Package leaflet: Information for the patient

Zemcelpro ≥ 0.23×10^6 viable CD34+ cells/mL / ≥ 0.53×10^6 viable CD3+ cells/mL dispersion for infusion
dorocubicel/ unexpanded CD34- cells

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zemcelpro is and what it is used for

Zemcelpro is a blood-based cell therapy. This medicine is specifically made for you from human blood stem cells (cells in your blood that can grow into any other type of blood cell) that are taken from donated umbilical cord blood. The medicine contains both the active substance dorocubicel together with unchanged donor cells (called CD34- cells).

Zemcelpro is used to treat adults with blood cancers who need a blood stem cell transplant after chemotherapy, and who don't have an available suitable donor.

How does Zemcelpro work
The blood stem cells in this medicine are changed and multiplied in the laboratory. This ensures they will work optimally to treat you. Before you are given this medicine, you will be given chemotherapy to destroy the cancer cells in your blood. When you are then given Zemcelpro, the new stem cells in this medicine will replace your own stem cells. This will help your immune system (your body's natural defences) protect you against or fight blood cancer.

If you have any questions about how Zemcelpro works or why Zemcelpro has been prescribed for you, ask your doctor.

2. What you need to know before you are given Zemcelpro

You must not be given Zemcelpro
- If you are allergic to any of the ingredients of this medicine (listed in section 6).
- If you cannot tolerate an appropriate chemotherapy treatment prior to receiving Zemcelpro.

Warnings and precautions

Zemcelpro is specifically made for you from donor blood cells and should only be given to you.

Before you are given Zemcelpro, tell your doctor if
- you notice the symptoms of your cancer are getting worse (such as fever, feeling weak, bleeding gums or bruising);
- have signs of infections (such as fever, cough, chills, sore throat).

Your doctor will check your lungs, heart and blood pressure, your blood for your general health status, and if your leukaemia (blood cancer) is getting worse.

During or after you have been given Zemcelpro
Tell your doctor or nurse immediately if you have any of the following:
- Chest tightness, cough, difficulty swallowing, dizziness, fast heartbeat, swelling, rash, itching, trouble breathing, while or after using this medicine. These may be symptoms of a serious allergic or infusion-related reactions that may warrant pausing or stopping the therapy (see section 3 – How Zemcelpro is given.
- Fever, which may be a symptom of an infection. Take your temperature twice a day for 3-4 weeks after treatment with Zemcelpro. If your temperature is high, see your doctor immediately as some infections may be life-threatening.
- Diarrhoea, fever, rash, unexplained weight gain, or yellow eyes (jaundice). These may be symptoms of serious conditions called graft-versus-host-disease (GvHD) or engraftment syndrome. They may be life threatening and additional treatment may be required.
- General feeling of illness, swollen glands, weight loss, or yellow skin and eyes. These may be signs of a secondary cancer, such as post-transplant lymphoproliferative disorder. Your doctor may administer additional tests.
- Shortness of breath, chest pain, fever, blood in the sputum may be signs of a pulmonary alveolar haemorrhage (PAH). PAH may be life-threatening that require additional treatment.
- Shortness of breath, cough, and fever may be signs of a pneumonitis (inflammation of your lungs). Pneumonitis, including Cryptogenic Organizing Pneumonia (COP) and Idiopathic Pulmonary Syndrome (IPS) may be life-threatening, and additional treatment may be required.
- Recurrent infections may be signs of a hypogammaglobulinaemia that may require additional treatment.
- Jaundice, liver tenderness (under the right ribs), fluid in the abdomen and sudden weight gain may be sign of veno-occlusive disease that may require specific treatment.
- Vomiting, bloody diarrhoea, stomach pain, fever, chills and headache may be sign of haemolytic uremic syndrome (HUS).
- Serious or frequent bleedings or infections may be sign of graft failure, a life-threatening condition that requires specific attention.

Zemcelpro is made from donated human blood. Some human blood products have transmitted certain viruses (such as HIV, hepatitis B or C) or may be related with theoretical risks associated with the donor (e.g. malignancies or genetic diseases) to people who have received them, although the risk is low. Human donors and donated blood are both tested for viruses to keep the transmission risk low. Talk with your doctor if you have concerns about this risk.

Your doctor will regularly monitor your blood counts after you receive Zemcelpro as you may experience a reduction in the number of blood cells and other blood components.

Speak to your doctor before considering donating blood, organs, tissues or cells.

Children and adolescents
Zemcelpro is not recommended to be used in children and adolescents below 18 years of age. This is because there is limited experience in this age group.

Other medicines and Zemcelpro
Before you are given Zemcelpro tell your doctor if you are taking, have recently taken or might take any other medicines, including live vaccines and medicines obtained without a prescription. This is because other medicines can affect the way Zemcelpro works.

Pregnancy and breast-feeding
Zemcelpro is not recommended during pregnancy and during breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine.

The effects of Zemcelpro during pregnancy are not known. This medicine may harm your unborn baby or your newborn/infant.
- If you become pregnant or think you may be pregnant after treatment with this medicine, talk your doctor immediately.
- If you are a woman who is able to have a baby, you will be given a pregnancy test before treatment starts. Zemcelpro should only be given if the result shows you are not pregnant.

It is not known if this medicine passes into breast milk. This medicine may harm your nursing infant.

Contraception
Effective methods of contraception should be used in males and females of reproductive potential who have received Zemcelpro. Talk to your doctor about them.

Driving and using machines
It is unknown whether Zemcelpro has an influence on your ability to drive and use machines. Medicines used in conjunction with Zemcelpro could cause fatigue or decrease alertness. Refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery during this initial period.

Zemcelpro contains sodium, potassium and dimethyl sulfoxide (DMSO)
This medicine contains 477 mg sodium per dose. This is equivalent to 24% of the recommended maximum daily dietary intake of sodium for an adult. You should be observed closely during the infusion period.

This medicine contains potassium, less than 1.3 mmol (50 mg) per dose, i.e. essentially 'potassium-free'.

This medicine also contains DMSO which may cause severe hypersensitivity reactions.

3. How Zemcelpro is given

Zemcelpro is given to you by a doctor in a qualified transplant centre.

Zemcelpro is a one-time treatment. Before you are given Zemcelpro, your doctor will give you a type of treatment called conditioning regimen to prepare your body for the stem cell transplant.

During the 30 to 60 minutes before you are given Zemcelpro you may be given other medicines. This is to help prevent infusion reactions and fever (see section 2 – What you need to know before you are given Zemcelpro). These other medicines may include antipyretics (against fever), histamine antagonists (anti-allergy), and antiemetics (against nausea and vomiting). This may also include corticosteroids to reduce the possibility of an infusion reaction.

How you are given Zemcelpro

- Your doctor will check that the individual patient identifiers on the Zemcelpro infusion bags match your details.
- Your doctor will give you this medicine as an infusion (drip) through a tube into your vein.
- You will receive 1 to 4 bags containing the active substance (dorocubicel, composed of cells grown and multiplied in the laboratory. This is the expanded component) followed by 4 bags of the unchanged donor cells (this is the unexpanded component). The time for infusion will vary, but usually each bag will be infused in less than 15 minutes.
- During the infusion your doctor will check if you have difficulty breathing or dizziness (possible symptoms of an allergic reaction) (see section 2 – What you need to know before you are given Zemcelpro). In certain cases, the infusion with Zemcelpro may be paused.

After Zemcelpro is given

As part of the transplant procedure, you will be given medicine to reduce the risk of graft-versus-host disease (GvHD), a complication that occurs when the cord blood stem cells recognise the patient's body as foreign and attack it. The medicine may initially be given through a central venous catheter (a thin tube into a large vein, also known as a central line), and then changed to a pill form when you can take medication orally.

You will also be given medicine to help your blood cells recover as quickly as possible and signals the bone marrow to make white blood cells, which are needed to fight and prevent infections. This medicine will be given to you through your central line or as an injection under the skin the day after you receive Zemcelpro. You will continue to receive it daily until the levels of your white blood cells recover.

Before and after you are given Zemcelpro

Your doctor will recommend that you stay at the hospital as an in-patient during the week before the infusion, so you can receive the conditioning regimen, and for 3-4 weeks after you have been given Zemcelpro. After your hospital stay, your doctor will ask you to come on a regular basis for follow-up visits. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss an appointment, call your doctor or the hospital as soon as possible to reschedule.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Before you start treatment, your doctor will discuss the risks of using this medicine.

Tell your doctor immediately if you get any of the following serious side effects after the Zemcelpro infusion.

Very common: *may affect more than 1 in 10 people*

- Abnormally low number of lymphocytes (lymphopenia), a type of white blood cell. This may increase your risk of infection
- Low number of red blood cells (anaemia). Signs include pale skin, weakness and breathlessness
- Abnormally low number of neutrophils (neutropenia), a type of white blood cell. This may increase your risk of infection
- Low number of blood platelets, components that help the blood to clot (thrombocytopenia). Signs include excessive or prolonged bleeding and bruising
- Low levels of white blood cells (leukopenia)
- Abnormally low levels of neutrophils with fever (febrile neutropenia)
- Graft-versus-host disease (a condition in which transplanted cells attack your body’s own cells). Symptoms include rash, nausea, vomiting, diarrhoea including bloody stools

- Frequent and persistent infections due to decreased antibodies in your blood (hypogammaglobulinaemia)
- Engraftment syndrome (a complication of stem cell transplants). Symptoms include cough, fever, shortness of breath, rash
- Infections caused by bacteria
- Infections caused by viruses
- Pneumonia (lung infection), leading to shortness of breath, chest pain, fever, cough
- High blood pressure (hypertension)

Other possible side effects
Other side effects are listed below. If these side effects become severe or serious, tell your doctor immediately.

Common: *may affect up to 1 in 10 people*
- Diarrhoea,
- Nausea,
- Sore mouth, bleeding in the mouth, inflammation in the gums (stomatitis),
- Abdominal pain
- Fever (pyrexia),
- Fatigue
- Liver condition blocking blood vessels (veno-occlusive liver disease). Symptoms include Jaundice, liver tenderness (under the right ribs), fluid in the abdomen, weight gain
- Infections caused by a fungus
- Abnormal blood test results (low number of CD34 lymphocytes - CD4 lymphocytes decreased, low level of immunoglobulins - Immunoglobulins decreased),
- High levels of liver enzymes in the blood (Alanine aminotransferase increased, Aspartate aminotransferase increased,). These are a sign that your liver may not be working normally
- Decreased appetite,
- High levels of sugar in the blood (Hyperglycaemia),
- Low blood levels of potassium (hypokalaemia) and phosphorus (hypophosphatemia). These are signs that kidneys may not be working normally
- Bone pain,
- Muscular weakness
- Uncontrolled high levels of white blood cells (post transplant lymphoproliferative disorder). Possible signs of swollen lymph nodes, fever, night sweats, weight loss, fatigue, general discomfort
- Headache
- Acute kidney injury. Signs that your kidneys are not working properly include little or no urine, swelling of legs and feet, fatigue, shortness of breath, confusion, nausea
- Inflammation of the bladder that results in bleeding (Cystitis haemorrhagic). Symptoms include blood in the urine, blood clots in urine, painful urination, fever, urge or inability to pee
- Inflammation of your lungs (Cryptogenic organizing pneumonia (pneumonitis) - COP). Symptoms include shortness of breath, dry cough, fever, fatigue, fever, loss of appetite
- Bleeding from the nose (epistaxis),
- Bleeding in your lungs (Pulmonary alveolar bleeding – PAH). Symptoms include cough, fever, chest pain, coughing up blood
- Blockage of your blood circulation in your lungs (Pulmonary embolism). Signs include sudden shortness of breath, chest pain, anxiety, fever, cough
- Skin rash (Rash maculo-papular)
- Damage to the smallest blood vessels (Microangiopathy). Symptoms include chest pain, discomfort, shortness of breast, fatigue.
- Failure of the transplant (graft failure). Symptoms include serious or frequent bleedings or infections.

- Vomiting, bloody diarrhoea, stomach pain, fever, chills and headache may be sign of haemolytic uremic syndrome (HUS).

Uncommon: *may affect up to 1 in 100 people*
- Tiredness or weakness, pale skin and easy bruising or bleeding may be signs of low blood cells or small blood clots (Autoimmune haemolytic anaemia, Cytopenia, Thrombotic microangiopathy)
- Chest pain, irregular heartbeat, heart inflammation or weakness and shortness of breath (Angina pectoris, Atrial fibrillation, Atrial flutter, Pericarditis, Right ventricular dysfunction)
- Frequent infections, fatigue and easy bruising or bleeding may indicate bone marrow failure or abnormal cell genes (Aplasia, Cytogenetic abnormality)
- Hearing loss (Hypoacusis)
- Fatigue or weakness, craving salt may be signs of low levels of hormone secreted by gland above the kidney (Adrenal insufficiency)
- Abdominal pain or cramping, diarrhoea or constipation, weight loss or poor appetite may be signs of bowel issues (Anal stenosis, Colitis, Enterocolitis, Jejunal perforation, Malabsorption, Pneumatosis intestinalis)
- Swelling, fatigue, and sore mouth/gut lining (Generalised oedema, Malaise, Mucosal inflammation)
- Yellow eyes (jaundice), dark urine may be signs of Hyperbilirubinemia
- Blood test or lung or cardiac function changes (Blood bilirubin increased, Blood bilirubin decreased, Carbon monoxide diffusing capacity decreased, CMV test positive, Electrocardiogram QT prolonged, Haemoglobin decreased, Neutrophil count decreased)
- Thirst or dry mouth, dizziness or confusion, headache or nausea may indicate low body fluids or low blood salt (Dehydration, Hyponatraemia)
- Dying skin or muscle (Soft tissue necrosis)
- Sudden weakness or numbness. trouble speaking or understanding, confusion may indicate a stroke or brain function problems (Cerebro vascular accident, Encephalopathy)
- Confusion, disorientation or repetitive thoughts/behaviours (Delirium, Obsessive compulsive disorder)
- Swelling, reduced urine output, high blood pressure may be signs of small clots damaging the kidneys (Renal limited thrombotic microangiopathy)
- Shortness of breath, chest pain or cough may indicate lung inflammation, fluid, or collapse (Idiopathic pneumonia syndrome (pneumonitis), Lung infiltration, Pneumothorax)
- Red inflamed skin, itchy or burning sensation, eruption can be signs of Eczema, Dermatitis acneiform, Pruritus
- Surgical removal of all or part of the colon (Colectomy)
- Dizziness, fatigue, blurred vision and localized swelling, lump or bruising may be signs of Decreased and nonspecific blood pressure disorders, Hematoma, Hypotension, Orthostatic hypotension

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Zemcelpro

The following information is intended for doctors and pharmacists only.

Do not use this medicine after the expiry date which is stated on the infusion bag label after EXP.

Store and transport below -150 °C. Do not thaw the product until it is ready to be used. Use within 1 hour of thawing. Once thawed it should not be refrozen.

Do not use this medicine if the infusion bags are damaged or leaking.

This medicine contains human blood cells. Local guidelines on handling of biological waste should be followed for used medicine or waste material.

6. Contents of the pack and other information

What Zemcelpro contains

Zemcelpro is a cryopreserved allogeneic hematopoietic stem and progenitor cell therapy containing two cell components, namely the expanded and unexpanded components, both derived from the same patient-specific umbilical cord blood unit (CBU).

- The expanded component, referred to as dorocubicel which is the expanded CD34+ cells, is composed of the CD34+ fraction expanded *ex-vivo* in the presence of UM171. This component is packaged in up to four bags containing at least 0.23×10^6 viable CD34+ cells/mL suspended in a dimethyl sulfoxide (DMSO) solution.
- The unexpanded component, referred to as unexpanded CD34- cells, is composed of the CD34- fraction from which the CD3+ cells are the active fraction. This component is packaged in four bags containing at least 0.53×10^6 viable CD3+ cells/mL suspended in a dimethyl sulfoxide (DMSO) solution.

The other ingredients are human serum albumin solution, dimethyl sulfoxide, sodium chloride, potassium chloride (E508), sodium gluconate (E576), sodium acetate (E262), and magnesium chloride (E511). See section 2, “Zemcelpro contains sodium, potassium and dimethyl sulfoxide (DMSO)”.

What Zemcelpro looks like and contents of the pack

Zemcelpro is a cell dispersion for intravenous infusion.
The expanded CD34+ cells component is a colourless to slightly yellow dispersion of cells. The unexpanded CD34- cells component is a reddish dispersion of cells.

Zemcelpro is supplied as one individual treatment dose comprises up to eight (8) infusion bags of 20 mL each, four (4) bags of unexpanded CD34- cells and up to four (4) bags of dorocubicel.

Marketing Authorisation Holder and Manufacturer

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This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Precautions to be taken before handling or administering the medicinal product

Zemcelpro must be transported within the facility in closed, break-proof, leak-proof containers.

Zemcelpro must be transported in a container maintaining the product below -150 °C and should be handled with appropriate protective gowning and gloves.

This medicinal product contains human blood cells. Healthcare professionals handling Zemcelpro must take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

Zemcelpro is composed of two (2) allogeneic hematopoietic cell components:
- Dorocubicel (expanded CD34+ cells)
- Unexpanded CD34- cells

Confirmation of the number of dorocubicel bags (1 to 4 bags) and the number of bags for unexpanded CD34- cells (always 4 bags) to be infused must be done based on release for infusion certificate (RfIC) prescription. The RfIC includes both components.

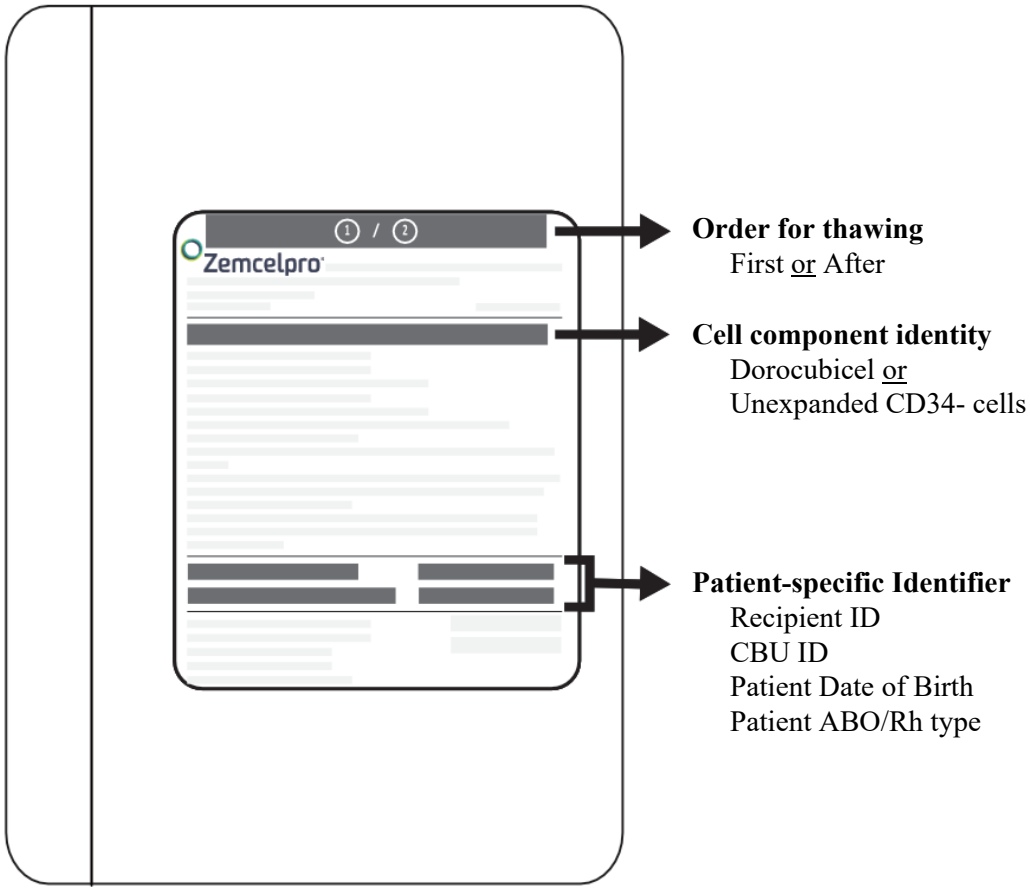
Dorocubicel is infused first, followed by the unexpanded CD34- cells. It is recommended that the unexpanded CD34- cells be infused the same day as dorocubicel, but no later than the following day.

Coordinate the timing of Zemcelpro thaw and infusion in the following manner: confirm the readiness of the patient to be infused in advance and adjust the start time of Zemcelpro thaw such that it will be available for infusion when the patient is ready.

Thawing

Prior to Zemcelpro thawing, confirm patient's identity and numbers of bags to infused according to the infusion certificate (RfIC). Thaw all prescribed bags of dorocubicel before bags from unexpanded CD34- cells. Thaw one (1) bag at a time. Wait to thaw the next bag until it is determined that the previous bag is safely administered.

Figure 1. Zemcelpro Storage Cassette



- Retrieve the storage cassette from the cryoshipper. Confirm i) the patient's identity with the patient identifiers on the cassette and ii) the cell component identity (dorocubicel or unexpanded CD34- cells) (Figure 1).
- After cassette verification, immediately remove the infusion bag from the cassette. Confirm i) the patient's identity with the patient identifiers on the infusion bag and ii) the cell component identity (dorocubicel or unexpanded CD34- cells) (Figure 2).
- Inspect the infusion bag(s) for any breaks or cracks prior to thawing. If a bag is compromised, do not infuse the contents.
- Place immediately the infusion bag contained in its sealed overwrap in a 37 °C water bath. When semi-liquid consistency is reached, start to gently knead the bag until no crystal ice remain. The complete thawing duration takes approximately 2-5 minutes per bag.
- Remove bag from the water bath. Once the infusion bag has been thawed, it should be infused as promptly as possible. Zemcelpro has been shown to be stable between 15 °C - 30 °C for up to 1 hour. Do not dilute, wash, or sample Zemcelpro prior to infusion.
- Unless prepared at the patient's bedside, transport the product to the bedside at room temperature in a closed box/bag to protect the product during transport.

Do not infuse Zemcelpro if the infusion bag is damaged or leaking or otherwise appears to be compromised.

Administration

Prescribed number of bags of dorocubicel (1 to 4 bags) and of unexpanded CD34- cells (always 4 bags) must be infused to complete a single dose of Zemcelpro. The total number of infusion bags to be administered must be confirmed with the patient specific information on the RfIC.

Dorocubicel is infused first, followed by the unexpanded CD34- cells. It is recommended that the unexpanded CD34- cells be infused the same day as dorocubicel, but no later than the following day.

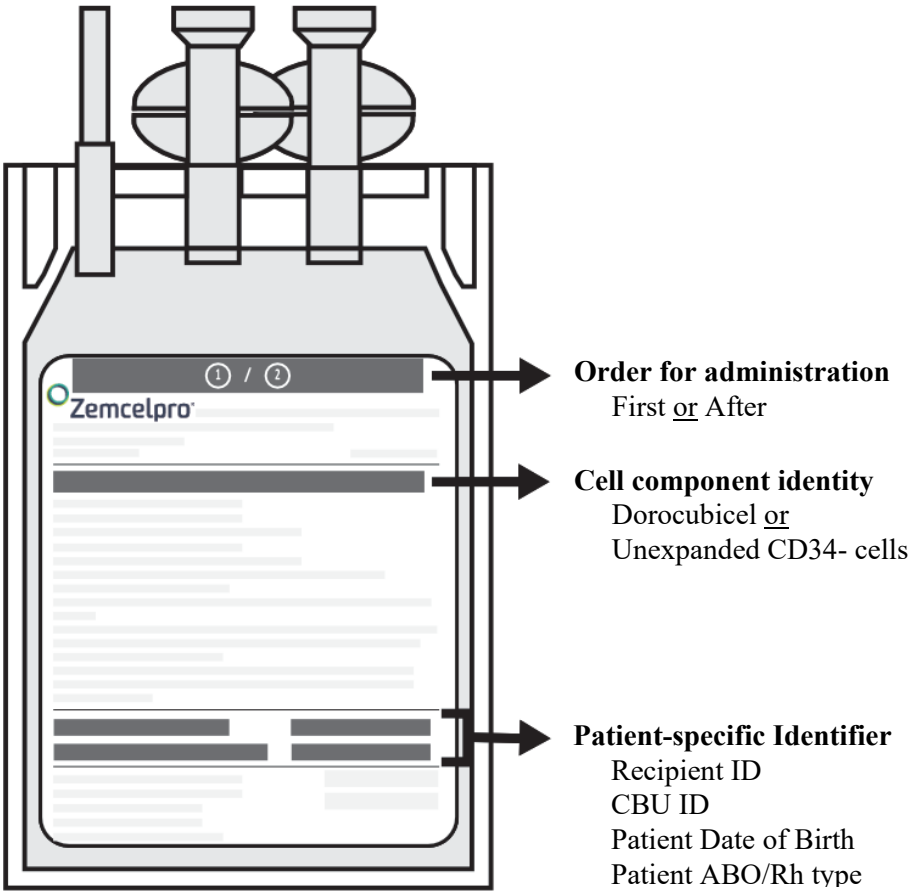
If dorocubicel is not administered, the unexpanded CD34- cells must not be infused to avoid any untoward immune reaction.

In case of infusion reaction, pausing infusion and instituting supportive care is recommended, as needed (see section 4.4).

Do not dilute, wash or sample Zemcelpro prior to infusion.

Intravenous use only. Central venous access is recommended for the infusion of Zemcelpro.

Figure 2. Zemcelpro Infusion Bag



- Prepare infusion material. A latex-free tubing with a standard infusion filter (170-260 µm) must be used. Do NOT use a leukocyte depleting filter.
- Confirm i) the patient's identity with the patient identifiers on the bag and ii) the cell component identity (dorocubicel or unexpanded CD34- cells) (Figure 2).
- Remove the overwrap and inspect the content of the thawed infusion bag for any visible cell aggregates. If visible cell aggregates are present, gently mix the contents of the bag, small aggregates of cellular material should disperse with gentle manual mixing. Remaining aggregates are effectively removed through filtration before infusion.
- The thawed and inspected bag must be infused promptly at approximately 10 to 20 mL per minute by gravity flow. Zemcelpro is stable between 15 °C – 30 °C for up to 1 hour after end of thawing.
    - Prime the tubing prior to infusion with sodium chloride 9 mg/mL (0.9%) solution for

injection.
- Infuse all contents of the infusion bag (20 mL per bag).
- Rinse twice the infusion bag with 10 mL to 30 mL sodium chloride 9 mg/mL (0.9%) solution for injection by back priming to ensure the totality of cells are infused into the patient.

- The procedure for infusion must be repeated for the other bags. Wait to thaw and infuse the next bag until it is determined that the previous bag is safely administered.

Do not infuse Zemcelpro if the infusion bag is damaged or leaking or otherwise appears to be compromised.

Measures to take in case of accidental exposure

Follow local guidelines on handling of human-derived material in case of accidental exposure. Work surfaces and materials which have potentially been in contact with Zemcelpro must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Zemcelpro (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human derived material.