ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

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.

The unexpanded component, referred to as unexpanded CD34- cells, is composed of the CD34- fraction from which the CD3+ cells are the active fraction.

2.1 Qualitative and quantitative composition

Dorocubicel

Each patient specific infusion bag of Zemcelpro contains a batch-dependent concentration of *ex-vivo* UM171 expanded CD34+ cells enriched population. The medicinal product is packaged in up to four infusion bags containing a dispersion for infusion of at least 0.23×10^6 viable CD34+ cells/mL suspended in a dimethyl sulfoxide (DMSO) solution.

Each infusion bag contains 20 mL dispersion for infusion.

Unexpanded CD34- cells

Each patient-specific infusion bag contains a batch-dependent concentration of unexpanded CD34- cells. The medicinal product is packaged in four infusion bags containing a dispersion for infusion of at least 0.53×10^6 viable CD3+ cells/mL suspended in a dimethyl sulfoxide (DMSO) solution.

Each infusion bag contains 20 mL dispersion for infusion.

Quantitative information

The quantitative information for each cell component of the medicinal product, including the batch dependent cell concentration and the number of infusion bags to be administered, is presented in the Release for infusion certificate (RfIC) accompanying the medicinal product for treatment. There is one RfIC for both cell components (see section 6).

Excipients with known effect

This medicinal product contains a maximum of 477 mg sodium, 50 mg potassium, and 10% v/v DMSO per dose (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion.

Dorocubicel

Colourless to slightly yellow cell dispersion for infusion.

Unexpanded CD34- cells

Reddish cell dispersion for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zemcelpro is indicated for the treatment of adult patients with haematological malignancies requiring an allogeneic haematopoietic stem cell transplantation following myeloablative conditioning for whom no other type of suitable donor cells is available.

4.2 Posology and method of administration

Zemcelpro must be administered in a qualified transplant centre with expertise in haematopoietic stem cell transplant by a physician with experience in the treatment of haematologic malignancies.

Posology

Treatment consists of a single dose for infusion containing a dispersion for infusion of expanded CD34+ cells in 1 to 4 infusion bags and unexpanded CD34- cells in 4 infusion bags.

The target dose is 0.4 to 7.5×10^6 viable CD34+ cells/kg for the expanded CD34+ cell component (dorocubicel) and $\geq 0.52\times10^6$ viable CD3+ cells/kg for the unexpanded CD34- cell component.

See the accompanying Release for infusion certificate (RfIC) for additional information pertaining to dose.

Cord blood unit selection

Erythrodepleted cord blood unit (CBU) for expansion is to be selected by the prescriber while respecting minimal requirement for human leukocyte antigen (HLA) matching and cell dose (i.e. pre-freeze CD34 cell count $\geq 0.5\times10^5$/kg and total nucleated cell (TNC) $\geq 1.5\times10^7$/kg). Matching for at least 4 of 6 HLA (HLA-A antigens, HLA-B antigens, and HLA-DRB1 alleles) is recommended, with a target 6 out of 8 HLA-match (high resolution typing). The HLA typing and nucleated cell content for each individual CBU used as starting material in the manufacture of Zemcelpro are provided in the accompanying RfIC.

Pre-treatment myeloablative conditioning (lymphodepleting chemotherapy)

An appropriate myeloablative conditioning regimen must be administered according to institutional guidelines. Selected regimen should be of high or intermediate intensity, i.e., with a transplant conditioning intensity (TCI) score of 2.5 and above. The conditioning regimen must not be initiated before ensuring that the availability of the patient-specific Zemcelpro is confirmed at the transplant centre.

The incorporation of anti-thymocyte globulin (ATG) is not recommended as part of the conditioning regimen (see section 4.5).

Prophylactic and supportive therapy for prevention of transplant complications

Prophylactic and supportive therapies for prevention of transplant complications (e.g., Graft-versus-Host Disease (GvHD), infection) must be administered according to institutional guidelines. Tacrolimus and mycophenolate mofetil combination is the preferred GvHD prophylaxis.

In the immediate post-transplant period, administration of granulocyte colony-stimulating factor (G-CSF) is recommended to minimize the risk of neutropenia and infection (see section 4.4).

Pre-medication

It is recommended that pre-medication with antipyretics, histamine antagonists, and antiemetics, according to local institutional guidelines, be administered 30-60 minutes before the infusion of both fractions of Zemcelpro to reduce the possibility of an infusion reaction. Moreover, pre-medication with corticosteroids is also recommended prior to administering the unexpanded CD34- component of Zemcelpro to reduce the possibility of an infusion reaction in case of major HLA histocompatibility.

Special populations

Elderly
The safety and efficacy of Zemcelpro in the elderly population (aged ≥65 years or older) have not been established.

Renal impairment
Zemcelpro has not been studied in patients with renal impairment. Patients should be assessed for renal impairment to determine transplant eligibility.

Hepatic impairment
Zemcelpro has not been studied in patients with hepatic impairment. Patients should be assessed for hepatic impairment to determine transplant eligibility.

Paediatric population
The safety and efficacy of Zemcelpro in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1.

Method of 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.

- 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).
- 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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Contraindications of the myeloablative chemotherapy must be considered.

4.4 Special warnings and precautions for use

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability, the name of the product, the batch number and the name of the treated patient must be kept for a period of 30 years after expiry date of the medicinal product.

Transmission of an infectious agent

A risk of transmission of infectious agents exists. Virus testing performed on cord blood units are human immunodeficiency virus (HIV) 1 and HIV 2, hepatitis B and hepatitis C, human T-cell lymphotropic virus (HTLV) I and HTLV II, syphilis and cytomegalovirus (CMV). Specific viruses from the mother may be documented as part of the medical history, such as transmissible spongiform encephalopathy (TSE), Epstein-Barr virus (EBV), toxoplasma, hepatitis E (HEV) and malaria. Cord banks also document if the infant is free of any finding suggestive of disease potentially transmissible through administration of a cord blood unit.

Test results may be found on the accompanying product documentation.

Healthcare professionals administering Zemcelpro must, therefore, monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Blood, organ, tissue and cell donation

Patients treated with Zemcelpro must not donate blood, organs, tissues or cells.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, may be due to ingredients contained in Zemcelpro, e.g., DMSO. Reactions should be treated appropriately in accordance with institutional guidelines.

Infections

Serious infections, including life-threatening or fatal infections occurred in patients after Zemcelpro infusion (see section 4.8). Median onset was 109 days post-transplant, with some late events (ranging 0-945). Patients should be informed of the importance of a prompt notification of signs of infection to their treating physician. Patients should be monitored for signs and symptoms of infection, using appropriate diagnostic tests, and treated appropriately in accordance with institutional guidelines. As appropriate, prophylactic antibiotics should be administered, and surveillance testing should be employed prior to and after treatment with Zemcelpro (see section 4.2).

Graft-vs-Host disease

Fatal and life-threatening events of acute and chronic Graft-vs-Host Disease (GvHD) have occurred following treatment with Zemcelpro (see section 4.8). GvHD following treatment with Zemcelpro do not differ from standard allogeneic stem cell transplant, with a median onset at 40 days post-transplant, and 93% of them resolving in a median of 18 days. It is recommended that patients be monitored for evidence of GvHD and appropriately treated in accordance with institutional guidelines. Prophylactic and supportive care should be considered following treatment with Zemcelpro. Tacrolimus and mycophenolate mofetil combination is the preferred GvHD prophylaxis (see section 4.2).

Engraftment syndrome

Life threatening cases of engraftment syndrome have been reported during clinical trials with Zemcelpro (see section 4.8), occurring at a median time of 13 days post-transplant. Occurrence of unexplained fever, rash, hypoxemia, weight gain, and pulmonary infiltrates in the peri-engraftment period should be monitored. Patients should be treated in accordance with institutional guidelines with corticosteroids as soon as engraftment syndrome is recognized to ameliorate symptoms. If untreated, engraftment syndrome may progress to multiorgan failure and death.

Graft failure

Life threatening cases of graft failure, defined as failure to achieve an absolute neutrophil count greater than 500 per microliter blood by Day 42 after transplantation, have been reported during clinical trials with Zemcelpro (see section 4.8). Patients should be monitored for laboratory evidence of hematopoietic recovery.

Because it could interfere with engraftment of cord blood cells, the use of ATG is not recommended as part of the conditioning regimen and prior to engraftment. Granulocyte colony-stimulating factor (G-CSF) should be administered to minimize the risk of neutropenia and infection, 5 µg/kg/day starting 1-3 days post-transplant until neutrophil count reaches 1 000 per microliter blood (see section 4.2).

Pulmonary alveolar haemorrhage (PAH)

PAH is a well-documented adverse reaction in patients undergoing treatment with Zemcelpro. Cases of PAH were reported, occurring at a median time of 22 days post-transplant, including fatal events (see section 4.8). It is characterized by the development of dyspnea, fever, sometimes haemoptysis, multifocal infiltrates on chest X-ray, and rapid progression to respiratory failure. It is recommended that patients be monitored for evidence of PAH and appropriately treated in accordance with institutional guidelines.

Pneumonitis

Pneumonitis, such as idiopathic pneumonia syndrome (IPS) or cryptogenic organizing pneumonia (COP), is a well-documented event after treatment with Zemcelpro. Cases of pneumonitis were reported in the clinical trials of Zemcelpro including fatal events (see section 4.8). Both IPS and COP usually manifest with shortness of breath, cough, and sometimes fever. While IPS usually occur on average on day +22 after transplant, partly related to pre-transplant conditioning regimen, COP usually occur 3-6 months after transplant. It is recommended that patients be monitored for evidence of pneumonitis and appropriately treated in accordance with institutional guidelines.

Post-transplant lymphoproliferative disorder (PTLD)

Post-transplant lymphoproliferative disorder (PTLD) is an adverse reaction observed in patients after treatment with Zemcelpro. Cases of PTLD have been reported among patients who were transplanted with Zemcelpro in the clinical trials (see section 4.8). PTLD is one of the most common post-transplant malignancies, in most cases associated with Epstein-Barr virus (EBV) infection of B cells, either as a consequence of reactivation of the virus post-transplant or from primary EBV infection. Serial monitoring of blood for EBV DNA may be warranted in patients with persistent cytopenias. PTLD must be appropriately treated in accordance with institutional guidelines.

Infusion-related reactions (IRR)

Infusion-related reactions may occur following infusion with Zemcelpro. These reactions predominantly occur during the initial infusion(s) and can be characterised by flushing, rash, fever, rigors, chills, dyspnoea, mild, and/or severe hypotension with(out) bronchospasms, cardiac dysfunction, and/or anaphylaxis.

Premedication with antipyretics, histamine antagonists, anti-emetics, and corticosteroids may reduce the incidence and intensity of infusion reactions. Monitor patients for signs and symptoms of infusion reactions during and after Zemcelpro administration. When an IRR occurs, pause the infusion and institute supportive care as needed (see section 4.2). Resuming the infusion must follow institutional guideline recommendations.

Hypogammaglobulinaemia

Hypogammaglobulineamia is a well-documented event that has been reported following treatment with Zemcelpro and that could be associated with decreased survival. It has been reported in 19% of the patients transplanted with Zemcelpro (see section 4.8). It is recommended that patients be monitored for laboratory evidence of hypogammaglobulinaemia and treated appropriately in accordance with institutional guidelines.

Veno-occlusive disease

Veno-occlusive disease (VOD) is a well-documented event sometimes reported following HSCT. Rare cases of VOD were reported in the clinical trials of Zemcelpro (see section 4.8, Table 1), including one fatal event. Whereas not different from a usual HSCT, it is recommended that patients be monitored for evidence of VOD and treated appropriately in accordance with institutional guidelines.

Haemolytic uremic syndrome

Haemolytic uremic syndrome (HUS) is a well-documented event sometimes reported following HSCT. Rare cases of HUS were reported in the clinical trials of Zemcelpro (see section 4.8, Table 1). Whereas not different from a usual HSCT, it is recommended that patients be monitored for evidence of HUS and treated appropriately in accordance with institutional guidelines.

Excipients

Sodium
This medicinal product contains 477 mg sodium per dose, equivalent to 24% of the WHO recommended maximum daily intake of sodium for an adult.

Potassium
This medicinal product contains potassium, less than 1.3 mmol (50 mg) per dose.

Dimethyl sulfoxide (DMSO)
This medicinal product contains 17.6 g DMSO per dose. For an adult of 70 kg, the DMSO infused represents 25% of daily maximal recommended dose of 1 g of DMSO/kg.
This excipient is known to possibly cause anaphylactic reaction following parenteral administration. All patients should be observed closely during the infusion period.

Theoretical risks associated with the donor

Whereas not supported by the clinical experience, clonal haematopoiesis and risks associated with the donor (e.g. malignancies or hereditary genetic disorders) could occur after treatment with Zemcelpro. Patients should be appropriately monitored in accordance with institutional guidelines.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Live vaccines

The safety of immunisation with live vaccines during or following treatment with Zemcelpro has not been studied. Vaccination with live vaccines is not recommended for at least 6 weeks prior to the start of conditioning regimen, and until immune recovery following treatment with Zemcelpro.

Anti-thymocyte globulin (ATG)

Use of ATG is not recommended as part of the conditioning regimen and prior to engraftment.

4.6 Fertility, pregnancy and lactation

For risks related to myeloablative conditioning therapy needed before the use of Zemcelpro and the concurrent advice, the product information of the myeloablative conditioning therapy should be consulted.

Women of childbearing potential

Female patients of childbearing potential must have a negative serum pregnancy test within 30 days before treatment with Zemcelpro and must be willing to use an effective contraceptive method.

Contraception in males and females

There is insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Zemcelpro. Effective methods of contraception should be used in males and females of reproductive potential who have received Zemcelpro.

Pregnancy

There are no data from the use of dorocubicel in pregnant women. No animal studies have been conducted with dorocubicel to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3). Zemcelpro should not be used during pregnancy or by women of

childbearing potential not using contraception.

Breast-feeding

It is unknown whether dorocubicel is excreted in human milk. Use of Zemcelpro is not recommended during breast-feeding.

Fertility

There is no human or animal data on the effect of dorocubicel on fertility.

4.7 Effects on ability to drive and use machines

It is unknown whether Zemcelpro has an influence on the ability to drive and use machines. As conditioning, prophylactic, and supportive therapy administered in conjunction with Zemcelpro may result in fatigue and alter mental ability, patients are advised to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery during this initial period.

4.8 Undesirable effects

Summary of the safety profile

The most frequently occurring adverse reactions of Grade 3 of higher were lymphopenia (46.6%), infections (44.8%), anaemia (44.0%), neutropenia (35.3%), thrombocytopenie (31.9%), leukopenia (20.3%), hypogammaglobulinaemia (18.1%), febrile neutropenia (15.5%), hypertension (12.9%), engraftment syndrome (11.2%), and pneumonia (11.2%). According to NIH criteria, acute GvHD was reported in 60.0% of patients, and chronic GvHD was reported in 16.0% of patients.

Fatal adverse reactions occurred in 7.8% of patients treated with Zemcelpro, including infections (2.6% including sepsis (0.9%), enterococcal infection (0.9%), pneumonia (0.9%), acute GvHD (1.7%), PAH (1.7%), IPS (0.9%), COP (0.9%), and pulmonary hypertension (0.9%).

Tabulated list of adverse reactions

The frequencies of adverse reactions with Zemcelpro included in Table 1 are based on pooled data from 5 studies (001, 002, 003, 004, and 007) in 116 patients, who received a dose of Zemcelpro and followed for a median duration of 24 months. The adverse reaction frequencies from clinical studies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes.

Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher and unusual grade 1-2 adverse reactions are presented below. These adverse reactions are presented by MedDRA system organ class and by frequency. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1 000 to < 1/100). Within each frequency grouping, adverse drug reactions are presented in the order of decreasing seriousness.

Table 1 CTCAE adverse reactions observed in clinical studies with Zemcelpro presented by System Organ Class

Blood and lymphatic system disorders	
Very common	Lymphopenia Anaemia Neutropenia Thrombocytopenia

	Leukopenia Febrile neutropenia
Uncommon	Autoimmune haemolytic anaemia Cytopenia Thrombotic microangiopathy
Cardiac disorders	
Uncommon	Angina pectoris Atrial fibrillation Atrial flutter Pericarditis Right ventricular dysfunction
Congenital, familial and genetic disorders	
Uncommon	Aplasia Cytogenetic abnormality
Ear and labyrinth disorders	
Uncommon	Hypoacusis
Endocrine disorders	
Uncommon	Adrenal insufficiency
Gastrointestinal disorders	
Common	Diarrhoea Nausea Stomatitis Abdominal pain
Uncommon	Anal stenosis Colitis Enterocolitis Jejunal perforation Malabsorption Pneumatosis intestinalis
General disorders and administration site conditions	
Common	Pyrexia Fatigue
Uncommon	Generalised oedema Malaise Mucosal inflammation
Hepatobiliary disorders	
Common	Venoocclusive liver disease
Uncommon	Hyperbilirubinaemia
Immune system disorders	
Very common	Acute GvHD (grade II-III)[*] Hypogammaglobulinaemia Engraftment syndrome Chronic GvHD[**]
Infections and infestations* **	
Very common	Bacterial infections (Including pneumonias) Viral infections
Common	Fungal infections Unspecified infections
Injury, poisoning and procedural complications	
Common	Graft failure
Investigations	
Common	CD4 lymphocytes decreased Alanine aminotransferase increased Immunoglobulins decreased Aspartate aminotransferase increased

Uncommon	Blood bilirubin increased Blood bilirubin decreased Carbon monoxide diffusing capacity decreased CMV test positive Electrocardiogram QT prolonged Haemoglobin decreased Neutrophil count decreased
Metabolism and nutrition disorders	
Common	Decreased appetite Hypokalaemia Hyperglycaemia Hypophosphatemia
Uncommon	Dehydration Hyponatraemia
Musculoskeletal and connective tissue disorders	
Common	Bone pain Muscular weakness
Uncommon	Soft tissue necrosis
Neoplasms benign, malignant and unspecified	
Common	Post transplant lymphoproliferative disorder
Nervous system disorders	
Common	Headache
Uncommon	Cerebro vascular accident Encephalopathy
Psychiatric disorders	
Uncommon	Delirium Obsessive compulsive disorder
Renal and urinary disorders	
Common	Haemolytic uremic syndrome (HUS) Acute kidney injury Cystitis haemorrhagic
Uncommon	Renal limited thrombotic microangiopathy
Respiratory, thoracic and mediastinal disorders	
Common	Cryptogenic Organizing Pneumonia Epistaxis PAH Pulmonary hypertension Pulmonary embolism
Uncommon	Idiopathic pneumonia syndrome (pneumonitis) Lung infiltration Pneumothorax
Skin and subcutaneous tissue disorders	
Common	Rash maculo-papular
Uncommon	Dermatitis acneiform Eczema Pruritus
Surgical and medical procedures	
Uncommon	Colectomy
Vascular disorders	
Very common	Hypertension
Common	Microangiopathy
Uncommon	Decreased and nonspecific blood pressure disorders Hematoma Hypotension Orthostatic hypotension

[*] as per NIH criteria (45.7% grade II, 10.3% grade III and 0.9% grade IV aGvHD at 100 days post-transplant)
[**] as per NIH criteria (7.8% moderate and 5.2% moderate-severe cGvHD at 1-year post-transplant).
[***] infections and infestations presented reflect high-level group terms.

Description of selected adverse reactions

Infections
Severe infections including life-threatening and fatal infections occurred after Zemcelpro infusion. The overall incidence of CTCAE Grade ≥3 post-transplant infections was 75.0% (62.1% severe, 6.0% life-threatening and 6.9% fatal). They were from bacterial (52.6% with sepsis and pneumonia being the most frequent), viral (45.7% with Epstein-Barr virus, cytomegalovirus, coronavirus and adenovirus being the most frequent), fungal (9.5%) or unspecified (8.6%) origins. Their onset is widely spread out with a median of 109 days post-transplant. Most of them resolved with a median duration of 13 days. Fatal infections include sepsis, septic shock and pneumonia. See section 4.4 for management recommendations.

Engraftment syndrome
Engraftment syndrome was reported in 11.2% (13/116) of patients transplanted with Zemcelpro, with an incidence of 8.6% without severe cases among those treated with tacrolimus/MMF as GvHD prophylaxis. The median onset was 13 days post-transplant (range: 8-25). All cases recovered with corticosteroid therapy with a median duration of 5 days (range: 1-18. See section 4.4 for management recommendations,

Pulmonary alveolar haemorrhage
Pulmonary alveolar haemorrhage was reported in 3 (2.6%) patients transplanted with Zemcelpro with a median onset of 22 days post-transplant (range: 20-355). Whereas one patient recovered at 9 days, 2 patients died despite appropriate therapy. See section 4.4 for management recommendations.

Pneumonitis
Pneumonitis was reported in 8 (6.9%) patients transplanted with Zemcelpro with a median onset of 157 days post-transplant (range: 7-283). Cases included 3 idiopathic pneumonia syndromes (IPS) (2.6%), 4 cryptogenic organizing pneumonia (3.4%) (COP) and 1 unspecified pneumonitis (0.9%). Recovery was achieved in 66.7% of cases, with a median duration of 29 days (range: 9-201). Two patients (1.7%) (one with IPS and one with COP) succumbed to the condition. See section 4.4 for management recommendations.

Post-transplant lymphoproliferative disease
Post-transplant lymphoproliferative disease was reported in 3 (2.6%) patients transplanted with Zemcelpro with a median onset of 90 days post-transplant (range: 70-112). All recovered with rituximab therapy with a median duration of 39 days (range: 33-157). See section 4.4 for management recommendations.

Graft versus host disease
Overall, the incidence of acute and chronic GvHD were 66.4% and 14.7%, respectively. At 100 days post-transplant, grade II, III and IV acute GvHD was reported in 52.0%, 11.8% and 1.0%, respectively. Similarly, mild and moderate-severe cases of chronic GvHD was reported at 1-year post-transplant in 12.9% and 8.6%, respectively. Most of the case could be controlled with a corticosteroid-based therapy with a median duration of 18 (0-321) days, but 2 (1.7%) patients died of GvHD-associated infections. GvHD management should follow local institution guidelines (See section 4.4 for management recommendations).

Graft failure
Graft failure was reported in 5.2% of patients transplanted with Zemcelpro with a median onset of 26.5 days post-transplant (range: 7-28). Rescue therapy could be implemented with a median duration of 23 days (range: 7-32) in all but one patient who died from a non-related non-relapse mortality event prior to been rescued.

Prolonged cytopenias
Prolonged cytopenias, including neutropenia (64.7%), thrombocytopenia (63.8%), leukopenia (62.9%), lymphopenia (61.2%), and anaemia (56.9%) are very common following a myeloablative conditioning regimen. See section 4.4 for management recommendations.

Paediatric population
Although data is limited, safety profile is similar to that in adults (Adverse Drug Reactions with a frequency ≥ 20%: anaemia, decreased appetite, febrile neutropenia, nausea, stomatitis, and epistaxis). Median follow-up time of 7 months does not allow further interpretations of the clinical outcomes.

Reporting of suspected adverse drug reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Risk of overdose is limited. There were no cases of overdose during clinical trials.

All 4 bags of the unexpanded CD34- cells component resulting from the manufacturing of Zemcelpro will always be infused. In very rare circumstances only, the release for infusion certificate (RfIC) will dictate not to administer all 4 bags of the expanded CD34+ cells component (dorocubicel) resulting from the manufacturing of Zemcelpro. Should this not be strictly followed, the resulting overdose of dorocubicel could be associated with an increased risk of infusion reactions and engraftment syndrome. Patients will need to be monitored for the occurrence of such events.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood substitutes and perfusion solutions, other blood products. ATC code: B05AX04

Mechanism of action

Dorocubicel is a cryopreserved UM171 ((1R, 4R)-N1-(2-benzyl-7-(2-methyl-2H-tetrazol-5-yl)-9H-pyrimido[4,5-b]indol-4-yl)cyclohexane-1,4-diamine dihydrobromide) expanded allogeneic hematopoietic progenitor cell therapy derived from a single cord blood unit and used as an allogeneic stem cell donor source.

The primary mechanism of action of dorocubicel lies in promoting hematopoietic recovery and immune reconstitution through the activity of expanded CD34+ hematopoietic stem cells.

The unexpanded CD34- cells, consisting primarily of CD3+ T cells, play a complementary role by supporting immune reconstitution and providing graft-versus-leukemia (GVL) effects post-transplantation.

Hematopoietic stem/progenitor cells from Zemcelpro migrate to the bone marrow where they divide, mature, and differentiate in all haematological cell lineages. The mature cells are released into the bloodstream, where some circulate and others migrate to tissue sites, partially or fully restoring blood counts and function, including immune function, of blood-borne cells of marrow origin.

Pharmacodynamic effects

Transplantation of Zemcelpro resulted in haematological reconstitution, with full donor chimerism in

all hematopoietic stem cell lineages. T cell reconstitution was also prompt, with T-cell receptor (TCR) diversity at 6- and 12-months post-transplant.

Clinical efficacy and safety

The safety and efficacy of Zemcelpro treatment in patients with haematological malignancies requiring a haematopoietic stem cell transplant has been evaluated in two open label, uncontrolled, single-arm studies without comparison to other types of donor cells; in patients with high-risk leukaemia and myelodysplasia (ECT-001-CB.002 (002), n=30 and ECT-001-CB.004 (004), n= 30).

The safety of Zemcelpro was also evaluated in 3 additional open label, uncontrolled, single-arm studies without comparison to other types of donor cells; (one (1) study in patients with blood cancers lacking standard HLA matched familial or unrelated donors (ECT-001-CB.001 (001); one (1) study in patients with high-risk multiple myeloma (ECT-001-CB.003 (003); n=18); one (1) study in paediatric patients with high risk myeloid malignancies (ECT-001-CB.007 (007); n=12). See section 4.8.

To assess efficacy of Zemcelpro in a representative population of adult patients with haematological malignancies requiring an allogeneic haematopoietic stem cell transplantation who lack a readily available suitable donor, pooled data from studies 002, and 004 were analysed, focusing on a pivotal population of 25 patients enrolled to receive cryopreserved Zemcelpro manufactured from a small CBU, following high or intermediate myeloablative conditioning regimen. See Table 2 for patients' characteristics. Small CB is defined as below the Be The Match & National Marrow Donor Program/ American Society for Transplantation and Cellular Therapy (NMDP/ASTCT)'s minimal cell dose criteria for single CB transplant, i.e., TNC and CD34 cell content prior to cryopreservation of less than 2.5×10^7 TNC/kg and 1.5×10^5 CD34 cells/kg, respectively.

Table 2 Pooled demographics, and baseline disease characteristics for patients in Zemcelpro Studies (at March 15, 2024)

Category	**Enrolled with Zemcelpro manufactured from small CB and cryopreserved (Intent-to-treat, n=25)**
Age (years)	
Median (IQR)	47 (40, 53)
Min-Max	24-64
Sex – n (%)	
Male	18 (72.0%)
Female	7 (28.0%)
Race	
White	17 (68.0%)
Black	1 (4.0%)
Asian	1 (4.0%)
Other	6 (24.0%)
Disease category	
Acute Myeloid Leukaemia	11 (44.0%)
Acute Lymphoid Leukaemia	3 (12.0%)
Myelodysplastic Syndrome	0 (0.0%)
Chronic Myelogenous Leukaemia (blast crisis)	0 (0.0%)
Hodgkin Lymphoma	0 (0.0%)
Non-Hodgkin lymphoma, aggressive lymphoma	0 (0.0%)

Category	Enrolled with Zemcelpro manufactured from small CB and cryopreserved (Intent-to-treat, n=25)
Adult T-cell Leukaemia/Lymphoma	0 (0.0%)
Chronic Lymphocytic Leukaemia and transformation to Hodgkin lymphoma	0 (0.0%)
Previous HSCT	7 (28.0%)

Of the 25 patients enrolled in the pivotal population, 24 patients received infusion with Zemcelpro. Efficacy was assessed through the endpoints of neutrophil and platelet engraftment (Table 3). At data cut-off date, Studies 002 and 004 are still ongoing.

Table 3 Efficacy results in adult patients with haematological malignancies treated with cryopreserved Zemcelpro derived from small CBU (n=25), 13.3 months median follow-up

Endpoints	Enrolled with Zemcelpro manufactured from small CBU and cryopreserved (Intent-to-treat, n=25[3])
Median time to neutrophils engraftment[*] (ANC ≥ 500/μL): Median (IQR)[range][1], Median (IQR)[range][2] (Worst-case scenario)	 20 days (17-29) [10-39] 25 days (17-30) [10-42]
Incidence of neutrophil engraftment ANC ≥ 500/μL at day 42 - n (%)	21/25[3] (84.0%)
Median time to platelet engraftment[*] (≥ 20 000/μL) Median (IQR)[range] Median (IQR)[range][2] (Worst-case scenario)	40 days (37-62) [29-175] 48 days (38-100) [29-175]
Incidence of platelet engraftment (≥ 20 000/μL) at day 100 – n (%)	17/25[3] (68.0%)
Median (IQR) follow-up (months)[**]	13.3 (0.9-38.2)

[*] All durations are reported as "time from infusion". The median duration of study enrolment to date of Zemcelpro availability at the clinical site was 31 days (IQR: 22-41 days) and median duration of study enrolment to date of Zemcelpro infusion was 42 days (IQR: 35-56 days).

[**] time from infusion to date of completion or discontinuation from follow-up prior to the data cut-off

ANC: absolute neutrophil count; IQR: interquartile range

[1] Granulocyte colony-stimulating factor (G-CSF) was administered in the immediate post-transplant period (5 μg/kg/day) to minimize the risk of neutropenia and infection

[2] In intent-to treat populations, in a worst-case scenario analysis, patients who did not reach neutrophil engraftment by Day 42 or platelet engraftment by Day 100 post-transplant, including the patients who were not transplanted, or failed to engraft for any reason (NRM or relapse prior to engrafting) were inferred to have failed at Day 42, or Day 100, respectively.

[3] Includes 1 patient who was not transplanted due to a shipment failure.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Zemcelpro in one or more subsets of the paediatric population in HSCTs in patients with haematological malignancies (see section 4.2 for information on paediatric use).

At time of approval in adults, paediatric data is limited to 9/12 subjects less than 18 years old transplanted with Zemcelpro for high-risk myeloid malignancies in 007 study (6 with AML, 3 with

MDS). Zemcelpro resulted in 88.9% and 77.8% neutrophil and platelet engraftment, respectively at a median time of 21.5 and 48 days, respectively.

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

In clinical studies, Zemcelpro resulted in a full donor chimerism (defined as ≥ 95% cells of donor's origin) in myeloid cells in all patients, as early as 0.5 months post-transplant. Only patients in the process of disease recurrence subsequently showed donor chimerism < 95% at later time points. In accordance with the longer time required for T cell reconstitution post-transplant, full donor chimerism in the T cell subset was achieved slightly later: 63% and 88% of patients achieved full donor chimerism in the T cell population at 0.5- and 1-month post-transplant.

5.3 Preclinical safety data

Engraftment of the UM171 expanded CD34+ cells after primary or secondary transplantation and haematological reconstitution for up to 28 weeks in immunocompromised NSG mice transplanted with up to 5 000 000 cells (equivalent to up to 2.5×10^8 cells/kg in human thus exceeding the human dose) did not result in adverse toxicity.

No repeated dose toxicity studies were conducted.

No carcinogenicity studies were conducted.

In vitro cytogenetic analysis of the expanded CD34+ cells did not reveal any abnormal chromosomal changes in the expanded cells.

Given the nature of the product, non-clinical studies on fertility, reproduction and development were not conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethyl sulfoxide
Human albumin solution
Magnesium chloride (E511)
Potassium chloride (E508)
Sodium acetate (E262)
Sodium chloride
Sodium gluconate (E576)

6.2 Incompatibilities

In the absence of compatibility studies, Zemcelpro should not be mixed with other medicinal products.

6.3 Shelf life

Cryopreserved: 1 year.

Once thawed: 1 hour at 15 °C – 30 °C.
Do not refreeze thawed medicinal product.

6.4 Special precautions for storage

Zemcelpro must be stored and transported in the vapour phase of liquid nitrogen (≤ −150 °C) and must remain frozen until the patient is ready for treatment to ensure viable cells are available for patient administration.

For storage conditions after thawing of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Zemcelpro is packaged in an ethylene vinyl acetate (EVA) infusion bag (50 mL) two ports containing 20 mL cell dispersion.

Each infusion bag is placed into an overwrap. This secondary packaging layer made of EVO copolymer is sealed twice. Each infusion bag in sealed overwrap is placed into a metallic cassette. The cassettes are subsequently placed in a labelled modpak within a standard, controlled cryoshipper.

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

Also provided with Zemcelpro is a cryovial containing the sample of the original cord blood unit for chimerism monitoring.

6.6 Special precautions for disposal and other handling

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 ºC 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.

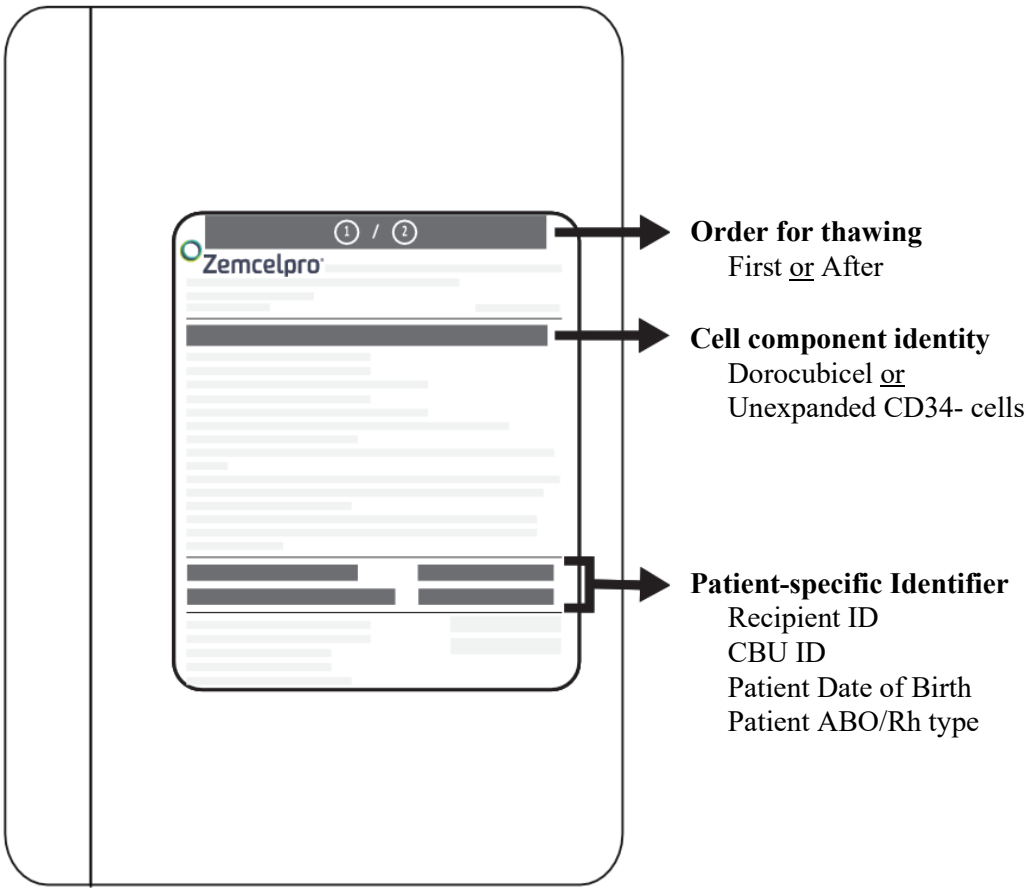
Dorocubicel is infused first, followed by the unexpanded CD34- cells. It is recommended that the unexpanded CD34- cells be infused the same day as dorocubicel, but no later than the following day.

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 remains. The complete thawing duration takes approximately 2-5 minutes per bag.
- Remove bag with overwrap 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.

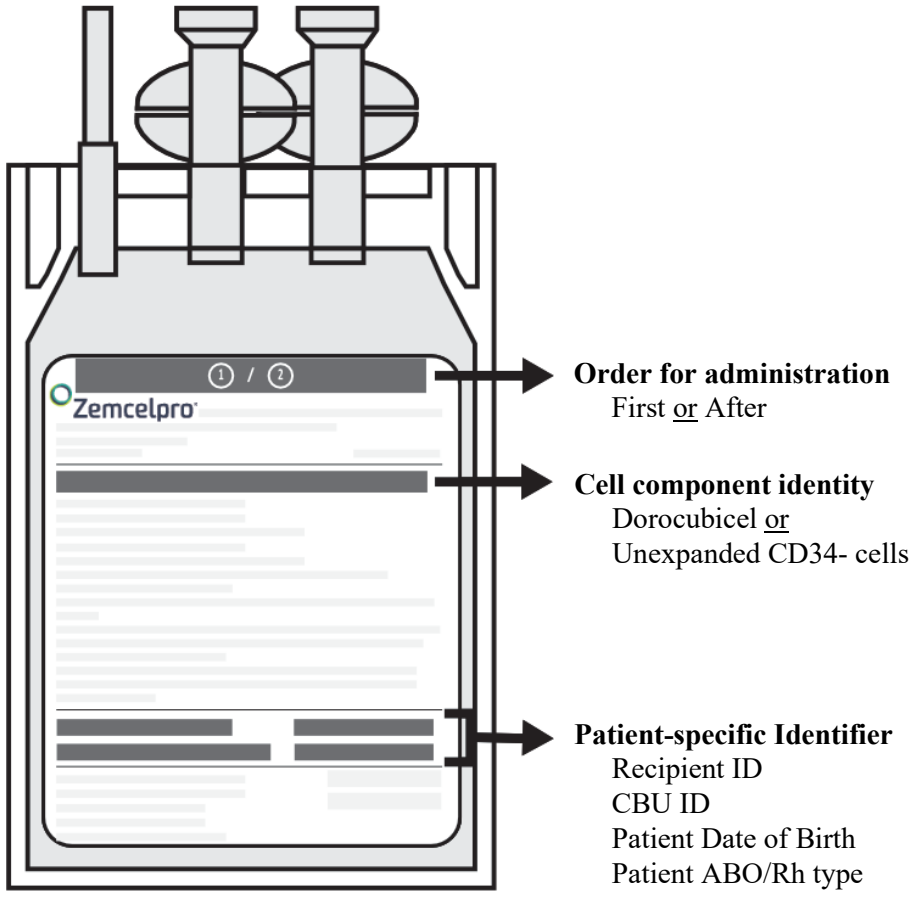
If dorocubicel is not administered, the unexpanded CD34- cells must not be infused to avoid any untoward immune reaction.

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 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.

7. MARKETING AUTHORISATION HOLDER

Cordex Biologics International Limited
5th Floor, Block E, Iveagh Court
Harcourt Road, Dublin, Ireland
Tel: 353 1 905 3140
e-mail: info@cordexbio.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1960/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Centre C3i Inc.
5415 De L'Assomption Boulevard
Montreal, Qc, H1T 2M4, Canada

Name and address of the manufacturer responsible for batch release

Cordex Biologics International Limited
5th Floor, Block E Iveagh Court, Harcourt Road
Dublin2, D02 YT22, Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and accordingly, the marketing authorization holder (MAH) shall submit PSUR every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorization holder (MAH) shall submit the first PSUR for this product within 6 months following authorization.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of Zemcelpro in adult patients with haematological malignancies requiring an allogeneic HSCT following myeloablative conditioning for whom no other type of suitable donor cells is available, the MAH shall submit the final results from Study ECT-001-CB.002: A Phase II Open-label Study of ECT-001-expanded Cord Blood Transplantation in Patients with High Risk Acute Leukemia/myelodysplasia.	28 February 2026
In order to confirm the efficacy and safety of Zemcelpro in adult patients with haematological malignancies requiring an allogeneic HSCT following myeloablative conditioning for whom no other type of suitable donor cells is available, the MAH shall submit the final results from Study ECT-001-CB.004: Phase II Open-Label Study of ECT-001-Expanded Cord Blood Transplantation in Patients with High and Very High-Risk Acute Leukemia/Myelodysplasia.	31 August 2026
In order to confirm the efficacy and safety of Zemcelpro in patients aged 18-21 years with haematological malignancies requiring an allogeneic HSCT following myeloablative conditioning for whom no other type of suitable donor cells is available, the MAH shall conduct and submit the results of the subgroup analysis of patients aged 18-21 years from study ECT-001-CB.010: A Prospective Randomized Phase II Trial of Allogeneic SCT with ECT-001-CB Expanded Cord Blood Transplant Without Serotherapy Versus Other Stem Cell Source in Pediatric Patients with High risk/refractory/relapsed Acute Myeloid Leukaemia, according to an agreed protocol.	30 June 2030
In order to confirm the efficacy and safety of Zemcelpro, and to further evaluate the dose parameters used in adult patients with high-risk and very high-risk acute leukaemia/MDS, the MAH shall submit the results of study ECT-001-CB.011: A Multicenter, Prospective, Randomized, Open-Label Phase III Study of ECT-001-CB (ECT-001-Expanded Cord Blood) Transplantation versus Best Alternative Allogeneic Stem Cell Source Transplantation (Haplo, MMUD) in Patients with High-Risk Acute Leukemia/Myelodysplasia which is conducted according to an agreed protocol.	30 June 2030
In order to confirm the efficacy and safety of Zemcelpro in adult patients with haematological malignancies requiring an allogeneic HSCT following myeloablative conditioning for whom no other type of suitable donor cells is available, the MAH shall conduct and submit the results of a prospective, non-interventional study based on data from a registry, and evaluate dose parameters collected for Zemcelpro lot manufactured for each patient enrolled in the study, according to an agreed protocol.	30 June 2031

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LABEL ON THE MODPAK COVERING BOTH CELL COMPONENTS

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

This medicine contains cells of human origin taken from donated umbilical cord blood. The medicine contains two cell components:

1) Dorocubicel (expanded CD34+ cells) contains ≥ 0.23×10^6 viable CD34+ cells/mL dispersion for infusion
2) Unexpanded CD34- cell component contains ≥ 0.53×10^6 viable CD3+ cells/mL dispersion for infusion

3. LIST OF EXCIPIENTS

Also contains: human albumin solution, dimethyl sulfoxide, sodium chloride, potassium chloride (E508), sodium gluconate (E576), sodium acetate (E262), and magnesium chloride (E511). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion

Combination package of up to 4 bags of expanded CD34+ cells and 4 bags of unexpanded CD34- cells.

Contents: 20 mL per bag.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use via central venous catheter
Administer as intravenous infusion by gravity flow.
Do not use leukocyte depleting filter.
Connect the infusion bag to the latex-free tubing with a standard infusion filter (170-260 μm).
Confirm patient's identity matches the infusion bag before infusion.
Read the package leaflet before use.
Administer all bags of dorocubicel first

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once thawed, the shelf life is 1 hour between 15 °C - 30 °C.

9. SPECIAL STORAGE CONDITIONS

Store and transport below -150 °C. Do not thaw the product until use. Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cordex Biologics International Limited
5th Floor, Block E, Iveagh Court
Harcourt Road, Dublin, Ireland
Tel: 353 1 905 3140
e-mail: info@cordexbio.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1960/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Recipient ID:	DOB:
CBU ID:	ABO/Rh:
Lot:	

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING (METAL CASSETTE)

DOROCUBICEL (EXPANDED CD34+ CELLS)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Dorocubicel (expanded CD34+ cells) contains ≥ 0.23×10^6 viable CD34 cells/mL dispersion for infusion

3. LIST OF EXCIPIENTS

Also contains: human albumin solution, dimethyl sulfoxide, sodium chloride, potassium chloride (E508), sodium gluconate (E576), sodium acetate (E262), and magnesium chloride (E511). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
Bag X/4 with expanded CD34+ cells
Contents: 20 mL per bag.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use via central venous catheter
Administer as intravenous infusion by gravity flow
Do not use leukocyte depleting filter.
Connect the infusion bag to the latex-free tubing with a standard infusion filter (170-260 µm).
Confirm patient's identity matches the infusion bag before infusion
Read the package leaflet before use.
Administer FIRST

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once thawed, the shelf life is 1 hour between 15 °C – 30 °C.

9. SPECIAL STORAGE CONDITIONS

Store and transport below -150 °C. Do not thaw the product until use. Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Harcourt Road, Dublin, Ireland
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e-mail: info@cordexbio.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1960/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Recipient ID: DOB:
CBU ID: ABO/Rh:
Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING (METAL CASSETTE)

UNEXPANDED CD34- CELLS COMPONENT

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Unexpanded CD34- cells component contains ≥ 0.53×10^6 viable CD3+ cells/mL dispersion for infusion

3. LIST OF EXCIPIENTS

Also contains: human albumin solution, dimethyl sulfoxide, sodium chloride, potassium chloride (E508), sodium gluconate (E576), sodium acetate (E262), and magnesium chloride (E511). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
Bag X/4 with unexpanded CD34- cells
Contents: 20 mL per bag.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use via central venous catheter
Administer as intravenous infusion by gravity flow
Do not use leukocyte depleting filter.
Connect the infusion bag to the latex-free tubing with a standard infusion filter (170-260 µm).
Confirm patient's identity matches the infusion bag before infusion
Read the package leaflet before use.
Administer AFTER completion of administration of all bags of dorocubicel.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once thawed, the shelf life is 1 hour between 15 °C – 30 °C.

9. SPECIAL STORAGE CONDITIONS

Store and transport below -150 °C. Do not thaw the product until use. Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1960/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Recipient ID: DOB:
CBU ID: ABO/Rh:
Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

INFUSION BAG LABEL – DOROCUBICEL (EXPANDED CD34+ CELLS)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Dorocubicel (expanded CD34+ cells) contains ≥ 0.23×10^6 viable CD34+ cells/mL dispersion for infusion

3. LIST OF EXCIPIENTS

Also contains: human albumin solution, dimethyl sulfoxide, sodium chloride, potassium chloride (E508), sodium gluconate (E576), sodium acetate (E262), and magnesium chloride (E511). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
1 bag out of 4 bags dorocubicel
20 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use via central venous catheter. Administer as intravenous infusion by gravity flow
Do not use leukocyte depleting filter.
Connect the infusion bag to the latex-free tubing with a standard infusion filter (170-260 µm).
Confirm patient's identity matches the infusion bag before infusion
Read the package leaflet before use.
Administer first

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once thawed, the shelf life is 1 hour between 15 °C – 30 °C.

9. SPECIAL STORAGE CONDITIONS

Store and transport below -150 °C. Do not thaw the product until use. Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1960/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Recipient ID: DOB:
CBU ID: ABO/Rh:
Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING

INFUSION BAG LABEL – UNEXPANDED CD34- CELLS COMPONENT

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Unexpanded CD34- cells component contains ≥ 0.53×10^6 viable CD3 cells/mL dispersion for infusion

3. LIST OF EXCIPIENTS

Also contains: human albumin solution, dimethyl sulfoxide, sodium chloride, potassium chloride (E508), sodium gluconate (E576), sodium acetate (E262), and magnesium chloride (E511). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
1 bag out of 4 bags unexpanded CD34- cells
20 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use via central venous catheter
Administer as intravenous infusion by gravity flow
Do not use leukocyte depleting filter.
Connect the infusion bag to the latex-free tubing with a standard infusion filter (170-260 µm).
Confirm patient's identity matches the infusion bag before infusion
Read the package leaflet before use.
Administer AFTER completion of administration of all bags of dorocubicel.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once thawed, the shelf life is 1 hour between 15 °C – 30 °C.

9. SPECIAL STORAGE CONDITIONS

Store and transport below -150 °C. Do not thaw the product until use. Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cordex Biologics International Limited
5th Floor, Block E, Iveagh Court
Harcourt Road, Dublin, Ireland
Tel: 353 1 905 3140
e-mail: info@cordexbio.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1960/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Recipient ID: DOB:
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14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

B. PACKAGE LEAFLET

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

Cordex Biologics International Inc.
5th Floor, Block E, Iveagh Court
Harcourt Road
Dublin, Ireland
Tel: 353 1 905 3140
e-mail: info@cordexbio.com

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.

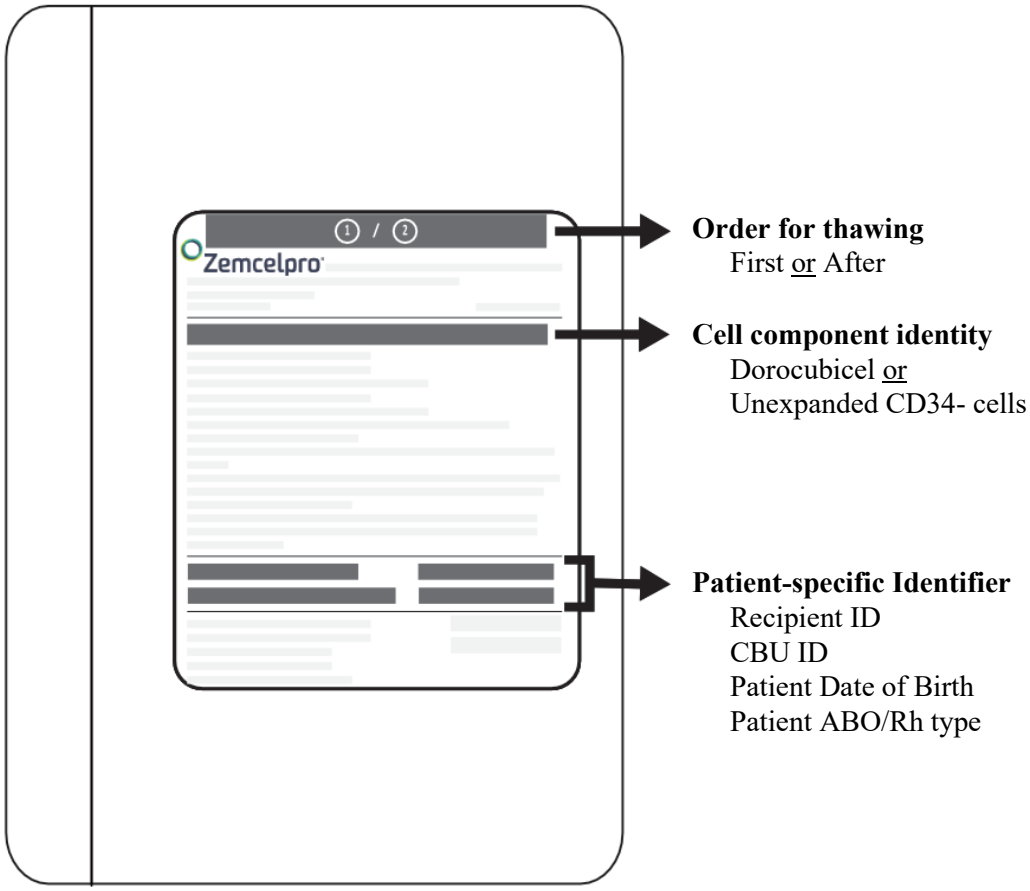
Dorocubicel is infused first, followed by the unexpanded CD34- cells. It is recommended that the unexpanded CD34- cells be infused the same day as dorocubicel, but no later than the following day.

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.

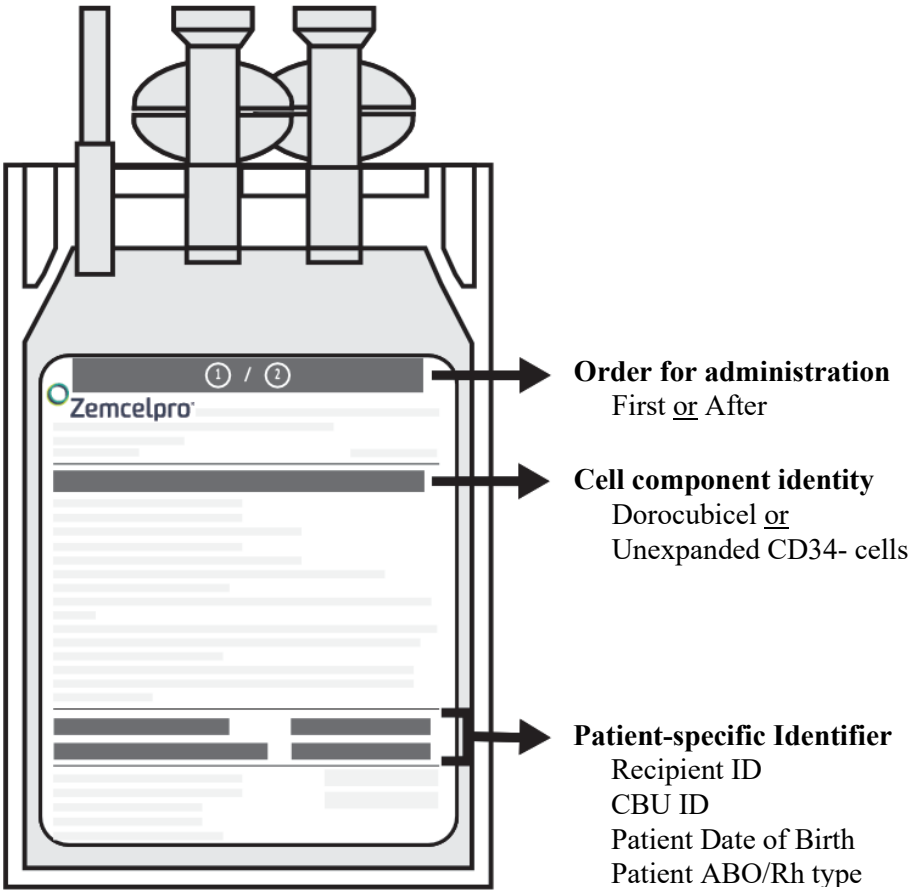
If dorocubicel is not administered, the unexpanded CD34- cells must not be infused to avoid any untoward immune reaction.

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.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.