristempa treatment.
Medication errors, including overdose	The effects of overdose of Ristempa are not known. Patients should tell their doctor if they receive more Ristempa than the doctor prescribed.
Drug interaction with lithium	The effects of using this medicine at the same time as lithium are not known. Since lithium promotes the release of a type of white blood cell called neutrophils, and Ristempa helps the body to make more neutrophils, there is a theoretical possibility that combination of these 2 substances could cause an increase in the white blood cell count to above the normal range (leukocytosis). This interaction has not been formally investigated, and so far there is no evidence that the use of both medicines together is harmful.

Risk	What is known
Use outside of its approved indications (off-label use)	It is known that pegfilgrastim has been used off-label to treat AML, MDS, peripheral blood stem cell apheresis/harvest, idiopathic neutropenia/agranulocytosis, and unspecified leukaemia. Information on how well Ristempa works in other conditions or what side effects could be seen is not available.
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 Ristempa may develop antibodies against the medicine, possibly resulting in the medicine not being effective or in allergic reactions. It is not known if or how frequently patients receiving Ristempa develop antibodies against the medicine and more information needs to be collected. While a small number of patients have shown an immune response to Ristempa, the response did not impact the activity of the protein, so that Ristempa was still effective, and the patients did not experience any adverse effects.
Formation and development of blood cells occurring outside of the inner space of the bone (extramedullary hematopoiesis)	Blood cells are normally produced in the inner space of bones (medullary cavity). When blood cells begin to form outside the medullary cavity, this can lead to blood disorders. It is possible that Ristempa could increase this effect.

Missing information

Risk	What is known
Use in children under 18 years of age	Information on the safety of Ristempa in children is limited.
Risks during pregnancy and breastfeeding	Ristempa has not been studied in pregnant women. Ristempa should not be used during pregnancy unless clearly necessary. Ristempa has not been studied in breastfeeding women. Women who are breastfeeding should not take Ristempa. The patient leaflet 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 Ristempa can be found on Ristempa's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

Not applicable

Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 03-2015.