SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

PHELINUN 200 mg powder and solvent for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PHELINUN 200 mg powder and solvent for concentrate for solution for infusion
One vial of powder for concentrate for solution for infusion contains 200 mg melphalan (as melphalan hydrochloride).

After reconstitution with 40 ml of solvent, the final concentration of the solution is 5 mg/ml.

Excipients with known effect
When reconstituted, one vial contains 2.72 mmol (62.52 mg) of sodium, 1.6 g of ethanol and 24.9 g of propylene glycol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for concentrate for solution for infusion

Powder: white to pale yellow freeze-dried powder or cake.
Solvent: clear colourless liquid solution.

The pH of the reconstituted solution is between 6.0 and 7.0 and the osmolality is 75 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

High-dose of PHELINUN used alone or in combination with other cytotoxic medicinal products and/or total body irradiation is indicated in the treatment of:

- multiple myeloma,
- malignant lymphoma (Hodgkin, non-Hodgkin lymphoma),
- acute lymphoblastic and myeloblastic leukemia,
- childhood neuroblastoma,
- ovarian cancer,
- mammary adenocarcinoma.

PHELINUN in combination with other cytotoxic medicinal products is indicated as reduced intensity conditioning (RIC) treatment prior to allogeneic haematopoietic stem cell transplantation (allo-HSCT) in malignant haematological diseases in adults.

PHELINUN in combination with other cytotoxic medicinal products is indicated as conditioning regimen prior to allogeneic haematopoietic stem cell transplantation in haematological diseases in the paediatric population as:

- Myeloablative conditioning (MAC) treatment in case of malignant haematological diseases
- RIC treatment in case of non-malignant haematological diseases.

4.2 Posology and method of administration

PHELINUN administration must be supervised by a physician experienced in the use of chemotherapeutic medicinal products and in conditioning treatment prior to haematopoietic stem cell transplantation.

Posology

Adults

Multiple myeloma, malignant lymphoma (Hodgkin, non-Hodgkin lymphoma), acute lymphoblastic and myeloblastic leukaemia (ALL and AML), ovarian cancer and mammary adenocarcinoma at a high-dose
The dose regimen is as follows: one dose between 100 and 200 mg/m^2 body surface area (approximatively 2.5 to 5.0 mg/kg body weight). The dose can be divided equally over 2 or 3 consecutive days. Autologous hematopoietic stem cell transplantation is required following doses above 140 mg/m^2 body surface area.

Malignant haematological diseases before allogeneic haematopoietic stem cell transplantation

The recommended dose is 140 mg/m^2 as a single daily infusion or 70 mg/m^2 once daily for two consecutive days.

Paediatric population

Acute lymphoblastic and myeloblastic leukaemia at high-dose
The dose regimen is as follows: one dose between 100 and 200 mg/m^2 body surface area (approximatively 2.5 to 5.0 mg/kg body weight). The dose can be divided equally over 2 or 3 consecutive days. Autologous hematopoietic stem cell transplantation is required following doses above of 140 mg/m^2 body surface area.

Childhood neuroblastoma
The recommended dose to consolidate a response obtained with a conventional treatment is one single dose between 100 mg/m^2 and 240 mg/m^2 body surface area (sometimes divided equally over 3 consecutive days) together with autologous haematopoietic stem cell transplantation. The infusion is used either alone or in combination with radiotherapy and/or other cytotoxic medicinal products.

Haematological diseases before allogeneic haematopoietic stem cell transplantation
The recommended dose is as follows:
- malignant haematological diseases: 140 mg/m^2 as a single daily infusion;
- non-malignant haematological diseases: 140 mg/m^2 as a single daily infusion or 70 mg/m^2 once daily for two consecutive days.

Thromboembolic complications

Thrombosis prophylaxis needs to be administered during at least the first 5 months of the treatment, in particular to patients who are more at risk of thrombosis. The decision to take antithrombotic prophylactic measures needs to be taken after a thorough assessment of the underlying risks for the individual patient (see sections 4.4 and 4.8).

Special populations

Elderly
There is no dose recommendation for the administration of PHELINUN to elderly. However, frequently conventional doses of melphalan are applied in the elderly. Experience in the use of high dose melphalan in elderly patients is limited. Consideration should therefore be given to ensure adequate performance status and organ function, before using high dose melphalan in elderly patients.

Renal impairment
The posology should be adjusted in patients with renal impairment (see section 4.4). The clearance of melphalan, although variable, may be reduced with impaired renal function.
High-dose melphalan with haematopoietic stem cell rescue has been used successfully even in dialysis dependent patients with end-stage renal failure.
As a guide, for high dose Melphalan treatment without haematopoietic stem cell rescue in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min) a dose reduction of 50% is usual. High dose Melphalan (above 140 mg/m2) without haematopoietic stem cell rescue should not be used in patients with more severe renal impairment.
For high intravenous doses of melphalan (100 to 240 mg/m^2 body surface area), the need for dose reduction depends upon the degree of renal impairment, whether haematopoietic stem cells are re-infused, and the therapeutic need. Melphalan

injection should be given with haematopoietic stem cell rescue at doses above 140 mg/m^2.

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment and that there are insufficient data in patients with moderate or severe heptic impairment.

Method of administration

It is recommended to ensure patients' adequate hydration and forced diuresis and the prophylactic administration of anti-infective agents (bacterial fungal, viral) (see sections 4.4).

Cyclophosphamide pre-treatment appears to reduce the severity of gastrointestinal damage induced by high-dose PHELINUN and the literature should be consulted for details (see sections 4.8).

Adoption of prohylactic measures such as the administration of anti-infective agents can be useful(see sections 4.8).

The occurrence of GvHD can be prevented by using immunosuppressive therapy after haematopoietic stem cell transplantation as prophylaxis (see sections 4.8).

PHELINUN is for intravenous use only.
Risk of extravasation could be observed when PHELINUN is administered via peripheral intravenous route. In case of extravasation, the administration should be interrupted immediately and a central venous line route should be used.

If high-dose is administered with or without transplantation, the administration as dilution via a central venous line is recommended to avoid extravasation.
It is recommended that PHELINUN as concentrate (5 mg/ml) is injected slowly into the port of a fast-running infusion solution.
If the injection of the concentrate (5 mg/ml) slowly into a fast-running infusion solution is not appropriate, PHELINUN may be administered further diluted with sodium chloride 9 mg/ml (0.9%) solution for injection in a "slow-running" solution in a infusion bag. The total time from preparation of the solution to the completion of infusion should not exceed 1 hour and 30 minutes. When further diluted in an infusion solution, PHELINUN has reduced stability and the rate of degradation increases rapidly with rise in temperature.

It is recommended to let the infusion run at a temperature below 25°C.

Precaution to be taken before manipulating or administering the product
The preparation of injectable cytotoxic solutions must be carried out by qualified healthcare professionals with knowledge of alkylating agents handling, under conditions that ensure the environment protection and the healthcare professional safety.
Excreta and vomit must be handled with care. Pregnant staff should be warned and avoid handling PHELINUN.
If PHELINUN accidentally contacts the skin, this must be immediately washed thoroughly with soap and water.
In case of accidental contact with the eyes or mucous membranes, rinse abundantly with water.
Inhalation of the product should be avoided.

Remnants of the medicinal product as well as all materials that have been used for reconstitution and administration must be disposed of according to standard procedures applicable to cytotoxic products, with due regard to local requirements related to the disposal of hazardous waste.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (only with respect to the treatment prior to HSCT) and breat-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Melphalan can cause local tissue damage. Should extravasation occur, it should not be administered by direct injection into a peripheral vein (see section 4.2).

Hepatic veno-occlusive disease is a major complication that can occur during treatment with melphalan.

Monitoring

Since melphalan is a potent myelosuppressive agent, it is essential that careful attention is paid to the monitoring of blood counts to avoid the possibility of excessive myelosuppression and the risk of irreversible bone marrow aplasia or irreversible bone marrow failure.
Cytopenia may continue to fall after treatment is stopped. So, at the first sign of an abnormally, large fall in leukocyte or severe thrombocytopenia, treatment should be temporarily interrupted.
PHELINUN should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity.

It is recommended to ensure patients' adequate hydration and forced diuresis and the prophylactic administration of anti-infective agents (bacterial fungal, viral). The administration of blood products should be considered if required.
It is recommended to monitor the general and renal status of patients receiving high-doses of PHELINUN.

The incidence of diarrhoea, vomiting and stomatitis becomes the dose-limiting toxicity in patients given high intravenous doses of PHELINUN in association with autologous bone marrow transplantation. Cyclophosphamide pre-treatment appears to reduce the severity of gastrointestinal damage induced by high-dose PHELINUN and the literature should be consulted for details.

Mutagenicity

Melphalan is mutagenic in animals and chromosome aberrations have been observed in patients being treated with the medicinal product.

Carcinogenicity

Acute myeloide leukemia (AML) and myelodysplastic syndromes.
Melphalan has been reported to be leukaemogenic (acute leukemia and myelodysplastic syndromes). There have been reports of acute leukaemia occurring after melphalan treatment for diseases such as amyloid, malignant melanoma, multiple myeloma, macroglobulinaemia, cold agglutinin syndrome and ovarian cancer.
The leukaemogenic risk must be balanced against the potential therapeutic benefit when considering the use of melphalan, in particular when used in combination with thalidomide or lenalidomide and prednisone, as it has been determined that these combinations increase the leukaemogenic risk. Before, during and after treatment the doctor needs to examine the patients with the usual checks to detect cancer early and start treatment if necessary.

Solid tumors
The use of alkylating agents has been linked to the development of a second primary malignancy (SPM). In particular when melphalan is used in combination with lenalidomide and prednisone, and to a lesser extent in combination with thalidomide and prednisone, it has been linked to an increased chance of solid SPM for elderly patients with newly diagnosed multiple myeloma.

Thromboembolic complications

The use of melphalan in combination with lenalidomide and prednisone or thalidomide or dexamethasone has been associated with an increased risk of thromboembolic complications.
Especially in patients with increased risk factors for thrombosis, antithrombotic prophylactic measures need to be taken into consideration (see section 4.2 and 4.8).
Should thromboembolic complications occur for the patient, treatment needs to be stopped and the standard anticoagulant therapy needs to be started. As soon as the patient is stabilised by the anticoagulant therapy and the complications of the thromboembolic incident are under control, melphalan can be used in combination with lenalidomide and prednisone, or thalidomide and prednisone or dexamethasone can be resumed in the original dose contingent on the assessment of the risks and benefits. The patient needs to continue the anticoagulant therapy during the melphalan treatment.

Renal impairment

Since patients with renal impairment may have marked bone marrow suppression, these patients should be closely monitored.

Melphalan clearance may be reduced in patients with renal impairment who may also have uraemic marrow suppression. Dose reduction may therefore be necessary and these patients should be closely controlled (see sections 4.2 and 4.8).

Paediatric population

The safety and efficacy of melphalan followed by allo-HSCT in children below the age of 2 years with AML has not been established because safety and overall survival (OS) data are not reported separately for this age category (see sections 4.8 and 5.1).

The safety and efficacy of melphalan as part of the conditioning regimen prior to allo-HSCT in children below the age of 2 years with ALL has not been established.

Melphalan should not be used in adolescents over the age of 12 years with AML as conditioning treatment followed by allo-HSCT because of an increased rate of transplant-related mortality (see section 5.1).

Excipients with known effect

Ethanol

PHELINUN 200 mg powder and solvent for concentrate for solution for infusion

This medicinal product contains 1.6 g of alcohol (ethanol) in each solvent vial which is equivalent to 42 mg/ml (0.42 % w/v). The amount in 40 ml of this medicine is equivalent to 40 ml beer or 17 ml wine.

For comparison, for an adult drinking a glass of wine or 500 ml of beer, the blood alcohol concentration (BAC) is likely to be about 50 mg/100 ml.

Co-administration with medicinal products containing propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.

Adults
A dose of 200 mg/m^2 of this medicine administered to adult weighing 70 kg would result in exposure to 40 mg/kg of ethanol which may cause a rise in BAC of about 6.67 mg/100 ml.
The amount of alcohol in this medicine is not likely to have an effect in adults.

Children and adolescents
A dose of 240 mg/m^2 of this medicine administered to a child 8 years of age and weighing 30 kg would result in exposure to 76.8 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 12.8 mg/100 ml.

A dose of 240 mg/m^2 of this medicine administered to an adolescent 12 years of age and weighing 40 kg would result in exposure to 110 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 18.3 mg/100 ml.

The alcohol in this preparation is likely to affect children and adolescents. These effects may include feeling sleepy and changes in behaviour. It may also affect their ability to concentrate and take part in physical activities.
To be taken into account in children and adolescents and high risk groups such as patients with liver disease or epilepsy.

Propylene glycol

PHELINUN 200 mg powder and solvent for concentrate for solution for infusion

This medicinal product contains 24.9 g propylene glycol in each 40 ml of solvent which is equivalent to 0.62 g/ml.

Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in children less than 5 years old.

While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

With high doses or prolonged use of propylene glycol have been reported various adverse events, such as hyperosmolality, lactic acidosis; renal dysfunction (acute tubular necrosis), acute renal failure; cardiotoxicity (arrhythmia, hypotension); central nervous system disorders (depression, coma, seizures); respiratory depression, dyspnoea; liver dysfunction; haemolytic reaction (intravascular haemolysis) and haemoglobinuria; or multisystem organ dysfunction.
Adverse events usually reverse following weaning off of propylene glycol, and in more severe cases following hemodialysis.

Medical monitoring is required.

Sodium

PHELINUN 200 mg powder and solvent for concentrate for solution for infusion

This medicinal product contains 62.52 mg sodium per vial, equivalent to 3% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Nalidixic acid

The administration of high-dose intravenous PHELINUN together with nalidixic acid in children has caused haemorrhagic entercolitis with fatal outcome. Combined treatment of melphalan with nalidixic acid should be avoided.

Busulfan

In the paediatric population, for the busulfan-melphalan regimen it has been reported that the administration of melphalan less than 24 hours after the last oral busulfan administration may influence the development of toxicities.

Cyclosporin

Impaired renal function has been described in bone marrow transplant patients who were pre-conditioned with high-dose intravenous melphalan and subsequently received cyclosporin to prevent graft versus host disease.

Attenuated live vaccines

A risk of general illness which may lead to fatal outcome has described. This risk is increased in patients who are already immunosuppressed by their underlying disease. An inactivated vaccines should be used when such a vaccine exists (poliomyelitis).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

As with all cytotoxic treatments, male and female patients that receive melphalan should use effective reliable contraceptive methods up until six months after cessation of treatment.

Pregnancy

There are no or limited amount of data from the use of melphalan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Risk for human is not know, but due to the mutagenic properties and structural similarity of melphalan with known teratogenic compounds, it is possible that melphalan can induce congenital malformations in offspring of treated patients.
The use of melphalan as anti-cancer treatment should be avoided whenever possible during pregnancy, particularly during the first trimester. In each case, the benefit of the treatment outweighing the potential risk to the fetus should be evaluated.
HSCT is contraindicated in pregnant women. Therefore melphalan is contraindicated during pregnancy for this indication (see section 4.3).

Breast-feeding

It is unknown whether melphalan or its metabolites are excreted in human milk. Due to its mutagenic properties, melphalan is contraindicated during breast-feeding (see section 4.3).

Fertility

Melphalan causes suppression of ovarian function in pre-menopausal women resulting in amenorrhoea in a significant number of patients.
There is evidence from animal studies that melphalan can have an adverse effect on spermatogenesis (see section 5.3). Therefore, it is possible that melphalan may cause temporary or permanent sterility in male patients. Cryopreservation of semen before treatment is advised.

4.7 Effects on ability to drive and use machines

Melphalan has moderate influence on the ability to drive and use machines. It is likely that certain adverse reactions of melphalan, like nausea and vomiting, could affect this ability. This medicinal product also contains alcohol, which is likely to affect children and adolescents (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were haematologic and gastrointestinal toxicities, and immune system disorders, these being considered as expected consequences of myelosuppression. Infections, acute and chronic Graft versus Host Disease (GvHD) were reported as the major causes of morbidity and mortality in the allo HSCT setting. Bone marrow failure, stomatitis, mucosal inflammation, gastrointestinal haemorrhage, diarrhea, nausea, vomiting, amenorrhoea, ovarian disorders and premature menopause were also commonly reported.

Tabulated list of adverse reactions

The adverse drug reactions (ADRs) described in this section were identified from information included in other melphalan containing products, the screening of the published literature and the European database EudraVigilance concerning the use of melphalan as part of combination regimens for allo-HSCT setting. With the exception of Stevens-Johnson syndrome and Toxic epidermal necrolysis identified for only one patient, ADRs reported for at least two patients have been captured in the table below. Frequencies are described as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100), yare (≥1/10 000 to <1/1 000), very rare (<1/10 000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	**Frequency**	**Adverse Drug Reactions**
Infections and infestations	Common	Infection
	Uncommon	Septic shock
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uncommon	Secondary primary malignancy, Secondary acute myeloid leukaemia Myelodysplastic syndrome
Blood and lymphatic system disorders	Very Common	Myelosuppression leading to Neutropenia, Thrombocytopenia Anaemia
	Uncommon	Thrombotic microangiopathy
	Rare	Haemolytic anaemia

MedDRA System Organ Class	Frequency	Adverse Drug Reactions
Immune system disorders	Very common	Acute graft versus host disease, Chronic graft versus host disease
	Rare	Hypersensitivity (urticaria, oedema, skin rashes and anaphylactic shock)
	Not known	Haemophagocytic lymphohistiocytosis
Nervous system disorders	Uncommon	Haemorrhage intracranial
Cardiac disorders	Rare	Cardiac arrest
	Not known	Cardiac failure, Cardiomyopathy, Pericardial effusion
Vascular disorders	Not known	Haemorrhage, Deep venous thrombosis and Lung embolism
Respiratory, thoracic and mediastinal disorders	Uncommon	Interstitial lung disease, Pulmonary fibrosis, Idiopathic pneumonia syndrome, Pulmonary haemorrhage, Respiratory failure, Acute respiratory distress syndrome, Pneumonitis
	Not known	Pulmonary hypertension
Gastrointestinal disorders	Common	Diarrhoea, Nausea, Vomiting Stomatitis, Gastrointestinal haemorrhage
Hepatobiliary disorders	Uncommon	Hepatotoxicity, Venoocclusive liver disease
	Rare	Liver function test abnormal, Jaundice
Skin and subcutaneous tissue disorders	Very common	Alopecia after high dose
	Common	Alopecia after conventional dose
	Uncommon	Rash maculo-papular, alopecia
	Rare	Pruritus
	Not known	Stevens-Johnson syndrome, Toxic epidermal necrolysis
Renal and urinary disorders	Uncommon	Acute kidney injury, Renal failure
	Not known	Cystitis haemorrhagic, Nephrotic syndrome

MedDRA System Organ Class	Frequency	Adverse Drug Reactions
Reproductive system and breast disorders	Common	Amenorrhoea, Ovarian failure, Ovarian disorder, Premature menopause, Azoospermia
General disorders and administration site conditions	Common	Mucosal inflammation Multiple organ dysfunction syndrome Pyrexia
	Uncommon	Feeling hot Paraesthesia
Investigations	Not known	Blood creatinine increased

Description of selected adverse reactions

Infections and GvHD although not directly related to melphalan, were the major causes of morbidity and mortality, especially in the setting of allogeneic transplantation.

Infections and infestations

All patients in the target population are at risk of infections due to their immunodeficient status. Myelosuppression and immunosuppressive effects induced by melphalan may facilitate the development of infections which may have fatal outcome in the most severe manifestations. Adoption of prohylactic measures such as the administration of anti-infective agents can be useful.

Graft versus host disease

GvHD is a very common complication in the allogeneic HSCT setting. Up to ≈ 60% patients develop acute and/or chronic GvHD. The severity of GvHD may vary from mild to fatal in the most severe manifestations of the disease.
The occurrence of GvHD can be prevented by using immunosuppressive therapy after haematopoietic stem cell transplantation as prophylaxis.

Paediatric population

Respiratory, thoracic and mediastinal disorders

On the basis of the identified safety reports in the literature, the paediatric population appears more susceptible to develop respiratory complications than adults. In particular, fatal respiratory complications were reported as higher for infants below 2 years than for children and adolescents.

Gastrointestinal disorders

On the basis of the identified safety reports in the literature, the paediatric population appears more susceptible to develop gastrointestinal complications.

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 via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms and signs

Gastro-intestinal effects, including nausea and vomiting are the most likely signs of acute intravenous overdose. Damage to the gastro-intestinal mucosa may also occur. Diarrhoea, sometimes haemorrhagic, has been reported after intravenous overdose. The principal toxic effect is bone marrow suppression, leading to anaemia, neutropenia and thrombocytopenia.

Treatment

There is no specific antidote. The blood picture should be closely monitored for at least four weeks following overdose until there is evidence of recovery. The treatment should be symptomatic: blood transfusion, antibiotic therapy, haematopoietic growth factors if necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, nitrogen mustard analogues, ATC code: L01AA03.

Mechanism of action

Melphalan is a bifunctional alkylating agent that prevents the separation and replication of DNA. Formation of carbonium intermediates from each of the two bis-2-chloroethyl groups enables alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross-linking the two DNA strands and thereby preventing cell replication.

Clinical safety and efficacy

Documentation on the safety and efficacy of PHELINUN in combination with other cytotoxic medicinal products derives from literature review. In total the studies report efficacy results for 3,096 patients of whom 607 were from studies reporting results only in the paediatric population (under the age of 18 years). Endpoints in these

studies were overall survival (OS), disease-free survival (DFS), event-free survival (EFS) and non-relapse mortality (NRM). The results of published clinical studies supporting the efficacy of melphalan are summarised below divided between adult and pediatric population.

Adults

Baron et al., 2015
This retrospective study, performed by the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation, compared the outcomes for a cohort of 394 AML patients receiving a sibling HSCT after fludarabine-busulfan (n=218) or fludarabine-melphalan (n=176). Busulfan dose was ranging from 7.1 to 8.9 mg/kg [oral] or from 6.0 to 6.9 mg/kg [intravenous]; melphalan dose was ranged between 130 to 150 mg/m^2. Both are considered RIC.
There was a statistically significant reduction in relapse risk at 2 years for fludarabine-melphalan (FM) versus fludarabine-busulfan (FB) in AML patients (FM 20%, FB 30%; p=0.007) which was confirmed in multivariate analysis (HR 0.5, 95%CI 0.3-0.8, p=0.01).

Kawamura et al., 2017
This retrospective study performed in Japan compared the transplant outcomes of patients aged 50 years or older with AML, ALL or MDS after fludarabine with melphalan (140 mg/m^2 i.v.) (FM, n=423), fludarabine with intermediate doses of busulfan (6.4 mg/kg i.v.) (FB2, n=463) and fludarabine with higher doses of busulfan (12.8 mg/kg i.v.) (FB4, n=721). FM and FB2 are considered RIC-regimens and FB4 is considered a MAC regimen. There was a statistically significant reduction in relapse risk at 3 years for fludarabine-melphalan versus fludarabine-busulfan intermediate dose (FB2) in AML/ALL/MDS patients (FM 27.4%, FB2 37.2%; p=0.0027), confirmed in multivariate analysis (HR 0.56, 95% CI 0.42-0.74, p<0.001).

Eom et al., 2013
This case-control study performed in South Korea in high-risk ALL patients in first or second complete remission, compared outcomes after RIC (melphalan 140 mg/m^2 and fludarabine 150 mg/m^2; n=60) or MAC (TBI 13,2 Gy + cyclophosphamide 120 mg/kg***;*** n=120) allo-HSCT. OS rate at 5 years for fludarabine-melphalan was 54.5%. There was no statistically significant difference in OS-rate at 5 years for fludarabine-melphalan versus TBI-cyclophosphamide in high-risk ALL patients, despite RIC-patients being older or having more co-morbidities and therefore ineligible for myeloablative conditioning.

Paediatric population

Malignant haematological diseases
Three retrospective studies demonstrated the safety and efficacy of PHELINUN in combination with other cytotoxic medicinal products prior to allogeneic HPCT in the paediatric population with malignant haematological diseases including AML and MDS.

Lucchini et al. 2017
This retrospective study, performed by the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation, compared the outcomes for children > 2 to <18 years of age undergoing a first allogeneic HSCT from a matched sibling or unrelated donor for AML in CR1 after either Busulfan-Cyclophosphamide-Melphalan (140 mg/m^2) (n=133), Busulfan-Cyclophosphamide (n=389) or TBI-cyclophosphamide (n=109). All are considered MAC.

There was a statistically significant reduction in relapse rate at 5 years for busulfan-cyclophosphamide-melphalan (BuCyMel) versus TBI-cyclophosphamide (TBICy) and busulfan-cyclophosphamide (BuCy): (BuCyMel 14.7%, TBICy 30%, BuCy 31.5%; p<0.01) confirmed in multivariate analysis (OR 0.44, 95% CI 0.25-0.80; p<0.01).
OS-rate and NRM-rate at 5 years for the BuCyMel regimen were 76.6% and 10.8%, with no statistically significant differences between groups in OS or NRM-rate at 5 years in multivariate analysis.

Locatelli et al., 2015
This retrospective study, performed by the AIEOP group analysed the results of 143 children including 39 patients between 0-1 years of age and 17 between 1-2 years who were given an allo-HSCT for consolidating remission after achievement of CR1 in AML. The conditioning regimen was busulfan, cyclophosphamide and melphalan (140 mg/m^2).
In a subgroup analysis of different age categories (<1 year, 1-2 year, 2-10 year, >10 year) there was no statistically significant difference in disease-free survival at 8 years. Analysis of the association of age and the endpoints OS and TRM was not reported.

Strahm et al., 2011
This retrospective study, performed by the European Working Group of MDS in Childhood, analysed 97 children with MDS treated with an allo-HSCT following induction by BuCyMel (melphalan 140 mg/m^2 single dose). OS-rate was 63%, EFS-rate was 59% and relapse rate was 21% at 5 years.

The study by Lucchini et al., 2017**,** did not include children below the age of two, and the study by Locatelli et al., 2015, did not report OS, safety data and TRM separately for this age category. Furthermore, in the study by Sauer et al., 2019, assessing the BuCyMel regimen in children with AML, TRM correlated with age with a rate of 9% in children younger than 12 years and 31% in older children and adolescents. Therefore, safety and efficacy in children <2 years of age with AML have not been established and melphalan should not be used in children with AML >12 years of age (see section 4.4).

Non-malignant haematological diseases
Ten studies assessed the safety and efficacy of PHELINUN in combination with other cytotoxic medicinal products prior to allogeneic HSCT in a total of 504 patients including the paediatric population (age range 2 months – 18 years) with non malignant haematological diseases including thalassaemia, sickle-cell disease, hemophagocytic lymphohistiocytosis (HLH) and X-linked lymphoproliferative disease, combined immune deficiency and common variable immunodeficiency, severe combined immune deficiency (SCID), non-Fanconi anaemia marrow failure disorders and metabolic disorders.
Most studies used a RIC-regimen of alemtuzumab, fludarabine and melphalan 140 mg/m^2. The largest study was performed by Marsh et al. 2015.

Marsh et al. 2015
In this restrospective study on allo-HSCT in non-malignant haematological diseases, 210 children received a RIC regimen of alemtuzumab, fludarabine, and melphalan 140 mg/m^2. The OS reported at 1 year was 78% and at 3 years was 69%. Three-year EFS was 84% for patients who underwent transplantation with an HLA-matched related donor compared with 64%, 57% and 14% for patients who underwent transplantation with a matched unrelated donor, 1 allele mismatched donor, or 2 allele

mismatched donor, respectively (P < .001). Five % of patients required retransplantation due to graft loss.

5.2 Pharmacokinetic properties

Absorption

The absorption of oral melphalan is highly variable with respect to both the time to first appearance of the medicinal product in plasma and peak plasma concentration.
In studies of the absolute bioavailability of melphalan, the mean absolute bioavailability ranged from 56 to 85%.
Intravenous administration can be used to avoid variability in absorption associated with myeloablative treatment.

Distribution

Melphalan is distributed in most tissues of the body. It is moderately bound to plasma proteins with reported binding ranging from 69% to 78%. There is evidence that the protein binding is linear in the range of plasma concentrations usually achieved in standard dose therapy, but that the binding may become concentration-dependent at the concentrations observed in high-dose therapy. Serum albumin is the major binding protein, accounting for about 55 to 60% the binding, and 20% is bound to α1-acid glycoprotein. In addition, melphalan binding studies have revealed the existence of an irreversible component attributable to the alkylation reaction with plasma proteins.

In 28 patients with various malignancies who were given doses between 70 and 200 mg/m^2 body surface area as a 2 to 20 min infusion, the mean volumes of distribution at steady state and central compartment were, respectively, 40.2 ± 18.3 litres and 18.2 ± 11.7 litres.

Melphalan displays limited penetration of the blood-brain barrier. Several investigators have sampled cerebrospinal fluid and found no measurable medicinal product. Low cerebrospinal fluid concentrations (~10% of that in plasma) were observed in a single high-dose study in children.

Biotrasformation

The chemical hydrolysis of melphalan to monohydroxymelphalan and dihydroxy melphalan is the most important metabolic route in humans. These metabolites are inactive.

In vivo and *in vitro* data suggest that spontaneous degradation rather than enzymatic metabolism is the major determinant of the medicinal product's half-life in man.

Elimination

In 15 children and 11 adults given high-dose intravenous melphalan (140 mg/m^2 body surface area) with forced diuresis, the mean initial and terminal half-lives were found to be 6.5 ± 3.6 min and 41.4 ± 16.5 min, respectively. Mean initial and terminal half-lives of 8.8 ± 6.6 min and 73.1 ± 45.9 min, respectively, were recorded in 28 patients with various malignancies who were given doses of between 70 and 200 mg/m^2 body surface area as a 2 to 20 min infusion. The mean clearance was 564.6 ± 159.1 ml/min.

Special populations

Renal impairment

Melphalan clearance may be decreased in renal impairment (see sections 4.2 and 4.4).

Elderly

No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life (see section 4.2).

5.3 Preclinical safety data

Mutagenicity

Melphalan was mutagenic in *Salmonella typhimurium*. Melphalan caused chromosomal aberrations *in vitro* (mammalian cells) and *in vivo* (rodents). Clinical information on potential toxicity of melphalan is provided in sections 4.4 and 4.6.

Carcinogenicity

Melphalan, in common with other alkylating agents, has been reported to be leukaemogenic. There have been reports of acute leukaemia occurring after melphalan treatment for diseases such as amyloid, malignant melanoma, multiple myeloma, macroglobulinaemia, cold agglutinin syndrome and ovarian cancer.

The potential therapeutic benefit when considering the use of melphalan must be balanced against the risk that may occur.

Reproductive toxicity and fertility

Melphalan was teratogenic in rats after single dose exposure in reproductive toxicity studies. In repeated dose reproductive toxicity studies, melphalan was maternal toxic and induced congenital malformations.

A single dose of melphalan in male mice induced cytotoxicity and chromosomal aberrations in sperm cells. In female mice a reduction in number of pups per litter was observed. After recovery, the number of pups per litter was also reduced over time, which was related to a reduced number of follicles.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Hydrochloric acid (pH adjustment) (E507)
Povidone (E1201)

Solvent
Water for injections
Propylene glycol (E1520)
Ethanol
Sodium citrate (E331)

6.2 Incompatibilities

PHELINUN is not compatible with infusion solutions containing glucose.
Only sodium chloride 9 mg/ml (0.9%) solution for injection is recommended to be used.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

PHELINUN 200 mg powder and solvent for concentrate for solution for infusion

Unopened vial
3 years.

After reconstitution and dilution

After reconstitution and dilution, chemical and physical stability has been demonstrated for 1 hour and 30 minutes at 25°C. Therefore the total time from

reconstitution and dilution to the completion of infusion should not exceed 1 hour and 30 minutes.
From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

The reconstituted solution should not be refrigerated as this will cause precipitation.

6.4 Special precautions for storage

Do not refrigerate.
Keep the vials in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder
Type I glass vial closed with coated chlorobutyl rubber stopper and sealed with aluminium flip-off cap.

Solvent
Type I glass vial closed with coated chlorobutyl rubber stopper and sealed with aluminium flip-off cap.

Pack size: one vial containing 50 mg or 200 mg melphalan and one vial containing 10 ml or 40 ml of solvent.

6.6 Special precautions for disposal

Preparation of PHELINUN solution

The powder should be reconstituted immediately after opening the vial.
PHELINUN should be prepared at a temperature below 25°C, by reconstituting the freeze-dried powder with 10 ml or 40 ml solvent and immediately shaking vigorously until a clear solution, without visible particles, is obtained. Only clear solution free from particles should be used.
Unless the concentrate is administered into a fast-running infusion solution via injection port, the reconstituted solution must be further diluted prior to administration with an appropriate volume of sodium chloride 9 mg/ml (0.9%) solution for injection in order to

obtain a final concentration between 0.45 and 4.0 mg/ml.
PHELINUN concentrate and solution have limited stability and should be prepared immediately before use.
The maximum time between reconstitution and dilution of the solution in sodium chloride 9 mg/ml (0.9%) solution for injection and the end of the infusion is 1 hour 30 minutes.

Handling and disposal

PHELINUN should be prepared for use in a dedicated preparation area. Healthcare professionals must have a suitable equipment, including long-sleeved clothes, face protection, protective caps, safety goggles, sterile disposable gloves, worktop protection shields, containers and bags for collecting waste. Any broken container should be treated with the same precautions and considered as contaminated waste.The procedures for the safe handling and disposal of antineoplastic agents must be followed by healthcare professionals or medical personnel and should comply with the current recommendations for cytotoxic medicinal products (see section 4.2).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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