Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
CSF antibodies		

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Reduction in the duration of the decrease in neutrophils (the main part of the white blood cells) after a bone marrow or blood stem cell transplant. Bone marrow is the soft tissue inside bones that makes blood cells. Blood stem cells are cells that can be collected from the blood stream following treatment with G-CSF.

- An organisation collecting information from 45 countries (including 39 Europeancountries) on the number of blood stem cell transplantations conducted per year, determined there were about 21,000 patients with cancer (not involving or affecting bone marrow) in 2010, who underwent blood stem cell transplantations. Prior to the stem cell transplantation, these patients first receive treatment to suppress bone marrow cell growth. Due to the treatment these patients experience a reduction in white blood cells (the cells defending the body against infections and foreign materials). Lenograstim is used to reduce the duration of having a reduction in white blood cells.

After cancer treatment, if the level of white blood cells is too low (called ‘neutropenia’)

- Nearly all chemotherapy used for cancer treatment will cause a reduction in the number of white blood cells (defending the body against infections and foreign materials), making patients more likely to suffer from infections. However, the severity may differ by type of chemotherapy. Most information is available for patients receiving chemotherapy for breast cancer and lymph gland cancer. About 17 to 36% of these patients experience a lack of white blood cells with fever. In patients receiving chemotherapy for cancer of the lymph glands, 25 to 50% experience a lack of white blood cells with fever. One study in patients with cancer of the breast, lung or ovaries found that 7% of the patients experienced a severe decrease of white blood cells with fever.

When patients need to increase their own blood stem cells or when people want to donate blood stem cells

- Certain blood stem cells are capable of forming mature blood cells, such as red blood cells (cells carrying oxygen), platelets (cells helping blood to clot) and white blood cells (defending the body against infections). Lenograstim can be used to encourage the bone marrow to produce extra blood stem cells, which can be collected from the blood of patients or donors. The blood stem cells can then be stored and given back to a patient in a transfusion with the purpose to restore their immune system. Healthy donors can donate blood stem cells to someone who needs them. In 2010 about 17,000 patients with cancer not involving or affecting bone marrow received a transfusion with their own blood stem cells and a further 12,000 patients received blood stem cells from donors.

VI.2.2 Summary of treatment benefits

- For the European Union (EU) indication ‘reduction in the duration of low white blood cell counts (neutropenia) in patients with cancer not involving or affecting bone marrow who are first treated

to suppress bone marrow cell growth, thereafter followed by bone marrow transplantation', beneficial effects of lenograstim on absolute neutrophil counts (neutrophils are a type of white blood cells defending the body against infections) were shown in 1 study to see if lenograstim was effective to treat this condition,and 2 studies to evaluate and expand information on safety and usefulness of lenograstim, in approximately 460 patients.

- For the EU indication 'reduction of low white blood cell count (neutropenia) caused by chemotherapy', beneficial effects of lenograstim were studied in 3 studies to see if lenograstim was effective to treat this condition, 4 studies to evaluate and expand information on safety and usefulness of lenograstim and 2 studies evaluating effectiveness, safety and usefulness. These research studies, (in which lenograstim treatment was compared to standard (control) treatment), included approximately 1,700 patients with breast-, lung-, lymph gland-, soft tissue or solid cancer, and two types of acute blood cancer. Lenograstim effects were evaluated on white blood cell counts, duration of low white blood cell counts, number of documented infections, chemotherapy effect, and recovery time to normal levels of white blood cells and platelets.
- For the EU indication 'mobilisation of blood stem cells into the peripheral blood', beneficial effects of lenograstim were studied in 4 studies to see if lenograstim was effective to treat this condition,and 1 study to evaluate and expand information on safety and usefulness of lenograstim, including about 260 patients with Hodgkin's disease, lymph gland-, or breast cancer, chronic blood cancer arising from abnormal growth in the blood-forming tissue of the bone marrow, acute blood cancer and a bone marrow disorder in which the bone marrow does not produce enough healthy blood cells.

VI.2.3 Unknowns relating to treatment benefits

Lenograstim is not recommended for use in children below 2 years of age because lenograstim has not been studied in this age group.

VI.2.4 Summary of safety concerns

Important identified risks for patients

Risk	What is known	Preventability
Serious pulmonary adverse events/ Acute respiratory distress disorder (ARDS) (adverse effects in the lungs, including scarring of the tissue and space around the air sacs of the lungs (so called "interstitial pneumonia")/serious breathing disorder	Rare adverse effects in the lungs, in particular scarring of tissue and space around the air sacs of the lungs), have been reported after administration of lenograstim or other products of the same class of medicines. Patients, who have recent experienced fluid in their lungs or a lung infection may be at higher risk. Rare cases of acute respiratory distress syndrome, a serious breathing disorder, have been reported with lenograstim.	Patients with risk factors (recent episode of fluid in the lungs or a lung infection) should be monitored. In patients, who develop acute lung symptoms such as cough, shortness of breath, and fever, in association with signs of fluid in their lungs and decreased function of the lungs, lenograstim treatment should be discontinued.
Acute febrile neutrophilic dermatosis,	Very rarely, a disorder characterized	There are no recommended

Risk	What is known	Preventability
a disorder characterized by fever, high white blood cell counts in blood, and tender, red skin papules and plaques that contain fluid overloaded with white blood cells (called “Sweet’s syndrome”)	by fever, high white blood cell counts in blood, and tender, red skin papules and plaques that contain fluid overloaded with white blood cells (Sweet’s syndrome), has been reported after administration of lenograstim or other products of the same class of medicines. Sweet’s syndrome has been mainly described in patients with blood cancer, but has also been noted in patients with low white blood cell counts not caused by cancer.	measures to prevent the development of Sweet’s syndrome. If severe Sweet’s syndrome develops, lenograstim administration should be interrupted until the event resolves.
Enlargement/rupture of the spleen	Enlargement of the spleen without symptoms is common. Rupture of the spleen has been reported very rarely following administration of lenograstim or other products of the same class of medicines.	Spleen size should be carefully monitored (for example by clinical examination or ultrasound). A rupture of the spleen may be suspected when left upper abdominal pain or shoulder tip pain is reported by the patient.
Anaphylactic shock (a serious, potentially life-threatening allergic reaction) including hypersensitivity	Allergic reactions including anaphylaxis have been reported very rarely after the first subcutaneous administration of lenograstim. The tip cap composition of the water for injection (Wfl)-pre-filled syringe used for reconstitution of the drug product contains latex rubber which may cause severe allergic reactions in susceptible patients.	Lenograstim should not be administered to patients with known hypersensitivity to lenograstim, or to any of its excipients. Patient with know hypersensitivity to latex should use another syringe than the one provided for reconstitution of the drug solution before administration.
Thrombocytopenia (reduced number of platelets in the blood)	A low platelet count in the blood is a very commonly observed adverse effect following administration of lenograstim.	Routine blood tests can help to identify decreases in platelet counts and allow for the lenograstim dosing regimen to be adjusted as appropriate.
Leukocytosis (an increase in the number of certain types of white blood cells)	A high white blood cell count is common in patients with cancer or for example conditions like infections and can also be a reaction to stress or intensive exercise. It is also the effect of the activity of lenograstim.	Since leukocytosis may develop, changes in blood test results should be monitored. Product information for health care professionals states that lenograstim should be stopped if patients develop leukocyte counts

Risk	What is known	Preventability
		higher than certain levels.
Capillary leak syndrome (a reversible leaking of blood plasma (from blood vessels into the space between the cells of the blood vessels and/or the surrounding tissue) and collapse of blood vessels, accompanied by an increase in the proportion of red blood cells in the blood and abnormal low level of albumin (a protein) in the blood)	Capillary leak syndrome, a medical condition consisting of reversible leaking of blood plasma, collapsing of blood vessels, an increase of red blood cells and abnormal low levels of a specific protein (albumin) in the blood, has been reported uncommonly following administration of lenograstim or other products of the same class of medicines.	Capillary leak syndrome is characterised by low blood pressure, low protein in blood, swelling due to fluid accumulation in e.g. hands or feet and thickening of the blood. Lenograstim should be stopped if patients develop symptoms of capillary leak syndrome and appropriate treatment for the symptoms should be given, which may include a need for hospital admission and/or treatment in an intensive care unit
Cutaneous vasculitis (inflammation of small or medium sized blood vessels in the skin)	Inflammation of small or medium sized blood vessels in the skin occurs in the setting of an underlying process, such as a medication exposure, infection, cancer, or connective tissue disease (a disease of the connective tissues of the body, which are the structural portions of the body that hold the cells of the body together), or as a manifestation of inflammation of blood vessel walls. It has been reported very rare following administration of lenograstim or other comparable products.	Cutaneous vasculitis is characterised by skin problems like red raised bruises on the legs or ulcers on the body with fever and joint pain. If patients develop these signs or symptoms, they should contact a doctor or pharmacist for advice.

Important potential risks for patients

Risk	What is known (Including reason why it is considered a potential risk)
Chromosomal abnormality (transient chromosomal changes), that is missing, extra, or irregular portion of one or more of the chromosomes (the parts in your cells that contain the genetic information)	Transient changes in one or more chromosomes (the parts in your cells that contain the genetic information) have been observed (for example missing, extra, or irregular portions) following the use of a protein, called granulocyte colony stimulating factor. This protein, that stimulates the bone marrow to produce granulocytes (a type of white blood cells) and stem cells is normally made by the body, but it is also produced in the form of medicines like lenograstim. The significance of these changes is unknown.
Leukaemia , a cancer of the blood with overproduction of immature white blood cells / Myelodyspastic syndrome, a medical	In laboratory tests it was found that the protein called granulocyte colony stimulating factor that is normally produced by your own body, but which is also used in medicines such as lenograstim, can promote growth of blood-forming cells in bone marrow (types of white blood cells) and similar effects

Risk	What is known (Including reason why it is considered a potential risk)
condition with too low or abnormal production of a specific type of blood cells	may be seen on some other cells outside bone marrow. Clinical research could not reveal if lenograstim influences the progression of myelodysplastic syndrome (a certain medical condition, in which the bone marrow does not produce enough or abnormal blood cells of a specific type, to acute myeloid leukaemia (an acute type of blood cancer, characterised by an overproduction of immature white blood cells from the bone marrow.
Promotion of cancer cell growth (promotion of cell division of cells with changes in the cell DNA, the parts of your cells that contain the genetic information)	In laboratory tests it was found that the protein called granulocyte colony stimulating factor that is normally produced by your own body, but which is also used in medicines such as lenograstim, can promote growth of blood-forming cells in bone marrow (granulocytes and monocytes which are a type of white blood cells) and similar effects may be seen on some other cells outside bone marrow. Clinical research could not reveal if lenograstim influences the progression of a certain medical condition, in which the bone marrow does not produce enough or abnormal blood cells of a specific type, to a type of blood cancer characterised by an overproduction of immature white blood cells from the bone marrow.
Secondary cancer, another cancer that develops as a complication to the intial diagnosed form of cancer	In laboratory tests it was found that the protein called granulocyte colony stimulating factor that is normally produced by your own body, but which is also used in medicines such as lenograstim, can promote growth of blood-forming cells in bone marrow (granulocytes and monocytes which are a type of white blood cells) and similar effects may be seen on some other cells outside bone marrow. Clinical research could not reveal if lenograstim influences the progression of a certain medical condition, in which the bone marrow does not produce enough or abnormal blood cells of a specific type, to a type of blood cancer characterised by an overproduction of immature white blood cells from the bone marrow. An increased risk of another type of blood cancer, that arises from abnormal growth in the blood-forming tissue of the bone marrow (and a certain medical condition, in which the bone marrow does not produce enough or abnormal blood cells of a specific type, after the use of the protein normally produced by your own body, called granulocyte colony stimulating factor, but which is also used in medicines like as lenograstim, has been reported in children with acute type of blood cancer, characterized by the overproduction of cancerous, immature white blood cells—known as lymphoblasts. A similar risk has been found in 25 clinical studies among in total 12,804 adult patients with solid tumours or lymph gland cancer). However, for the adult patients in these studiesthis risk did not had a negative impact on the outcome of their disease in the long run.
Graft versus host disease, a medical condition which is a complication of	Blood stem cell transplantation may be associated with an increased risk for chronic medical disease which is a complication of the stem cell

Risk	What is known (Including reason why it is considered a potential risk)
blood stem cells transplantation from a donor to a patient	transplantation from a donor to a patient. In this disease, particular types of white blood cell in the donated stem cells attack the patient's own body cells, because the donated cells (the graft) see the patient's body cells (the host) as foreign and attack them.
Cytokine release syndrome (an infusion reaction, resulting from the release of cytokines (small proteins affecting the behaviour of other cells)	In cytokine release syndrome, symptoms such as fever, nausea, chills, low blood pressure, rapid heartbeat, extreme fatigue or drowsiness, headache, rash, scratchy throat, and shortness of breath can occur. In most patients, the symptoms are mild to moderate in severity and are managed easily. However, some patients may experience severe, life-threatening reactions that result from massive release of cytokines. So far there are no known cases of cytokine release syndrome in patients treated with lenograstim. In the international literature there is no evidence of a connection between granulocyte colony stimulating factor (such as lenograstim) and cytokine release syndrome.
Sickle cell crisis in patients with sickle cell disease (occlusions in blood vessels leading to severe pain in patients wih sickle cell disease)	Sickle cell disease refers to an inherited blood disorder that affects red blood cells. Red blood cells become sickle-shaped. The sickle-shaped red blood cells are hard and sticky and do not easily pass through blood vessels. Therefore, blood vessels can sometimes become clogged, preventing blood from flowing through them. A clogged blood vessel is called an "occlusion." Occlusions in blood vessels can lead to severe pain. Although not the only form, this is the most common type of what is called a "sickle cell crisis". Sickle cell crises, in some cases fatal, have been reported with the use of other G-CSFs in patients with sickle cell disease.
Immunogenicity related to incidence and clinical implications of anti-G-CSF antibodies (development of antibodies which neutralise lenograstim's activity or cause other side effects)	Medicines like lenograstim that are "foreign" proteins given by injection can cause the body to react by making antibodies (disease-fighting substances in the blood). Sometimes antibodies against medicines can cause the medicines to work less effective or cause other side effects such as severe allergic reactions. In animal studies, development of antibodies to lenograstim was seen but this did not seem to cause the medicine to work less effective or to cause side effects.

Missing information for patients

Risk	What is known
Limited information on use in children < 2 years-old (off-label use)	There is insufficient information on the effects of lenograstim in patients < 2 years-old. Therefore, lenograstim is not indicated for use in these patients.
Limited information on use in pregnant and lactating women	There is insufficient information on the effects of lenograstim in pregnant or breast-feeding women and the offspring. Studies in animals have shown reproductive toxicity. The use of lenograstim during pregnancy is not recommended, unless strictly necessary. The use of lenograstim during breast-feeding is neither recommended because it is unknow whether the drug is excreted in breast-milk.

Important identified risks for donors

Risk	What is known	Preventability
Thrombocytopenia (reduced number of platelets in the blood)	A low blood platelet count in the blood is a very commonly observed adverse effect following administration of lenograstim.	Routine blood tests can help to identify decreases in values and allow for the regular amount of lenograstim given to be adjusted as appropriate. Leukapheresis (a method used to selectively separate and remove certain white blood cells (leukocytes) from withdrawn blood,) should not be performed in donors, who use blood thinning drugs or who have known defects in their blood clotting. If more than one leukapheresis session is required, particular attention should be paid to donors with platelet count below a certain value (below 100 million platelets per liter blood) prior to blood being drawn from the donor and separated into different components, such as platelets and specific white blood cells. In general this withdrawal of blood from a donor (including a specific component kept separate) should not be done if the donor's platelets are lower than 75 million platelets per liter of blood.
Leukocytosis (an increase in the number of certain types of white blood cells)	A high white blood cell count is common in patients with cancer or for example with conditions like infections and can also be a reaction to stress or intensive exercise. It is also the effect of the activity of lenograstim.	Since leukocytosis may develop, changes in blood test results should be monitored. Lenograstim should be stopped if donors develop leukocyte counts higher than certain levels.
Enlargement/rupture of the spleen	Enlargement of the spleen without symptoms is common. Rupture of the spleen has been reported very rarely following administration of lenograstim or other products of the same class of medicines.	Spleen size should be carefully monitored (for example by clinical examination or ultrasound). A rupture of the spleen may be suspected when left upper abdominal pain or shoulder tip pain is reported by the donor.
Anaphylactic shock (a serious, potentially life-threatening allergic	Allergic reactions including anaphylaxis have been reported very	Lenograstim should not be administered to donors with known

Risk	What is known	Preventability
reaction) including hypersensitivity	rarely after the first subcutaneous administration of lenograstim. The tip cap composition of the Wfl pre-filled syringe used for reconstitution of the drug product contains latex rubber which may cause severe allergic reactions in susceptible donors.	hypersensitivity to lenograstim or to any of its excipients. Donors with know hypersensitivity to latex should use another syringe than the one provide for reconstitution of the drug solution before administration.
Capillary leak syndrome (a reversible leaking of blood plasma (from blood vessels into the space between the cells of the blood vessels and/or the surrounding tissue) and collapse of blood vessels, accompanied by an increase in the proportion of red blood cells in the blood and abnormal low level of albumin (a protein) in the blood)	Capillary leak syndrome, a medical condition consisting of reversible leaking of blood plasma, collapsing of blood vessels, an increase of red blood cells and abnormal low levels of a specific protein (albumin) in the blood, has been reported uncommonly following administration of lenograstim or other products of the same class of medicines.	Capillary leak syndrome is characterised by low blood pressure, low protein in blood, swelling due to fluid accumulation in e.g. hands or feet and thickening of the blood. Lenograstim should be stopped if patients develop symptoms of capillary leak syndrome and appropriate treatment for the symptoms should be given, which may include a need for hospital admission and/or treatment in an intensive care unit
Cutaneous vasculitis (inflammation of small or medium sized blood vessels in the skin).	Inflammation of small or medium sized blood vessels in the skin occurs in the setting of an underlying process, such as a medication exposure, infection, cancer, or connective tissue disease (a disease of the connective tissues of the body, which are the structural portions of the body that hold the cells of the body together), or as a manifestation of inflammation of blood vessel walls. It has been reported very rare following administration of lenograstim or other comparable products.	Cutaneous vasculitis is characterised by skin problems like red raised bruises on the legs or ulcers on the body with fever and joint pain. If patients develop these signs or symptoms, they should contact a doctor or pharmacist for advice.

Important potential risks for donors

Risk	What is known (Including reason why it is considered a potential risk)
Chromosomal abnormality (transient chromosomal changes), that is missing, extra, or irregular portion of	Transient changes in one or more chromosomes (the parts in your cells that contain the genetic information) have been observed (for example missing, extra, or irregular portions) following the use of a protein, called granulocyte

Risk	What is known (Including reason why it is considered a potential risk)
one or more of the chromosomes (the parts in your cells that contain the genetic information)	colony stimulating factor. This protein, that stimulates the bone marrow to produce granulocytes (a type of white blood cells) and stem cells releasing them into the bloodstream, is normally made by your body, but it is also produced in the form of medicines like lenograstim. The significance of these changes is unknown.
Promotion of cancer cell growth (promotion of cell division of cells with changes in the cell DNA, the parts of your cells that contain the genetic information	In laboratory tests it was found that the protein called granulocyte colony stimulating factor that is normally produced by your own body, but which is also used in medicines such as lenograstim, can promote growth of blood-forming cells in bone marrow (granulocytes and monocytes which are a type of white blood cells) and similar effects may be seen on some other cells outside bone marrow. In several countries, donors are being followed for a longer period of time to monitor their health. Nevertheless, the risk of donors developing cancerous bone marrow cell clones following the treatment with lenograstim cannot be excluded.
Cytokine release syndrome (an infusion reaction, resulting from the release of cytokines (small proteins affecting the behavior of other cells).	In cytokine release syndrome, symptoms such as fever, nausea, chills, low blood pressure, rapid heartbeat, extreme fatigue or drowsiness, headache, rash, scratchy throat, and shortness of breath can occur. In most patients, the symptoms are mild to moderate in severity and are managed easily. However, some patients may experience severe, life-threatening reactions that result from massive release of cytokines. So far there are no known cases of cytokine release syndrome in patients treated with lenograstim. In the international literature there is no evidence of a connection between granulocyte colony stimulating factor (such as lenograstim) and cytokine release syndrome.
Multiple sclerosis, an inflammatory disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged	After treatment with granulocyte colony stimulating factor (such as lenograstim), the health of donors is being monitored over time (called follow-up). Based on the results of this follow-up, the authorities requested donors to beclosely monitored for the development ofmultiple sclerosis. So far there is no evidence of a connection between the development of multiple sclerosis and the use of lenograstim.
Arthritis, a form of joint disorder that involves inflammation (the response of your blood vessels to harmful things like damage of the walls) of one or more joints	After treatment with granulocyte colony stimulating factor (such as lenograstim), the health of donors is being monitored over time (called follow-up). Based on the results of this follow up, the authorities requested donors to be closely monitored for the development of arthritis. So far there is no evidence of a connection between the development of arthritis and the use of lenograstim.
Immunogenicity related to incidence and clinical implications of anti-G-CSF antibodies (development of antibodies which neutralise lenograstim's activity or cause other	Medicines like lenograstim that are "foreign" proteins given by injection can cause the body to react by making antibodies (disease-fighting substances in the blood). Sometimes antibodies against medicines can cause the medicines to work less effective or cause other side effects such as severe allergic reactions.

Risk	What is known (Including reason why it is considered a potential risk)
side effects)	In animal studies, development of antibodies to lenograstim was seen but this did not seem to cause the medicine to work less effective or to cause side effects.

Missing information for donors

Not applicable.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a document called the Summary of Product Characteristics (SmPC), which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. A shortened version of this document in lay language, intended for the use by the patients, is provided in the form of so called Package Leaflet (PL). The information on the correct use of the medicine, including possible warnings for patients with specific diseases and the possible or known side effects of the medicine, in these documents are known as routine risk minimisation measures.

For this medicine the company uses additional tools outside SmPC and PL to encourage and ensure the safe and effective use of lenograstim (additional risk minimisation measures), i.e. additional communication in the form of a direct health care professional communication (DHPC). This is a letter by which important information is delivered directly to individual healthcare professionals by a company bringing a medicine onto the market or by the responsible health authorities from the country/ies where the medicine is being sold, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product in order to protect the health of their patients.

These additional risk minimisation measures are for the following risks:

Safety concern in lay terms: Reversible leaking of blood plasma (from blood vessels into the space between the cells of the blood vessels and/or the surrounding tissue) and collapse of blood vessels accompanied by an increase in the proportion of red blood cells in the blood and abnormal low level of albumin (a protein) in the blood.

Safety concern in medical terms: Capillary leak syndrome

Risk minimisation measure: Direct health care professional communication
Objective and rationale
Additional communication to healthcare professionals (HCPs) is needed to inform HCPs about the risk of capillary leak syndrome.
Additional communication will include: Communication to prescribers of lenograstim to inform them about the risk of capillary leak syndrome by means of a letter. This letter was disseminated in all EU member states where lenograstim is marketed, and in agreement with the national competent authorities. The letter distribution started on 17 February 2014 in Lithuania and was completed in all EU countries on 23 May 2014. On request of the UK National Competent Authority the letter was not distributed in the UK to avoid duplication of messages, because a letter on capillary leak syndrome was already distributed by Amgen in the UK in August 2013.

VI.2.6 Planned post authorisation development plan

There are no planned or ongoing post-authorisation safety studies for lenograstim and no ongoing or proposed post-authorisation efficacy studies for lenograstim.

VI.2.7 Summary of changes to the Risk Management Plan over time

The summary of significant changes to the RMP over time, is provided in the table below.

Version	Date	Safety Concerns	Comment
1.0	13-Feb-2014		First version of the lenograstim RMP.
1.1	09-Oct-2014	Leukocytosis added as important identified risk for patients Cutaneous vasculitis added as important identified risks for patients and donors Sickle cell disease crisis added as important potential risk for patients Serious pulmonary adverse events (including interstitial pneumonia and ARDS) added as important identified risk for patients Interstitial lung disease/Acute respiratory distress disorder removed as important identified risk for patients Severe splenomegaly/splenic rupture added as important identified risk for patients and donors. Splenic rupture removed as important identified risk for patients and donors Use in pregnant and lactating women added as missing information in patients Use in children <2 years old (off-label use) added as missing information in patients Capillary leak syndrome (CLS)	The previous term Interstitial lung disease/Acute respiratory distress disorder for patients was updated to Serious pulmonary adverse events (including interstitial pneumonia and ARDS) for patients. The previous term Splenic rupture was updated to Severe splenomegaly/splenic rupture for patients and donors. The start and completion date of the dissemination of the DHPC letter on CLS in European countries was included.
1.2	2 - an-2015	Sickle cell disease crisis removed as important potential risk for patients Sickle cell crisis in patients with SCD added as important potential risk for patients Immunogenicity related to incidence	The previous term Sickle cell disease crisis was updated to Sickle cell crisis in patients with SCD