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

Zalmoxis 5-20 x 10^6 cells/mL dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2).

2.2 Qualitative and quantitative composition

Each bag of Zalmoxis contains a volume of 10-100 mL of frozen dispersion at the concentration of 5-20 x 10^6 cells/mL. The cells are of human origin and genetically modified with a replication-defective γ-retroviral vector coding for the HSV-TK and ΔLNGFR genes so that these sequences are integrated in the genome of the host cells.

The cellular composition and the final cell number will vary according to the weight of the patient. In addition to T cells, NK cells and residual levels of monocytes and of B cells may be present.

Excipient with known effect

Each bag contains approximately 13.3 mmol (305.63 mg) of sodium per dose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for infusion
Opaque, off-white frozen dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zalmoxis is indicated as adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies (see section 5.1).

4.2 Posology and method of administration

Zalmoxis must be administered under the supervision of a physician experienced in HSCT for haematological malignancies.

Posology
The recommended dose and schedule is 1 ± 0.2 x 10^7 cells/kg given as an intravenous infusion at a time interval of 21-49 days from transplantation, in the absence of spontaneous immune reconstitution

and/or development of graft-versus-host disease (GvHD). Additional infusions are administered at approximately one month intervals for a maximum of four times, until a circulating T lymphocyte count is equal to or more than 100 per µL.

Zalmoxis should not be administered if the circulating T lymphocytes are ≥100 per µL at the day of planned infusion after haploidentical HSCT.

Paediatric population
The safety and efficacy in children and adolescents (less than 18 years) have not been established. No data are available. Zalmoxis is therefore not recommended for use in children and adolescent below 18 years.

Method of administration
Zalmoxis is solely for use as patient specific medicinal product to be administered after HSCT and it is administered by intravenous infusion.

Zalmoxis should be infused intravenously over a period of 20-60 minutes. The entire volume of the bag should be infused.

If the infusion must be interrupted, it should not be resumed if the infusion bag has been held at room temperature (15 °C-30 °C) for more than 2 hours.

Precautions to be taken before handling or administering the medicinal product
Before infusion it must be confirmed that the patient identity matches the essential unique information reported on the Zalmoxis bag label and on the related Certificate of Analysis (CoA).

The bag should be removed from the liquid nitrogen, put in a double bag container and thawed in a pre-warmed water bath at 37 °C. Upon full cell dispersion thawing, the bag is dried, disinfected and ready to be infused at a rate prescribed by the physician. Once the bag is infused, it is flushed 2 to 3 times with sodium chloride solution in order to completely administer Zalmoxis. The entire volume of the bag has to be infused.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Immune reconstitution defined as circulating T lymphocytes ≥100 per µL at the day of planned infusion after haploidentical HSCT.

GvHD requiring systemic immunosupressive therapy.

4.4 Special warnings and precautions for use

General
Zalmoxis is a patient specific product and should under no circumstances be administered to other patients. It must not be administered if the following conditions occur:

a) infections requiring administration of ganciclovir (GCV) or valganciclovir (VCV) at the time of infusion;
b) GvHD requiring systemic immunosupressive therapy;
c) ongoing systemic immunosupressive therapy or administration of granulocyte colony stimulating factor (G-CSF) after haploidentical HSCT.

Patients characterized by condition a) could be administered Zalmoxis 24 hours following the antiviral therapy discontinuation; patients characterized by conditions b) and c) could be administered Zalmoxis after an adequate wash out period.

Zalmoxis 5-20 x 10^6 cells/mL cell dispersion for infusion contains 13.3 mmol (305.63 mg) of sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

It is strongly recommended that, at the end of Zalmoxis infusion, the product label is removed from the bag and placed in the patient record sheet.

Treatment should be discontinued in case of occurrence of any 3-4 grade event related to Zalmoxis administration or grade 2 adverse event not resolving in a grade 1 or less in the next 30 days.

Zalmoxis is obtained by donor blood cells. Even if donors are preliminary tested and found negative for transmissible infectious disease, precautions should be employed when handling Zalmoxis. Healthcare professionals handling Zalmoxis should therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Cases in which Zalmoxis cannot be supplied / infused
In some cases, the patient may be unable to receive Zalmoxis because of manufacturing issues.

There may be cases in which the treating physician may still consider preferable to give the treatment or select an alternative treatment.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
The risk on virus shedding vertical viral transmission is theoretically negligible however not excluded. Women of childbearing potential have to provide a negative pregnancy test (serum or urine) within 14 days prior to start the treatment. Both male and female patients (to be) treated with Zalmoxis and their partners need to use effective contraception during and up to 6 months after treatment with Zalmoxis.

Pregnancy
There are no data from the use of Zalmoxis in pregnant women.
Studies in animals have not been performed. Given the intended clinical use in the context of a haploidentical bone marrow transplantation, a need for treatment during pregnancy is not expected. As a precautionary measure, Zalmoxis must not be administered during pregnancy and in women of childbearing potential not using contraception.

It has been shown that Zalmoxis cells may circulate for years after the last administration. In the event of pregnancy following Zalmoxis treatment adverse effect on pregnancy and the developing foetus are not expected as lymphocytes do not pass the placenta.

Breast-feeding
There are no data on the use of Zalmoxis during breast-feeding. Immune cells are excreted in human milk in low amounts.
It is recommended not to breast-feed during or after treatment with Zalmoxis therapy.

Fertility
There are no data on the effect of Zalmoxis treatment on fertility. However myeloablative conditioning regimens performed in the context of a haploidentical bone marrow transplantation is associated with sterility.

4.7 Effects on ability to drive and use machines

Zalmoxis has no or negligible influence on the ability to drive and use machines.

No detrimental effects on such activities are predicted from the pharmacology of the medicinal product. The clinical status of the patient and the ADR profile of Zalmoxis should be born in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

4.8 Undesirable effects

Summary of the safety profile
In the clinical study TK007, 30 patients with high-risk haematological malignancies undergoing HSCT received Zalmoxis monthly up to a maximum of four infusions.
The most common adverse reaction reported by patients treated with Zalmoxis in clinical trial TK007 was acute GvHD.

Tabulated list of adverse reactions
Undesirable effects recorded in the clinical study TK007 are listed in Table 1 by system organ class and by frequency of occurrence.
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Zalmoxis adverse reactions recorded in TK007 study

System Organ Class	Frequency and Adverse reactions	
	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)
Neoplasm benign, malignant and unspecified (including cysts and polyps)		Post transplant lymphoproliferative disorder
Immune system disorders	Acute GvHD (33% of patients)	Chronic GvHD
Gastrointestinal disorders		Intestinal haemorrhage
Hepatobiliary disorders		Hepatic failure
Blood and lymphatic system disorders		Febrile neutropenia Haemoglobin decreased Platelet count decreased
Infections and infestations		Bronchitis
General disorders and administration site conditions		Pyrexia

Description of selected adverse reactions
Globally, acute episodes of GvHD occurred in 10 patients (33%) with a median time to onset of 90 days after HSCT and 42 days after last infusion of Zalmoxis cells. Severity of acute GvHD was grade 1 in one case (3%), grade 2 in seven (23%), grade 3 in one (3%) and grade 4 in one (3%). All acute GvHD events fully resolved after a median duration of 12 days. Only one patient (3%) developed an extensive chronic GvHD that occurred 159 days and 129 days from HSCT and last infusion, respectively, and fully resolved after 107 days. There were no GvHD-related deaths or long-term complications. Both acute and chronic GvHD events developed only in patients who had achieved immune reconstitution.
For treating Zalmoxis-related GvHD through activation of the suicide gene, patients received GCV intravenously or VCV orally, for better patient convenience. All signs and symptoms of grade 2 to 4 acute and extensive chronic GvHD fully resolved after a median treatment duration of GCV or VCV of 15 days. One patient with grade 1 acute GvHD did not receive any treatment. Seven patients needed to add an immunosuppressive treatment consisting of steroids, mycophenolate and/or cyclosporine.

Paediatric population
No specific paediatric group has been studied at present. Only one 17-year-old male, affected by T lymphoblastic lymphoma, was treated in the TK007 trial with two infusions of Zalmoxis. No adverse reactions were reported for this patient.

Other special populations
In the TK007 clinical study only one 66-year-old female was treated with one infusion of Zalmoxis. The patient did not experience any adverse reactions. No implications on the use of Zalmoxis in patients of 65 and older have been established.

Reporting of suspected adverse 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 the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms of overdose are not known. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: not yet assigned

Mechanism of action
The primary mechanism of action of Zalmoxis relies on its ability to engraft and stimulate immune-reconstitution.
Zalmoxis is constituted of donor's T lymphocytes genetically modified to express the HSV-TK Mut2, as suicide gene. This allows the selective killing of dividing cells upon administration of the pro-drug GCV, which is enzymatically phosphorylated to an active triphosphate analogue by HSV-TK. Triphosphate GCV competitively, inhibits incorporation of deoxyguanosine triphosphate (dGTP) into elongating DNA, thus killing the proliferating cells.
If GvHD occurs, GCV/VCV will be administered. The activated, transduced T lymphocytes that are causing the GvHD should convert the GCV to its toxic form and thereby undergo apoptosis. This strategy allows the direct targeting of those T lymphocytes that are initiating the GvHD response.

Pharmacodynamic effects
Overall, in the clinical study TK007, the 30 treated patients received their first infusion of Zalmoxis cells at a median time of 43 days from the date of HSCT. The median interval time between the first and the subsequent infusions of Zalmoxis cells was 30 days.
Immune-reconstituted patients reached a $CD3^+$ cell count $\geq 100/\mu L$ at a median of 77 days after HSCT. In particular, at immune reconstitution Zalmoxis represents a high proportion of the circulating lymphocytes, while at later time points the proportion of Zalmoxis progressively decreases and untransduced lymphocytes expand from donor-derived precursors. One year post-Zalmoxis administration the newly reconstituted T cell repertoire is dominated by untransduced cells of donor origin which displayed a polyclonal pattern comparable to healthy individuals.

Clinical efficacy and safety
Zalmoxis was evaluated in a phase I/II clinical study (TK007) in adult patients with haematological malignancies at high risk of relapse who have received a stem-cell transplantation from a human leukocyte antigen (HLA) mismatched (haploidentical) donor. High-risk haematological malignancies

treated with Zalmoxis included acute myeloid leukaemia (AML), secondary AML, acute lymphoblastic leukaemia, myelodysplastic syndrome and non-Hodgkin lymphoma.
Treatment plan consisted of the administration of genetically modified donor's T lymphocytes (ranging from 1 x 10^6 to 1 x 10^7 cells/kg body weight). Primary aims of the TK007 study were to evaluate incidence and time to immune reconstitution, defined by the number of circulating $CD3^+ \geq$ 100/μL for two consecutive observations, and incidence of GvHD and response to GCV. Criteria for receiving Zalmoxis infusions included the lack of both immune reconstitution and GvHD.

Of 30 patients receiving Zalmoxis, 23 patients (77%) obtained immune reconstitution, with a median time of 31 days after the first infusion. For the patients who achieved immune reconstitution, a non-relapse mortality (NRM) of 17% was reported, with 35% of these patients being disease free at 5 years and 34% alive at 10 years.

Results from a matched-pair analyses that included 36 Zalmoxis patients (22 from TK007 trial and 14 from the ongoing phase III TK008 trial) and 127 control patients, showed that the Zalmoxis treated patients that had survived the first 3 weeks post-transplant without relapse benefited in terms of 1 year overall survival (OS) (40% vs 51% (p=0.03)) and 1-year NRM (42% vs 23% (p=0.04)). There was no significant difference regarding leukaemia free survival and the chance for relapse.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Zalmoxis in one or more subsets of the paediatric population in the following condition: adjunctive treatment in haematopoietic cell transplantation (see section 4.2 for information on paediatric use).

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

The nature and the intended use of the product are such that conventional studies on pharmacokinetics including absorption, distribution, metabolism and excretion are not applicable.

5.3 Preclinical safety data

Conventional toxicology, carcinogenicity, mutagenicity and reproductive toxicology studies have not been performed.
Non clinical safety data obtained in two different immunedeficient animal models for GvHD did not indicate special hazards for humans, but allowed only a very limited safety assessment. *In vitro* evaluation of oncological potential indicate that the risk of malignant transformation is low.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Human serum albumin
Dimethyl sulfoxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

18 months when stored in liquid nitrogen vapour.

The product should be administered immediately after thawing. In-use storage times and conditions should not exceed 2 hours at room temperature (15 °C – 30 °C).

6.4 Special precautions for storage

Store in liquid nitrogen vapour.

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

One individual treatment dose in 50-500 mL ethylene-vinyl-acetate cryo bag, inside a plastic bag and then a metal box.

6.6 Special precautions for disposal and other handling

Zalmoxis is a patient specific medicinal product. The identity of the patient must be matched with the essential unique donor information prior to infusion.

Zalmoxis is obtained by donor blood cells. Even if donors are preliminary tested and found negative for transmissible infectious disease, precautions should be employed when handling Zalmoxis (see section 4.4).

This medicinal product contains genetically-modified cells. Local biosafety guidelines applicable for such products should be followed for unused medicinal product or waste material.

Work surfaces and material which have potentially been in contact with Zalmoxis must be decontaminated with appropriate disinfectant.

7. MARKETING AUTHORISATION HOLDER

MolMed S.p.A.
Via Olgettina 58
20132 Milano
Italy
+39-02-212771
+39-02-21277220
e-mail: info@molmed.com

8. MARKETING AUTHORISATION NUMBER

EU/1/16/1121/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER 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

MolMed SpA
Via Olgettina 58
20132
Milan
Italy

MolMed SpA
Via Meucci 3
20091
Bresso (MI)
Italy

Name and address of the manufacturer responsible for batch release

MolMed SpA
Via Olgettina 58
20132
Milan
Italy

MolMed SpA
Via Meucci 3
20091
Bresso (MI)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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**

The requirements for submission of periodic safety update reports 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 authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The 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.

- **Additional risk minimisation measures**

Prior to launch of Zalmoxis in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials for the Health Care Professionals (HCPs), with the National Competent Authority.

The MAH shall ensure that in each Member State where Zalmoxis is marketed, all HCPs who are expected to prescribe, dispense, and administer Zalmoxis are provided with a guidance document containing the following key elements:

1. Relevant information about the safety concerns of Graft versus Host Disease (GvHD)

During and after treatment with Zalmoxis the physician must be aware of acute and chronic sign and symptoms of GvHD at any time and ensure that either ganciclovir or valganciclovir is available at ward for early treatment of GvHD.

If at any time during or after treatment with Zalmoxis an acute GvHD of grade equal to or greater than 2 or a chronic GvHD develop, the patient has to be treated with ganciclovir at a dose of 10 mg/kg/day divided into 2 administrations intravenously, or valganciclovir 900 mg two times per day orally for 14 days.

In case of GvHD progression after 3 days of treatment with ganciclovir or valganciclovir alone, a standard immunosuppressive therapy has to be added.

Zalmoxis should be administered after a 24-hour discontinuation period of ganciclovir or valganciclovir and immunosuppressive therapy.

2. Relevant information about the safety concern of Concomitant administration of Ganciclovir and Valganciclovir

The treating physician must ensure that patients do not receive ganciclovir or valganciclovir within 24 hours prior to the administration of Zalmoxis. A longer interval might apply in case of renal failure.

3. Relevant information about the safety concern of Concomitant immunosuppressive therapy

Patients should not be administered Zalmoxis in case of:

- Onset of GVHD requiring systemic immunosuppressive therapy
- Ongoing systemic immunosuppressive therapy or administration of granulocyte colony stimulating factor (G-CSF) after haploidentical hematopoietic stem-cell transplantation

Patients could be treated with Zalmoxis 24 hours after the antiviral or immunosuppressive therapy discontinuation.

Zalmoxis shall not be administered to patients with concurrent systemic immunosuppressive therapy as the efficacy of Zalmoxis treatment in early immune reconstitution may be reduced. Immunosuppressive therapy also affects immunocompetent cells as such infused with Zalmoxis. An adequate wash-out period shall be applied prior to infusion of this medicinal product.

4. Remarks on the importance of reporting ADRs and encourage patients to be enrolled into study TK011 (linked with the EBMT registry)

5. A Detailed step-by step description of Zalmoxis administration procedure, also focusing on:

- The room requirements for Zalmoxis administration
- Storage, transport and thawing of Zalmoxis bag
- Surveillance of Zalmoxis efficacy (Immune reconstitution - IR)

To monitor IR, the quantification analyses of CD3+ cells should be performed weekly during the first month after Zalmoxis administration. In absence of IR, an additional Zalmoxis dose has to be administered with an interval of 30 days up to a maximum number of four doses. In case of IR achievement, documented by two consecutive CD3+ cell counts ≥ 100/µL, Zalmoxis treatment has to be stopped.

Obligation to complete post-authorisation measures

Description	**Due date**
Non Interventional PASS: In order to investigate the safety and effectiveness in real clinical practice as well as long-term safety and effectiveness in all patients treated with Zalmoxis, the MAH should conduct and submit the results of study TK011 using the EBMT registry including all patients treated with Zalmoxis. Progress updates should be submitted yearly with the annual renewal. The clinical study report should be submitted by Q4 2022.	Q4 2022

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

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
The MAH shall complete, within the stated timeframe, the below measures: In order to confirm the efficacy and safety of Zalmoxis as an adjunctive treatment in haploidentical haematopoietic stem-cell transplantation of adult patients with high-risk haematological malignancies, the MAH should submit the results of study TK008, a randomized phase III trial of haploidentical HCT with an add back strategy of HSV-Tk donor lymphocytes in patients with high risk acute leukaemia. In addition updates on recruitment should be submitted within the PSURs. The clinical study report should be submitted by March 2021.	March 2021

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Zalmoxis 5-20 x 10^6 cells/mL dispersion for infusion

Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and herpes simplex I virus thymidine kinase (HSV-TK Mut2)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

The bag contains a volume of 10-100 mL of frozen dispersion at a concentration of 5-20 x 10^6 cells/mL

3. LIST OF EXCIPIENTS

Human serum albumine, dimethyl sulphoxide, sodium chloride.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
Bag volume:_____mL
Dose: 1x10^7 cells /kg
Concentration: _____x10^x cells/mL
Total cell number: _____x10^X

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Patient specific product not to be administered to other patients

8. EXPIRY DATE

EXP:
Shelf life after thawing: 2 hours at room temperature (15 °C – 30 °C)

9. SPECIAL STORAGE CONDITIONS

Store in liquid nitrogen vapour.

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

This medicinal product contains genetically-modified cells. Local biosafety guidelines applicable for such products should be followed for unused medicinal product or waste material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MolMed S.p.A.
Via Olgettina 58
20132 Milano
Italy

12. MARKETING AUTHORISATION NUMBER

EU/1/16/1121/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Batch:
Patient code:
Donor code**:**

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 IMMEDIATE PACKAGING

PLASTIC BAG

1. NAME OF THE MEDICINAL PRODUCT

Zalmoxis 5-20 x 10^6 cells/mL dispersion for infusion

Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and herpes simplex I virus thymidine kinase (HSV-TK Mut2)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

The bag contains a volume of 10-100 mL of frozen dispersion at a concentration of 5-20 x 10^6 cells/mL

3. LIST OF EXCIPIENTS

Human serum albumine, dimethyl sulphoxide, sodium chloride.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
Bag volume:_____mL
Dose: 1x10^7 cells /kg
Concentration: _____x10^x cells/mL
Total cell number: _____x10^X

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Patient specific product not to be administered to other patients

8. EXPIRY DATE

EXP:
Shelf life after thawing: 2 hours at room temperature (15 °C – 30 °C)

9. SPECIAL STORAGE CONDITIONS

Store in liquid nitrogen vapour.

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

This medicinal product contains genetically-modified cells. Local biosafety guidelines applicable for such products should be followed for unused medicinal product or waste material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MolMed S.p.A.
Via Olgettina 58
20132 Milano
Italy

12. MARKETING AUTHORISATION NUMBER

EU/1/16/1121/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

Batch:
Patient code:
Donor code:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Not applicable

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

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BAG

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zalmoxis 5-20x10^6 cells/mL dispersion for infusion
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

Expiry date:
Shelf life after thawing: 2 hours

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Batch:
Patient code:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Total cell number: ____x10^X

6. OTHER

MolMed SpA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zalmoxis 5-20 x 10^6 cells/mL dispersion for infusion

Allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)

▼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 start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or a physician experienced in the medical treatment of blood cancer.
- If you get any side effects, talk to your doctor, or a physician experienced in the medical treatment of blood cancer. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. WHAT ZALMOXIS IS AND WHAT IT IS USED FOR

Zalmoxis consists of white blood cells called T cells that are obtained from the donor. These cells will be genetically modified by introducing a "suicide" gene (HSV-TK Mut2) in their genetic code which can be activated later on in case of graft-versus-host disease. This will ensure that the cells can be eliminated before they can cause damage to the patient's cells.

Zalmoxis is intended for use in adults with certain tumours of the blood known as high-risk haemotological malignancies. It is given after haploidentical bone marrow transplantation (haematopoietic cell transplantation). Haploidentical means that the cells have been obtained from a donor whose tissues partially match the patient's tissue. Zalmoxis is given to prevent a complication of transplantations that are not fully matched known as 'graft-versus-host disease' whereby the cells of the donor attack the patient's own cells.

2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN ZALMOXIS

Do not use Zalmoxis:

- If you are allergic to the active substance or any of the ingredients of this medicine (listed in section 6).
- If, before infusion, the value of $CD3^+$ lymphocytes in your tests is equal to or more than 100 per μL.

- If you suffer from graft-versus-host disease which requires the use of medicines to suppress your immune system.

Warnings and precautions

Zalmoxis is a patient specific product and should under no circumstances be administered to other patients.
Your doctor will closely supervise the treatment therapy. You should tell your doctor before using Zalmoxis if:

- You suffer from infections requiring administration of ganciclovir (GCV) or valganciclovir (VCV) (antiviral) at the time of infusion. In this case treatment with Zalmoxis should be delayed until 24 hours after the end of the antiviral therapy.
- You suffer from graft-versus-host disease which requires the use of medicines to suppress your immune system.
- If you are taking medicines to suppress your immune system or you are taking G-CSF (that stimulates the bone marrow to produce blood cells) after receiving stem-cell transplantation . In this case, Zalmoxis may be administered after an adequate wash out period (the time necessary to remove a medicine from your body).
- If you have previously experienced any adverse reaction following Zalmoxis administration and this has not been resolved within 30 days after its occurrence.

When Zalmoxis cannot be given

In some cases you may not be able to receive a scheduled infusion of Zalmoxis. This may be because of manufacturing issues.

In such cases your physician will be informed and may still consider preferable to give the treatment or may select an alternative treatment for you.

Children and adolescents

Currently, no data are available for these patients. The use of Zalmoxis is not recommended for children and adolescents under the age of 18.

Other medicines and Zalmoxis

No interaction studies have been performed.
Please inform your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding

The safe use of Zalmoxis has not been demonstrated during pregnancy and breast-feeding.
Zalmoxis must not be used in pregnant and breast-feeding women.
Women of childbearing potential have to use effective contraception during and up to 6 months after treatment with Zalmoxis.
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 taking this medicine.

Driving and using machines

Zalmoxis should not have any effects on your ability to drive and use machines. However, you should pay attention to your overall status when considering performing tasks that require judgment, motor or cognitive skills.

Zalmoxis contains sodium

Zalmoxis 5-20 x 10^6 cells/mL cell dispersion for infusion contains 13.3 mmol (305.63 mg) of sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

3. HOW ZALMOXIS IS GIVEN TO YOU

Zalmoxis can only be prescribed and administered in a hospital by a doctor or a nurse who is trained in administering this medicine. Practical information for handling and administration of Zalmoxis for the doctor or nurse can be found at the end of this leaflet.

Zalmoxis has been manufactured specifically for you and cannot be administered to any other patient. The amount of cells to be administered depends on your body weight. The dose corresponds to 1 ± 0.2 x 10^7 cells/kg.

Zalmoxis is given intravenously (into a vein) as a drip infusion over approximately 20-60 minutes at a time interval of 21-49 days from transplantation. Additional infusions are given once a month, for up to 4 months. The decision to proceed with the next treament is determined by your physician/doctor and is related to your immune status.

If you receive more Zalmoxis than you should

As this medicine is prescribed by a doctor, each dose is prepared for you only and each preparation consists of a single dose. It is unlikely that you will be given too much.

If you forget to use Zalmoxis

This medicine is prescribed by a doctor and given in a hospital under strict survelliance and predetermined schedule so that you cannot forget your dose.

If you have any further questions on the use of this medicine, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these side effects may be serious and may lead to hospitalization.

If you have any questions about symptoms or side effects, or if any symptoms concern you
→ Talk immediately to your doctor.

Very common side effects (may affect more than 1 in 10 people)

Acute graft-versus-host disease (a complication that can occur after a stem-cell or bone marrow transplantation in which the newly transplanted donor cells attack the patient's body).

Common side effects (may affect up to 1 in 10 people)

- Post-transplantation lymphoproliferative disorder (increase in the number of white blood cells in the blood after a transplantation)
- Chronic graft-versus-host disease (a complication that can occur after a stem-cell or bone marrow transplantation in which the newly transplanted donor cells attack the patient's body)
- Intestinal haemorrage (bleeding in the gut)
- Hepatic failure (liver malfunction)
- Febrile neutropenia (fever associated with reduction of the number of white blood cells)
- Decreased haemoglobin (reduction of the number of red blood cells)

- Decreased platelet count (reduction of the number of platelets in the blood)
- Bronchitis (lung infection)
- Pyrexia (fever)

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 ZALMOXIS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

Store in liquid nitrogen vapour.

The infusion solution should be used immediately after thawing. Maximum time elapsed from thawing and infusion is 2 hours at room temperature (15 °C – 30 °C).

The package is checked for the presence of any abnormality in the outer box and the label is checked for patient/donor correspondance.

Any unused medicine or waste should be disposed of as biological hazard material containing genetically modified organisms and in accordance with local requirements.

The hospital staff are responsible for the correct storage of the product both before and during its use, as well as for correct disposal.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Zalmoxis contains

The **active substance** consists of allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2).

Each bag contains a volume of 10-100 mL of frozen dispersion at a concentration of 5-20 x 10^6 cells/mL.

The **other ingredients** are sodium chloride, human serum albumin and dimethyl sulfoxide (see section 2).

What Zalmoxis looks like and contents of the pack

Zalmoxis is a cell dispersion for infusion appearing as opaque, off-white frozen dispersion of cells.

Zalmoxis is supplied as one individual treatment dose in a 50-500 mL ethylene-vinyl-acetate cryo bags.

Marketing Authorisation Holder

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This leaflet was last revised in

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

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Practical information for medical or healthcare professionals on the handling and administration of Zalmoxis.

Zalmoxis must be administered under the supervision of a physician experienced in haematopoietic stem cell transplantation for haematological malignacies.

It is important that you read the entire content of this procedure prior to administering Zalmoxis.

Dose and course of treatment

One bag contains donor T cells genetically modified to express HSV-TK and ΔLNGFR at the concentration of 5-20 x 10^6 cells/mL.

The course of treatment is a maximum of four infusions at approximately one month intervals. The decision to proceed with a new treatment depends on the immune reconstitution status of the patient achieved when a circulating T lymphocyte count is equal to or more than 100 per µL.

Handling instructions

Before handling or administering Zalmoxis

- Zalmoxis is shipped directly to the medical facility where the infusion will be administered. The shipping is performed in liquid nitrogen vapour. The bag is put in a second bag (intermediate container) and this one is placed in an aluminium box (outer container). The whole package is secured in a liquid nitrogen container designed to maintain the appropriate transportation and storage temperature until the time of infusion. If the medicinal product is not immediately prepared for infusion, transfer the bag in liquid nitrogen vapour. Do not irradiate.
- Zalmoxis is prepared from human blood of a specific donor and it consists of genetically modified cells. Donors are tested for transmissible infectious agents in line with applicable local requirements. However, the risk of transmitting infectious viruses to healthcare professionals cannot be totally excluded. Accordingly, healthcare professionals should take appropriate precautions (e.g. wearing gloves and glasses) when handling Zalmoxis.
- The outer and intermediate package should be checked to verify the product and patient-specific-label located on the top of the box and on the intermediate bag.

What to check before infusion

- Check that the Certificate of Analysis containing the patient identifiers, expiry date and approval for infusion has been received from the Marketing Authorization Holder.
- Check that the patient identity matches the essential and unique patient information reported on the Zalmoxis bag and on the Certificate of Analysis.
- Once the patient is prepared for infusion, inspect the Zalmoxis bag for integrity. The bag should appear as an opaque, off-white frozen cell dispersion. If the bag appears to have clear breaks or to be non-intact, do not use the product.
- Put the bag into two plastic envelopes (double envelopment) to avoid direct contact with water.
- While holding the top of the envelope bag out of the water, put it in a 37±1°C water bath being careful not to allow water to penetrate the seal. If leakage occurs during thawing, do not use the product.

Administration

- When completely thawed, remove the Zalmoxis bag out from the double envelopment, dry it off and disinfect the outside.
- Proceed with the infusion as quickly as possible, avoiding keeping the bag in the water bath after thawing.
- The entire volume of the bag must be infused. The recommended infusion time is around 20-60 minutes

After the infusion

- At the end of infusion, wash the bag 2 or 3 times with a physiological solution using a sterile technique, in order to completely administer Zalmoxis.
- Upon completion of washing, the patient specific label on the bag should be removed and adhered to the patient specific file.
- The cryobag and any unused product or waste material contains genetically modified organisms and should be disposed of in accordance with local requirements.

Do not infuse Zalmoxis if

- You have not received the Certificate of Analysis.
- The Certificate of Analysis is marked as rejected.
- The expiry date has passed.
- The unique patient information on the infusion bag does not match that of the scheduled patient.
- The product integrity has been breached in anyway.

Shelf life and special precautions for storage

- Zalmoxis has a shelf life of 18 months when stored in liquid nitrogen vapour.

- Zalmoxis must be used be immediately after removal from the shipping container. If not used immediately, transfer the Zalmoxis bag from the shipping container to liquid nitrogen vapour.
- Shelf life after thawing is of 2 hours.

Annex IV

Conclusions on the granting of the conditional marketing authorisation and similarity 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.