General Product Information

Human Allogeneic Hematopoietic Stem Cells collected from Peripheral Blood (PBSC/HPC, apheresis)

1. Identification of the Medicinal Product

1.1 Name: (Human Allogeneic Hematopoietic Stem Cells collected from Peripheral Blood, Allogeneic (L))

1.2 Substance Group:
Allogeneic Hematopoietic Stem Cell Preparation from Peripheral Blood

2. Area of Application

Hematological and immunological reconstitution of bone marrow following conditioning treatment

3. Application information

3.1 Contraindications
3.1.1 Absolute Contraindications
Absolute contraindications for the use of stem cell preparations are not known.

3.1.2 Relative Contraindications
• Pregnancy
• Lactation
• Intolerance or known hypersensitivity to any of the ingredients (plasma proteins, anticoagulants: ACD-A)

3.2 Precautions for application
• Stem cell preparations must not be irradiated.
• Stem cell preparations must only be stored under controlled and monitored conditions at the specified temperature (see container labeling).
• Stem cell preparations are only applicable before the specified expiration date and for the indicated recipient (see container labeling and accompanying document)
• The correct identification (identity) of the recipient specified by the manufacturer must be ensured.
• Stem cell preparations must only be administered by qualified personnel (see guidelines of the Federal Medical Association and the Paul-Ehrlich-Institute).
• Medication prophylaxis against allergic or hemolytic reactions should be administered prior to stem cell preparation.
• A transfusion set with a standard filter with a pore size of 170 – 230 µm without leucocyte filtration filter should be used to remove clots.
• Transfusion should be performed as rapidly as possible, with the transfusion rate adjusted to the patient's clinical condition.
• In children, the recommended transfusion volume of 10 -15 ml/kg body weight should not be exceeded during administration of the medicinal product. Otherwise, there is a risk of volume overload, especially in patients with impaired cardiovascular function.
• Adequate monitoring of the recipient with monitoring of vital parameters must be ensured during and after administration of the stem cell preparation.
• HLA incompatibility increases the risk of graft-versus-host disease (GvHD) or rejection.
• In cases of major blood group incompatibility, a reduction in the erythrocyte content of the stem cell preparation and, if necessary, prophylaxis with forced diuresis may be required.
• In cases of minor blood group incompatibility, a reduction in the plasma content of the stem cell preparation may be necessary. Delayed hemolysis may occur due to "passenger lymphocyte syndrome."
• Following transplantation, regular CMV screening should be performed depending on the recipient/donor constellation.

3.3 Interactions with other pharmaceuticals and main incompatibilities
• Blood transfusions, infusion therapy, and other medication should not be given simultaneously in the same transfusion set together with the stem cell preperation. Particularly, attention should be paid to the risk of hypotonic lysis due to hypotonic solutions and clot formation due to calcium-containing solutions.
• Adding drugs or solutions to the stem cell transplant is not permissible.
• Blood products, antibiotics, liposomal antifungals, and medications that could impair stem cell function should only be administered at an adequate time interval from stem cell administration.

3.4 Application in specific patient groups
• Women of childbearing age: Before starting treatment for transplantation, pregnancy should be excluded, and if necessary, contraception should be performed.
• Pregnancy and lactation: During pregnancy and lactation, attention should be paid to potential fetal or child hazards, particularly due to stem cell preparation ingredients and the necessary pretreatment or concomitant therapy, and individual risk assessment is necessary. Breastfeeding should be discontinued before starting treatment (see section 3.1.2).
• Infants and young children: Special attention should be paid to intolerance reactions, volume overload, and citrate intoxication in infants and young children.
• Impact on driving ability and operating of machines: Allogeneic stem cell preparations are generally administered in an in-patient setting.

3.5 Warnings
• If full transfusion of the stem cell preparation is not possible, there is an increased risk of delayed or absent engraftment with delayed, partial, or absent reconstitution of hematopoiesis and an increased risk of transplant rejection, depending on the transfused cell count.
• Due to prolonged complete immune reconstitution, there is an increased risk of infections, especially severe viral and fungal infections.
• Malignant transformation of donor cells in the recipient organism is possible.

4. Guidelines for proper application

4.1 Dosage
The minimum dose recommended for allogeneic transplantation of vital cells per recipient's body weight (BW) is currently for:

Peripheral blood stem cell preparation:
4 x 10^6 CD34+ cells per kg body weight

Consideration should be given in the case of significant overweight of the recipient (e.g., BMI > 35 kg/m^2) regarding the calculation of the minimum dose. The individual dosage depends on the donor and the recipient's underlying disease, as well as HLA compatibility and, if applicable, selection and depletion procedures. The dose specifications of the corresponding therapy protocols must be considered. The product specification is defined by the user in an individual prescription and confirmed by the manufacturer through appropriate quality controls.

4.2 Method of Administration
Suspension for intravenous infusion.

4.3 Frequency of Administration
According indication
Stem cell preparations are generally administered as a single intravenous transfusion. In special clinical situations such as patients with osteopetrosis or after non-myeloablative pretreatment, multiple administrations may be indicated to improve treatment success.

4.4 Duration of Treatment
According indication

Transfusion should be performed as rapidly as possible to maintain stem cell functionality, with the transfusion rate adjusted to the patient's clinical condition.

4.5 Overdosage
There is no risk of CD34+ cell overdose. However, at very high doses of nucleated cells with a corresponding high number of T-lymphocytes, there is a higher risk of both the incidence and severity of acute and chronic graft-versus-host disease (GvHD).

4.6 Underdosage
Significantly lower deviaton of the minimum dose increases the risk of delayed or absent engraftment of the transplant with absent, delayed, or only partial hematopoiesis regeneration or rather increased risk of transplant rejection.

4.7 Emergency Measures
If severe adverse reactions occur, it could be necessary to interrupt or discontinue the administration, depending on the patient's condition and the dose already administered. Appropriate treatment according to current emergency therapy guidelines should be initiated based on the severity of the symptoms.

5. Side effects when used as directed

5.1 Immunological Reactions
• Acute and chronic graft-versus-host disease (GvHD)
• Host-versus-graft reaction (e.g., rejection)
• Acute and delayed hemolytic reactions (e.g., "passenger lymphocyte syndrome")
• Transfusion-related acute lung injury (TRALI)
• Febrile, non-hemolytic transfusion reactions due to anti-leucocyte antibodies or cytokines.
• Allergic and anaphylactoid intolerance reactions such as urticaria, eyelid or glottis edema, up to shock in case of hypersensitivity to plasma components, anticoagulants, or other pharmaceutical excipients of the stem cell preparation, or anaphylactic reactions in recipients with congenital IgA deficiency.
• Immunization against erythrocyte, leucocyte, or platelet antigens or plasma proteins or other components of the stem cell preparation.
• Post-transfusion purpura.

5.2 Infectious Complications
• When using drugs prepared from human blood or bone marrow, the transmission of infectious agents, even of unknown nature, cannot be completely ruled out. This also applies to infectious diseases such as hepatitis B and C and, less frequently, acquired immunodeficiency syndrome (AIDS). This risk is minimized by selecting donors and testing donations (see section 8.3).
• Individual cases have been reported in the United Kingdom of Great Britain and Northern Ireland where recipients of blood products, whose donors later developed variant Creutzfeldt-Jakob disease (vCJD), also tested positive for the "agents" of this disease (so-called prions). vCJD is a disease not observed in Germany.
• The risk of bacterial contamination of the stem cell preparation or toxin formation cannot be completely ruled out, especially with fresh, non-cryopreserved preparations.

5.3 Other Complications
• Intolerance reactions such as nausea, vomiting, diarrhea, headache, tachycardia, blood pressure increase due to hypersensitivity to one of the ingredients (see section 7.4). Especially in infants and young children, intolerance reactions and reactions due to citrate intoxication are possible with rapid transfusion.
• Volume overload with large-volume stem cell preparations or with too rapid transfusion or in close temporal association with other circulatory-effective infusions and transfusions.
• Hypothermia due to too rapid transfusion of the cooled stored stem cell preparation. The use of blood warming devices is not indicated.
• Microcirculatory disorders due to platelets or cell aggregates.

• Hemolytic stem cell preparations due to osmotic or mechanical damage to erythrocytes during manufacturing or application, or due to improper storage or other causes such as enzyme defects.

Reporting suspected side effects
Reporting suspected adverse reactions is of great importance. It enables continuous monitoring of the benefit-risk ratio of the medicinal product. Healthcare professionals are requested to report any suspected adverse reaction, except for GvHD (see section 5.1.1), to Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel, Paul-Ehrlich-Institut, Paul-Ehrlich-Straße 51-59, 63225 Langen, Telephone +49 6103-773116, Fax: +49 6103-771268, Website: www.pei.de respectively www.pei.de/haemovigilanz-formulare Email: pharmakovigilanz2@pei.de. In addition, in accordance with legal requirements and regulations, any suspicion of a serious incident or a serious adverse reaction must be reported immediately to the pharmaceutical entrepreneur or manufacturer.
Patients should be informed to contact their doctor or medical professional if they notice any side effects. This also applies to side effects not listed in this package insert and product information. Reporting side effects can provide more information about the safety of this medicinal product.

6. Pharmacological and Toxicological Properties

6.1 Preclinical data concerning safety
Not available. Testing the toxicity of human stem cells in animal models is of limited relevance and does not allow determination of a toxic or lethal dose.

6.2 Pharmaceutical Active Ingredients (Active Substance)
Pharmaceutical active ingredients of hematopoietic stem cell preparations are morphologically and functionally intact stem and progenitor cells for the reconstitution of hematopoiesis and the immune system after myeloablative or non-myeloablative pretreatment. Stem cells can maintain the character of a stem cell (self-replication) after cell division and can also differentiate into mature cells such as granulocytes, erythrocytes, platelets, monocytes/macrophages, osteoclasts, and lymphocytes (= asymmetric division). The cells considered to have the greatest hematopoietic potency express the CD-34 antigen as a surrogate marker, which is used for quality determination (see active substance content section 7.4.1).
After transplantation, stem cells are capable of colonizing in sites of blood formation (especially in the bone marrow, initially also in the spleen and liver) and, with a sufficient number of vital stem cells, ensuring permanent reconstitution of hematopoiesis and lymphopoiesis. The first mature blood cells (granulocytes, platelets, erythrocytes, and lymphocytes) are detectable after 10 to 30 days. It usually takes several weeks for complete hematopoiesis to be established, and several months for lymphopoiesis to be reconstituted. The speed of reconstitution depends on the type and number of stem and progenitor cells and, in particular, on recipient-related factors such as the underlying disease and any accompanying diseases. Furthermore, the immune reconstitution and the T-lymphocytes (CD3+ cells) of the stem cell preparation are intended to provide an anti-tumor effect (graft-versus-tumor (GvT)) as an important part of treatment. However, T-lymphocytes can also lead to severe immune reactions against recipient organs (see section 5. GvHD).

6.3 Other Components
Residual cells and plasma:
The residual content of erythrocytes can lead to the release of hemoglobin, especially in ABO major incompatibility, with mainly nephrotoxic side effects. A high residual content of CD3+ cells, as observed especially in peripheral blood stem cells, can lead to severe GvHD. The residual plasma content can lead to allergic reactions in case of protein intolerance and to a hemolytic reaction in case of ABO minor incompatibility.

Stabilizer ACD-A / (formulation according to Ph. Eur.):
The total amount of stabilizer is indicated on the container label or in the accompanying document in order to assess the risk of hypocalcemic reactions.

7. Additional Information

7.1 Shelf Life Information

The stem cell preparation is shelf-stable under the conditions specified in section 7.2 until the expiration date indicated on the container label or in the accompanying document. The medicinal product must not be used after the expiration date.

The preparation must be administered immediately upon opening the container and must not be refrozen for transplantation purposes.

7.2 Storage and Transportation Information
The specified storage and transportation conditions must be maintained and documented. The cold chain must not be interrupted. The storage duration of non-cryopreserved preparations should be kept as short as possible. During storage and transportation, care must be taken to ensure that the quality and functionality of the stem cells are not compromised, the stem cell preparations must never be irradiated, and unauthorized access is prevented. The transportation of the stem cell preparation must be carried out in a suitable and appropriately labeled container by a courier who has been instructed on the importance of the transplant and its transportation conditions.

Storage: +2 to +6°C
Transport: +2 to +6°C

7.3 Visual Inspection
Immediately before transfusion, each stem cell preparation must undergo visual inspection (check for aggregate formation, integrity and correct allocation to the recipient). The use despite quality deficiencies must be medically justified and documented. Associated risks must be minimized, and appropriate measures taken if necessary. The application of the stem cell preparation is the responsibility of the treating physician.

7.4 Composition of the Finished Medicinal Product
7.4.1 Active Ingredient (by type and quantity)
► Product-specific information on the active ingredient content: See container label and accompanying document!

Target dose: ≥4 x 10^6 viable CD34+ cells per kg body weight

7.4.2 Other Ingredients
► Additional information on other ingredients required for proper preparation: See container label and accompanying document!
Residual cell counts (hematocrit: <0.1 ml/ml, plasma 0.895 – 0.905 ml/ml, anticoagulants ACD-A 0.095 – 0.105 ml/ml)

7.5 Dosage form and content, container
300 to 550 ml per product bag
Suspension in a plastic bag with CE certification
1 to 2 bags per transplant.

7.6 Information on the Marketing Authorization Holder / License Holder
Universitätsklinikum Leipzig AöR
Kaufmännischer Vorstand
Liebigstraße 18

7.7 Information on the Manufacturer Authorizing the Release of the Finished Medicinal Product
Universitätsklinikum Leipzig AöR
Institut für Transfusionsmedizin
Johannisallee 32
04103 Leipzig

7.8 Approval Number or License Number
PEI.G.03719.01.1

7.9 Date of Approval or License Issuance
November 29, 2010

7.10 Drug Status
Prescription only

8. Further instructions

8.1 Measures to Reduce the Risk of Transmission of Infectious Agents
To minimize the risk of transmission of infectious agents, the donor was tested with negative results for the following markers during the suitability examination:

- Human Immunodeficiency Virus (Anti-HIV-1/2 antibodies, HIV-1 genome)
- Hepatitis B Virus (HBsAg, Anti-HBc antibodies, HBV genome)
- Hepatitis C Virus (Anti-HCV antibodies, HCV genome)
- Hepatitis E Virus (HEV genome)
- West Nile Virus (WNV genome) from June to December
- Treponema pallidum (antibody screening)
- Epstein-Barr Virus (Anti-EBV-IgG and IgM)
- Toxoplasmosis (Anti-Toxoplasma IgG and IgM)
- Human T-lymphotropic Virus (Anti-HTLV1/2 antibodies)

In case of a repeatedly reactive result in screening for Anti-HBc antibodies, according to the announcement of the Paul-Ehrlich-Institut (BAnz AT 18.03.2014 B6), the finding must be evaluated as nonspecific through further testing, or in the case of specifically reactive Anti-HBc finding, it must be ensured that virological criteria (HBV genome negative, Anti-HBs titer ≥ 100 IU/L) speak for a resolved HBV infection.
The donor was tested for Human Cytomegalovirus (Anti-CMV-IgG and -IgM, if necessary CMV genome).
For fresh stem cell preparations, the donor was retested for the above parameters during stem cell collection.
► Results: See accompanying document! If the current results are not available at the time of dispensing fresh stem cell preparations, they will be provided promptly. In case of demonstrated infectivity, the preparation is appropriately labeled (Caution: Biological hazard!) and must be transported and stored separately.

8.2 Quality Assurance
For the transplantation of stem cell preparations, healthcare facilities must take measures within the framework of quality assurance according to legal requirements. These include, among others, detailed instructions for:
- Indication,
- Pre- and post-treatment,
- Measures for transplantation-associated complications,
- Selection of the type and quantity of stem cell preparation,
- Precautionary measures to maintain the integrity of the transplant and the functionality of the stem cells,
- Follow-up examination of the patient to determine transplantation success,
- Patient-related documentation, and
- Reporting obligations.

The criteria for donor selection and, if necessary, for special processing of the stem cell preparation, as well as prophylactic measures during application and monitoring of application, must be defined within the framework of patient-related quality assurance.

8.3 Special Precautions for Disposal

After use the primary containers of the stem cell preparations must be sealed sterilely and stored at +2°C to +10°C for 24 hours for any necessary follow-up examinations. Unused preparations must be reported to the manufacturer and disposed of properly. They must not be used for recipients other than those specified by the manufacturer. The proper disposal of opened or no longer usable preparations must be ensured in accordance with the guidelines of the healthcare facility. Utilization for scientific purposes is possible with the donor's consent. The application and whereabouts of all stem cell preparations must be documented within a quality assurance system.

9. References

The product-specific information on the container label and the accompanying document must be observed. Also, to be considered are the current german “Richtlinie zur Herstellung und Anwendung von hämatopoetischen Stammzellzubereitungen” (Guideline for the Production and Application of Hematopoietic Stem Cell Preparations) and any additional publications and announcements by Bundesärztekammer und des Paul-Ehrlich-Instituts (german Federal Medical Association)

10. Date of Last Revision

April 15, 2024