ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PHELINUN 50 mg powder and solvent for concentrate for solution for infusion
PHELINUN 200 mg powder and solvent for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PHELINUN 50 mg powder and solvent for concentrate for solution for infusion
One vial of powder for concentrate for solution for infusion contains 50 mg melphalan (as melphalan hydrochloride).

After reconstitution with 10 ml of solvent, the final concentration of the solution is 5 mg/ml.

Excipients with known effect
When reconstituted, one vial contains 0.68 mmol (15.63 mg) of sodium, 400 mg of ethanol and 6.2 g of propylene glycol.

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.

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).

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.

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.

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.
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 not be given without haematopoietic stem cell rescue at doses above 140 mg/m^2.

Method of administration

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 PHELINUN 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 handling or administering the medicinal 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.
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. 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).

PHELINUN should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity.

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

Patients who have received prior radiation therapy greater than or equal to three cycles of chemotherapy, or prior progenitor cell transplant may be at an increased risk (see section 4.8).

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.

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).

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).

Ethanol
PHELINUN 50 mg powder and solvent for concentrate for solution for infusion
This medicinal product contains 0.4 g of alcohol (ethanol) in each solvent vial which is equivalent to 42 mg/ml (0.42% w/v). The amount in 10 ml of this medicine is equivalent to 10 ml beer or 4 ml wine.

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 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 blood alcohol concentration (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 50 mg powder and solvent for concentrate for solution for infusion
This medicinal product contains 6.2 g propylene glycol in each 10 ml of solvent which is equivalent to 0.62 g/ml.
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 50 mg powder and solvent for concentrate for solution for infusion

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially "sodium free".

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.

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), rare (≥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 and Myelodysplastic syndrome
Blood and lymphatic system disorders	Very Common	Myelosuppression leading to Neutropenia, Thrombocytopenia and Anaemia
	Uncommon	Thrombotic microangiopathy
	Rare	Haemolytic anaemia
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

MedDRA System Organ Class	Frequency	Adverse Drug Reactions
	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
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.

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 and immunomodulating agents, antineoplastic agents, alkylating 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)
Povidone

Solvent
Water for injections
Propylene glycol
Ethanol
Sodium citrate

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 50 mg powder and solvent for concentrate for solution for infusion

Unopened vial
3 years.

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 and other handling

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

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

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB)
Italy
tel: + 39 0240700445
e-mail: adienne@adienne.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1487/001
EU/1/20/1487/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 November 2020

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 (S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

NERPHARMA S.R.L.
Viale Pasteur, 10
20014 Nerviano (MI)
Italy

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB) 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 (PSURs)**

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

PHELINUN 50 mg powder and solvent for concentrate for solution for infusion

melphalan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 mg melphalan (as melphalan hydrochloride)

After reconstitution with 10 ml of solvent, the final concentration of the solution is 5 mg/ml.

3. LIST OF EXCIPIENTS

Excipients:

Powder: hydrochloric acid and povidone

Solvent: water for injections, propylene glycol, ethanol and sodium citrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for concentrate for solution for infusion

One vial of 50 mg powder
One vial of 10 ml solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstituton and dilution.

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

Cytotoxic

8. EXPIRY DATE

EXP

After reconstitution/dilution: the product should be used immediately.
See the leaflet for further information.

9. SPECIAL STORAGE CONDITIONS

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

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB)
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1487/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Powder vial

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

PHELINUN 50 mg powder for concentrate for solution for infusion

melphalan

Intravenous use after reconstitution and dilution.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg

6. OTHER

Cytotoxic

ADIENNE S.r.l. S.U.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Solvent vial

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

Solvent for PHELINUN 50 mg

2. METHOD OF ADMINISTRATION

For dissolving purpose only.

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

ADIENNE S.r.l. S.U.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

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

melphalan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 200 mg melphalan (as melphalan hydrochloride)

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

3. LIST OF EXCIPIENTS

Excipients:

Powder: hydrochloric acid and povidone

Solvent: water for injections, propylene glycol, ethanol and sodium citrate. See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for concentrate for solution for infusion

One vial of 200 mg powder
One vial of 40 ml solvent

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstituton and dilution.

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

Cytotoxic

8. EXPIRY DATE

EXP

After reconstitution/dilution: the product should be used immediately.
See the leaflet for further information.

9. SPECIAL STORAGE CONDITIONS

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

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB)
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1487/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Powder vial

1. NAME OF THE MEDICINAL PRODUCT

PHELINUN 200 mg powder for concentrate for solution for infusion

melphalan

Intravenous use after reconstitution and dilution.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 200 mg melphalan (as melphalan hydrochloride)

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

3. LIST OF EXCIPIENTS

Excipients: hydrochloric acid and povidone. See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

One vial of 200 mg powder

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstituton and dilution.

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

Cytotoxic

8. EXPIRY DATE

EXP

After reconstitution/dilution: the product should be used immediately.
See the leaflet for further information.

9. SPECIAL STORAGE CONDITIONS

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

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ADIENNE S.r.l. S.U.
Via Galileo Galilei, 19
20867 Caponago (MB)
Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1487/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Solvent vial

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

Solvent for PHELINUN 200 mg

2. METHOD OF ADMINISTRATION

For dissolving purpose only.

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40 ml

6. OTHER

ADIENNE S.r.l. S.U.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

PHELINUN 50 mg powder and solvent for concentrate for solution for infusion
melphalan

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.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PHELINUN is and what it is used for

PHELINUN contains the active substance called melphalan which belongs to a group of medicines called cytotoxics (also called chemotherapy) and it works by reducing the number of certain cells.

PHELINUN can be used, alone or in combination with other medicines or with total body irradiation for the treatment of:
- different types of bone marrow cancer: multiple myeloma, acute lymphoblastic leukaemia (also called acute lymphocytic leukaemia ALL) and acute myeloid leukaemia (AML)
- malignant lymphoma (Hodgkin lymphoma and non-Hodgkin lymphoma) - cancer that affects some types of white blood cells called lymphocytes (cells that fight against infections)
- neuroblastoma, a type of cancer that grows from abnormal nerve cells in the body
- advanced cancer of the ovaries
- advanced breast cancer

PHELINUN is also used, in combination with other cytotoxic medicines, as a preparation medicine before blood stem cell transplantation to treat cancer of the blood in adults and cancer and non-cancerous disorders of the blood in the paediatric population.

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

If you have any doubts, do not hesitate to ask your doctor for advice.

You must not be given PHELINUN
- if you are allergic to melphalan or any of the other ingredients of this medicine (listed in section 6)
- if you are pregnant (only with respect to the treatment prior to blood stem cell transplantation) or breast-feeding.

Warnings and precautions

If you are going to be treated with melphalan careful monitoring of the blood will be performed as this medicine is a potent cytotoxic that results in profound decrease of blood cells.

Before treatment with melphalan, tell your doctor if any of the following apply to you:

- if you have had recent radiotherapy or cancer medicines because they frequently decrease the number of blood cell levels;

- if you have signs of an infection (fever, chills, etc.). In case of treatment with melphalan, your doctor may prescribe medicines such as antibiotics, antifungals or antivirals to prevent infections. Your doctor may also consider giving you blood products (for example, red blood cells and platelets);

- if you are going to have a vaccination or were recently vaccinated. This is because some live attenuated vaccines (like polio, measles, mumps and rubella) may give you an infection while you are being treated with melphalan;

- if you have kidney problems or kidney failure (your kidneys don't work well enough). In this case the dose of PHELINUN must be reduced;

- if you ever had a blood clot in your vein (thrombosis). The use of melphalan in combination with lenalidomide and prednisone or thalidomide or dexamethasone may increase the risk of development of blood clots. Your doctor can decide to give you medication to prevent the latter from happening.

Adequate hydration and forced diuresis (large volume of fluids given in the vein by a drip) is recommeded when you are given melphalan.

Children and adolescents
Children and adolescents may be more likely to develop serious breathing and gastrointestinal complications. Tell your doctor or nurse at once if any breathing or gastrointestinal disturbances occur.

Melphalan should not be used as a preparation medicine before blood stem cell transplantation, in adolescents over the age of 12 years with acute myeloid leukaemia.
Safety and efficacy of the use of melphalan as a preparation medicine before blood stem cell transplantation in children less than 2 years for the treatment of acute myeloid leukaemia and acute lymphoblastic leukemia has not been established.

Other medicines and PHELINUN
Tell your doctor or nurse if you are taking or have recently taken any other medicines including medicines obtained without a prescription.

In particular, tell your doctor or nurse if you are taking any of the following:

- other cytotoxic medicines (chemotherapy)
- vaccination or you have been recently vaccinated (see warnings and precautions) because of possible general illness which may lead to a fatal outcome
- nalidixic acid (an antibiotic used to treat urinary tract infections). It can cause haemorrhagic enterocolitis with fatal outcome in children when given in combination with melphalan
- busulfan (used to treat a certain type of cancer). In children, 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.

Cases of impaired renal function have been reported when cyclosporin is used to prevent graft-versus-host disease after blood stem cell transplantion.

Pregnancy, breast-feeding and fertility
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 you receive this medicine.

Pregnancy
Blood stem cell transplantation is contraindicated in pregnant woman. For the other indications, treatment with melphalan is not recommended during pregnancy because it may cause permanent damage to the foetus.

If you are already pregnant, it is important to talk to your doctor before being given melphalan.
You and your doctor will need to consider the risks and benefits of treatment with melphalan to you and your baby.

You must take adequate contraceptive precautions to avoid pregnancy while you or your partner are having melphalan and during 6 months thereafter.

Breast-feeding
It is not known if melphalan passes into breast milk. Do not breast-feed during the treatment with PHELINUN.

Fertility
Melphalan can affect ovaries or sperm, which may cause infertility (inability to have a baby).
In women, the ovulation, and as a consequence the menstruation, can stop (amenorrhoea). In men, based on findings in animal studies, there may be an absence or low amount of viable sperm cells. Therefore, men are advised to have a consultation on sperm preservation before treatment.

Male and female contraception
It is recommended that men and female who are receiving melphalan must use effective contraceptive precautions during treatment and up to 6 months afterwards.

Driving and using machines
This medicine can cause nausea and vomiting, which may reduce your ability to drive or use machines. This medicine also contains alcohol, which is likely to affect children and adolescents (see below for further information).

PHELINUN contains ethanol (alcohol)
This medicine contains 0.4 g of alcohol (ethanol) in each solvent vial, which is equivalent to 42 mg/ml (0.42% w/v). The amount in solvent vial of this medicine is equivalent to 10 ml beer or 4 ml wine.

Adults
The amount of alcohol in this medicine is not likely to have an effect in adults.

The amount of alcohol in this medicine may alter the effects of other medicines.
Talk to your doctor or pharmacist if you are using other medicines.
If you are pregnant or breast-feeding, talk to your doctor or pharmacist before using this medicine. See also the information under pregnancy above.
If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

Children and adolescents
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. If you have epilepsy or liver problems, talk to your doctor or pharmacist before using this medicine.

The amount of alcohol in this medicine may alter the effects of other medicines.
Talk to your doctor or pharmacist if you are using other medicines.
If you are pregnant or breast-feeding, talk to your doctor or pharmacist before using this medicine. See also the information under pregnancy above.
If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

PHELINUN contains propylene glycol
This medicine contains 6.2 g propylene glycol in each 10 ml of solvent which is equivalent to 0.62 g/ml. If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they use other medicines that contain propylene glycol or alcohol.

If you are pregnant or breast-feeding, do not take this medicine unless recommended by your doctor. See also the information under pregnancy above.

If you suffer from a liver or kidney disease, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are using this medicine.

Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects.

Use this medicine only if recommended by a doctor. Your doctor may carry out extra checks while you are using this medicine.

PHELINUN contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3. How PHELINUN is given

PHELINUN will always be given to you by a healthcare professional with experience in the use of cancer medicines or stem cell transplantation.

Your doctor will calculate the dose of PHELINUN according to your body surface or weight and your disease and how well your kidneys are working.

When PHELINUN is used as a treatment before blood stem cell transplantation, it is always given in combination with other medicines.

Use in adults
The recommended dose range is between 100 and 200 mg/m^2 body surface area. The dose can be divided equally over 2 or 3 consecutive days.

Use in paediatric population
The dose regimen is as follows: one dose between 100 and 240 mg/m^2 body surface area. The dose can be divided equally over 2 or 3 consecutive days.

Use in patients with decreased kidney functioning
The dose is usually lower depending on the severity of the kidney problem.

Administration
PHELINUN will be given by infusion (drip) into your vein.

If PHELINUN is accidentally infused outside the vein and into the surrounding tissue or leaks from the vein into the surrounding tissue, the administration of PHELINUN should be interrupted immediately because it can cause severe tissue damage. This usually results in pain such as stinging and burning. If the patients cannot express that they experience pain, it should be observed if other signs such as redness and swelling of the injection site occur.

If you are given more PHELINUN than you should
If you think you have been given too much or have missed a dose, tell your doctor or nurse.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
You should contact your doctor, pharmacist or nurse immediately if you experience any of the following side effects.

Very common side effects (may affect more than 1 in 10 people)
- Graft versus host disease after blood stemcell transplantation (where transplantated cells attack your body, which is potentially life-threatening)
- Decrease in blood circulating cells and platelets, which can lead to anaemia (decreased number of red blood cells), abnormal bleeding, haematoma
- Alopecia (hair loss) - for high doses

Common side effects (may affect up to 1 in 10 people):
- Infection sometimes severe and life-threatening
- Gastrointestinal bleeding
- Nausea
- Vomiting
- Diarrhoea
- Inflamation in and around the mouth (stomatitis)
- Dysfunction of two or more organ systems which may cause discomfort and can be life-threatening
- Fever, chills
- Absence of menstrual periods (amenorrhea)
- Female reproductive function disorders which may cause ovarian dysfunction and premature menopause
- For men: the absence of sperm in the semen (azoospermia)
- Alopecia (hair loss) - for normal doses

Uncommon side effects (may affect up to 1 in 100 people):
- Septic shock
- Progression, relapse or recurrence of cancer, appearance of a new cancer
- Leukaemia, myelodysplastic syndrome (certain type of blood cancer)
- Respiratory disorders: respiratory failure, shortness of breath (acute respiratory distress syndrome), inflammation of the lungs (pneumonitis, idiopathic pneumonia syndrome), thickening of tissues in the lungs (interstitial lung disease, pulmonary fibrosis), bleeding in the lungs
- Blood clot formation in small blood vessels throughout the body damaging brain, kidneys and heart
- Bleeding in the brain
- Liver disorders: toxic injury to the liver, blocking of a liver vein
- Skin disorder: reddening of the skin with small confluent bumps (maculo-papular rash)
- Kidney damage (acute kidney injury, nephrotic sindrome), reduced kidney function

Rare side effects (may affect up to 1 in 1,000 people):
- Severe and sometimes fatal allergic reaction; the signs may include urticaria, oedema, cutaneous eruptions, loss of consciousness, labored breathing, low blood pressure, heart failure and death
- Collapse (due to cardiac arrest)
- Pruritus
- Liver problems which may show up in your blood tests or cause jaundice (yellowing of the whites of eyes and skin)
- An illness where the red blood cells are being broken down prematurely - this can make you feel very tired, breathless and dizzy and can give you headaches or make your skin or eyes yellow

Not known (frequency cannot be estimated from the available data):

- Cardiovascular disorders: changes and abnormalities in the heart's ability to pump causing fluid retention, shortness of breath, feeling tired (cardiac failure cardiomyopathy), and inflammation around the heart (pericardial effusion)
- Increased blood pressure within the arteries of the lungs
- Inflammation of the bladder with blood in urine
- Severe inflammatory and immunologic complications (haemophagocytic lymphohistiocytois)
- Severe skin damage (e.g. lesions, bullae, flaking in severe cases peeling) potentially involving the full body surface and which can be life-threatening (Steven-Johnson Syndrome, toxic epidermal necrolysis)
- Blood creatinine elevated
- Bleeding
- Blood clots forming in a deep vein, in particular in the legs (deep venous thrombosis) and a closing of the lung artery (lung embolism)

Patients with serious blood disease may feel hot or get a tingling sensation.

Children and adolescents may be more likely to develop serious breathing and gastrointestinal complications.

If you notice any side effects not listed in this leaflet or if any of the side effects become serious, please tell your doctor or pharmacist.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse.
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 PHELINUN

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 vials label and carton after "EXP". The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What PHELINUN contains

- The active substance is melphalan. One vial of powder contains 50 mg melphalan (as melphalan hydrochloride). After reconstitution with 10 ml of solvent, the final concentration of the solution is 5 mg/ml melphalan.

- The other ingredients are:
  Powder: hydrochloride acid and povidone
  Solvent: water for injections, propylene glycole, ethanol and sodium citrate (see section 2).

What PHELINUN looks like and contents of the pack
PHELINUN is a powder and solvent for concentrate for solution for infusion.

The powder is provided in a clear glass vial with white to pale yellow powder or cake. The solvent is a colourless clear solution provided in a clear glass vial.

Each pack of PHELINUN contains: one vial with 50 mg of powder (melphalan) and one vial with 10 ml of solvent.

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This leaflet was last revised in month YYYY.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu
This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

PHELINUN 50 mg powder and solvent for concentrate for solution for infusion

As with all high dose chemotherapy, the preparation and handling of this product requires a number of precautions to ensure the protection of both healthcare professionals and their environment, taking into account the safety conditions required for the patient.

In addition to the usual precautions to preserve the sterility of injectable preparations, it is necessary to:

- put on a long-sleeved clothes and tight cuffs to prevent any splashing of the solution on the skin;
- wear a disposable surgical mask and safely goggles;
- put on disposable gloves after aseptic hands washing;
- prepare the solution into a dedicated area;
- interrupt the infusion in case of extravation;
- dispose the materials used for the preparation of the solution (syringes, compresses, fields, vial) in containers reserved for this purpose;
- destroy contaminated waste;

- handle excreta and vomit with precaution.

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.

Pregnant women should avoid handling cytotoxic medicinal products.

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).
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.

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.

Special populations

Elderly
There is no dose recommendation for the administration of PHELINUN to elderly.
However, frequent 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.
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 not be given without haematopoietic stem cell rescue at doses above 140 mg/m^2.

Preparation of PHELINUN solution
Do not use this medicine if you notice visible signs of deterioration.
PHELINUN should be prepared at a temperature below 25°C, by reconstituting the freeze-dried powder with 10 ml solvent and immediately shaking vigorously until a clear solution, without visible particles, is obtained. Only clear solutions free from particles should be used.

Unless the concentrate is administered into the port of 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 in sodium chloride 9 mg/ml (0.9%) solution for injection and the end of the infusion is 1 hour 30 minutes.

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.

Should any visible turbidity or crystallisation appear in the reconstituted or diluted solutions, the preparation must be discarded.

Method of administration
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.

It is recommended that PHELINUN as concentrate (5 mg/ml) is injected slowly into the port of a fast-running infusion solution.

If high-dose PHELINUN is administered with or without transplantation, the administration as dilution via a central venous line is recommended to avoid extravasation. 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 an infusion bag.
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.

Disposal

Any solution unused after 1.5 hours should be discarded according to standard guidelines for handling and disposal of cytotoxic medicinal products.

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

Package leaflet: Information for the user

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

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.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What PHELINUN is and what it is used for

PHELINUN contains the active substance called melphalan which belongs to a group of medicines called cytotoxics (also called chemotherapy) and it works by reducing the number of certain cells.

PHELINUN can be used, alone or in combination with other medicines or with total body irradiation for the treatment of:
- different types of bone marrow cancer: multiple myeloma, acute lymphoblastic leukaemia (also called acute lymphocytic leukaemia ALL) and acute myeloid leukaemia (AML)
- malignant lymphoma (Hodgkin lymphoma and non-Hodgkin lymphoma) - cancer that affects some types of white blood cells called lymphocytes cells that fight against infections)
- neuroblastoma, a type of cancer that grows from abnormal nerve cells in the body
- advanced cancer of the ovaries
- advanced breast cancer

PHELINUN is also used, in combination with other cytotoxic medicines, as a preparation medicine before blood stem cell transplantation to treat cancer of the blood in adults and cancer and non-cancerous disorders of the blood in the paediatric population.

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

If you have any doubts, do not hesitate to ask your doctor for advice.

You must not be given PHELINUN
- if you are allergic to melphalan or any of the other ingredients of this medicine (listed in section 6)
- if you are pregnant (only with respect to the treatment prior to blood stem cell transplantation) or breast-feeding.

Warnings and precautions

If you are going to be treated with melphalan careful monitoring of the blood will be performed as this medicine is a potent cytotoxic that results in profound decrease of blood cells.

Before treatment with melphalan, tell your doctor if any of the following apply to you:

- if you have had recent radiotherapy or cancer medicines because they frequently decrease the number of blood cell levels;

- if you have signs of an infection (fever, chills, etc.). In case of treatment with melphalan, your doctor may prescribe medicines such as antibiotics, antifungals or antivirals to prevent infections. Your doctor may also consider giving you blood products (for example, red blood cells and platelets);

- if you are going to have a vaccination or were recently vaccinated. This is because some live attenuated vaccines (like polio, measles, mumps and rubella) may give you an infection while you are being treated with melphalan;

- if you have kidney problems or kidney failure (your kidneys don't work well enough). In this case the dose of PHELINUN must be reduced;

- if you ever had a blood clot in your vein (thrombosis). The use of melphalan in combination with lenalidomide and prednisone or thalidomide or dexamethasone may increase the risk of development of blood clots. Your doctor can decide to give you medication to prevent the latter from happening.

Adequate hydration and forced diuresis (large volume of fluids given in the vein by a drip) is recommeded when you are given melphalan.

Children and adolescents
Children and adolescents may be more likely to develop serious breathing and gastrointestinal complications. Tell your doctor or nurse at once if any breathing or gastrointestinal disturbances occur.

Melphalan should not be used as a preparation medicine before blood stem cell transplantation, in adolescents over the age of 12 years with acute myeloid leukaemia.
Safety and efficacy of the use of melphalan as a preparation medicine before blood stem cell transplantation in children less than 2 years for the treatment of acute myeloid leukaemia and acute lymphoblastic leukemia has not been established.

Other medicines and PHELINUN
Tell your doctor or nurse if you are taking or have recently taken any other medicines including medicines obtained without a prescription.

In particular, tell your doctor or nurse if you are taking any of the following:

- other cytotoxic medicines (chemotherapy)
- vaccination or you have been recently vaccinated (see warnings and precautions) because of possible general illness which may lead to a fatal outcome
- nalidixic acid (an antibiotic used to treat urinary tract infections). It can cause haemorrhagic enterocolitis with fatal outcome in children when given in combination with melphalan
- busulfan (used to treat a certain type of cancer). In children, 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.

Cases of impaired renal function have been reported when cyclosporin is used to prevent graft-versus-host disease after blood stem cell transplantion.

Pregnancy, breast-feeding and fertility
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 you receive this medicine.

Pregnancy
Blood stem cell transplantation is contraindicated in pregnant woman. For the other indications, treatment with melphalan is not recommended during pregnancy because it may cause permanent damage to the foetus.

If you are already pregnant, it is important to talk to your doctor before being given melphalan.
You and your doctor will need to consider the risks and benefits of treatment with melphalan to you and your baby.

You must take adequate contraceptive precautions to avoid pregnancy while you or your partner are having melphalan and during 6 months thereafter.

Breast-feeding
It is not known if melphalan passes into breast milk. Do not breast-feed during the treatment with PHELINUN.

Fertility
Melphalan can affect ovaries or sperm, which may cause infertility (inability to have a baby).
In women, the ovulation, and as a consequence the menstruation, can stop (amenorrhoea). In men, based on findings in animal studies, there may be an absence or low amount of viable sperm cells. Therefore, men are advised to have a consultation on sperm preservation before treatment.

Male and female contraception
It is recommended that men and female who are receiving melphalan must use effective contraceptive precautions during treatment and up to 6 months afterwards.

Driving and using machines
This medicine can cause nausea and vomiting, which may reduce your ability to drive or use machines.
This medicine also contains alcohol, which is likely to affect children and adolescents (see below for further information).

PHELINUN contains ethanol (alcohol)
This medicine 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 solvent vial of this medicine is equivalent to 40 ml beer or 17 ml wine.

Adults
The amount of alcohol in this medicine is not likely to have an effect in adults.

The amount of alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are using other medicines.
If you are pregnant or breast-feeding, talk to your doctor or pharmacist before using this medicine. See also the information under pregnancy above.
If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

Children and adolescents
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. If you have epilepsy or liver problems, talk to your doctor or pharmacist before using this medicine.

The amount of alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are using other medicines.
If you are pregnant or breast-feeding, talk to your doctor or pharmacist before using this medicine. See also the information under pregnancy above.
If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.

PHELINUN contains propylene glycol
This medicine contains 24.9 g propylene glycol in each 40 ml of solvent which is equivalent to 0.62 g/ml.
If your child is less than 5 years old, talk to your doctor or pharmacist before giving them this medicine, in particular if they use other medicines that contain propylene glycol or alcohol.

If you are pregnant or breast-feeding, do not take this medicine unless recommended by your doctor. See also the information under pregnancy above.

If you suffer from a liver or kidney disease, do not take this medicine unless recommended by your doctor. Your doctor may carry out extra checks while you are using this medicine.
Propylene glycol in this medicine can have the same effects as drinking alcohol and increase the likelihood of side effects.

Use this medicine only if recommended by a doctor. Your doctor may carry out extra checks while you are using this medicine.

PHELINUN contains sodium
This medicine contains 62.52 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 3 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How PHELINUN is given

PHELINUN will always be given to you by a healthcare professional with experience in the use of cancer medicines or stem cell transplantation.

Your doctor will calculate the dose of PHELINUN according to your body surface or weight and your disease and how well your kidneys are working.

When PHELINUN is used as a treatment before blood stem cell transplantation, it is always given in combination with other medicines.

Use in adults
The recommended dose range is between 100 and 200 mg/m^2 body surface area. The dose can be divided equally over 2 or 3 consecutive days.

Use in paediatric population
The dose regimen is as follows: one dose between 100 and 240 mg/m^2 body surface area. The dose can be divided equally over 2 or 3 consecutive days.

Use in patients with decreased kidney functioning
The dose is usually lower depending on the severity of the kidney problem.

Administration
PHELINUN will be given by infusion (drip) into your vein.

If PHELINUN is accidentally infused outside the vein and into the surrounding tissue or leaks from the vein into the surrounding tissue, the administration of PHELINUN should be interrupted immediately because it can cause severe tissue damage. This usually results in pain such as stinging and burning. If the patients cannot express that they experience pain, it should be observed if other signs such as redness and swelling of the injection site occur.

If you are given more PHELINUN than you should
If you think you have been given too much or have missed a dose, tell your doctor or nurse.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
You should contact your doctor, pharmacist or nurse immediately if you experience any of the following side effects.

Very common side effects (may affect more than 1 in 10 people)
- Graft versus host disease after blood stemcell transplantation (where transplantated cells attack your body, which is potentially life-threatening)
- Decrease in blood circulating cells and platelets, which can lead to anaemia (decreased number of red blood cells), abnormal bleeding, haematoma
- Alopecia (hair loss) - for high doses

Common side effects (may affect up to 1 in 10 people):
- Infection sometimes severe and life-threatening
- Gastrointestinal bleeding
- Nausea
- Vomiting
- Diarrhoea
- Inflamation in and around the mouth (stomatitis)
- Dysfunction of two or more organ systems which may cause discomfort and can be life-threatening
- Fever, chills
- Absence of menstrual periods (amenorrhea)
- Female reproductive function disorders which may cause ovarian dysfunction and premature menopause
- For men: the absence of sperm in the semen (azoospermia)
- Alopecia (hair loss) - for normal doses

Uncommon side effects (may affect up to 1 in 100 people):
- Septic shock
- Progression, relapse or recurrence of cancer, appearance of a new cancer
- Leukaemia, myelodysplastic syndrome (certain type of blood cancer)
- Respiratory disorders: respiratory failure, shortness of breath (acute respiratory distress syndrome), inflammation of the lungs (pneumonitis, idiopathic pneumonia syndrome), thickening of tissues in the lungs (interstitial lung disease, pulmonary fibrosis), bleeding in the lungs
- Blood clot formation in small blood vessels throughout the body damaging brain, kidneys and heart
- Bleeding in the brain
- Liver disorders: toxic injury to the liver, blocking of a liver vein
- Skin disorder: reddening of the skin with small confluent bumps (maculo-papular rash)
- Kidney damage (acute kidney injury, nephrotic sindrome), reduced kidney function

Rare side effects (may affect up to 1 in 1,000 people):
- Severe and sometimes fatal allergic reaction; the signs may include urticaria, oedema, cutaneous eruptions, loss of consciousness, labored breathing, low blood pressure, heart failure and death
- Collapse (due to cardiac arrest)
- Pruritus
- Liver problems which may show up in your blood tests or cause jaundice (yellowing of the whites of eyes and skin)
- An illness where the red blood cells are being broken down prematurely - this can make you feel very tired, breathless and dizzy and can give you headaches or make your skin or eyes yellow

Not known (frequency cannot be estimated from the available data):

- Cardiovascular disorders: changes and abnormalities in the heart's ability to pump causing fluid retention, shortness of breath, feeling tired (cardiac failure cardiomyopathy), and inflammation around the heart (pericardial effusion)
- Increased blood pressure within the arteries of the lungs
- Inflammation of the bladder with blood in urine
- Severe inflammatory and immunologic complications (haemophagocytic lymphohistiocytois)
- Severe skin damage (e.g. lesions, bullae, flaking in severe cases peeling) potentially involving the full body surface and which can be life-threatening (Steven-Johnson Syndrome, toxic epidermal necrolysis)
- Blood creatinine elevated
- Bleeding
- Blood clots forming in a deep vein, in particular in the legs (deep venous thrombosis) and a closing of the lung artery (lung embolism)

Patients with serious blood disease may feel hot or get a tingling sensation.

Children and adolescents may be more likely to develop serious breathing and gastrointestinal complications.

If you notice any side effects not listed in this leaflet or if any of the side effects become serious, please tell your doctor or pharmacist.

Reporting of side effects
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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 PHELINUN

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 vials label and carton after ”EXP”. The expiry date refers to the last day of that month.

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

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What PHELINUN contains
- The active substance is melphalan. One vial of powder contains 200 mg melphalan (as melphalan hydrochloride). After reconstitution with 40 ml of solvent, the final concentration of the solution is 5 mg/ml melphalan.

- The other ingredients are:
  Powder: hydrochloride acid and povidone
  Solvent: water for injections, propylene glycole, ethanol and sodium citrate (see section 2).

What PHELINUN looks like and contents of the pack
PHELINUN is a powder and solvent for concentrate for solution for infusion.
The powder is provided in a clear glass vial with white to pale yellow powder or cake. The solvent is a colourless clear solution provided in a clear glass vial.

Each pack of PHELINUN contains: one vial with 200 mg of powder (melphalan) and one vial with 40 ml of solvent.

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Other sources of information
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The following information is intended for healthcare professionals only:

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

As with all high dose chemotherapy, the preparation and handling of this product requires a number of precautions to ensure the protection of both healthcare professionals and their environment, taking into account the safety conditions required for the patient.

In addition to the usual precautions to preserve the sterility of injectable preparations, it is necessary to:
- put on a long-sleeved clothes and tight cuffs to prevent any splashing of the solution on the skin;
- wear a disposable surgical mask and safely goggles;
- put on disposable gloves after aseptic hands washing;
- prepare the solution into a dedicated area;
- interrupt the infusion in case of extravation;
- dispose the materials used for the preparation of the solution (syringes, compresses, fields, vial) in containers reserved for this purpose;
- destroy contaminated waste;
- handle excreta and vomit with precaution.

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.

Pregnant women should avoid handling cytotoxic medicinal products.

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).
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.

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.

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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.

Special populations

Elderly
There is no dose recommendation for the administration of PHELINUN to elderly.
However, frequent 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.
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 not be given without haematopoietic stem cell rescue at doses above 140 mg/m^2.

Preparation of PHELINUN solution
Do not use this medicine if you notice visible signs of deterioration.
PHELINUN should be prepared at a temperature below 25°C, by reconstituting the freeze-dried powder with 40 ml solvent and immediately shaking vigorously until a clear solution, without visible particles, is obtained. Only clear solutions free from particles should be used.

Unless the concentrate is administered into the port of 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 in sodium chloride 9 mg/ml (0.9%) solution for injection and the end of the infusion is 1 hour 30 minutes.

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.

Should any visible turbidity or crystallisation appear in the reconstituted or diluted solutions, the preparation must be discarded.

Method of administration
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.

It is recommended that PHELINUN as concentrate (5 mg/ml) is injected slowly into the port of a fast-running infusion solution.

If high-dose PHELINUN is administered with or without transplantation, the administration as dilution via a central venous line is recommended to avoid extravasation. 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 an infusion bag.
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.

Disposal
Any solution unused after 1.5 hours should be discarded according to standard guidelines for handling and disposal of cytotoxic medicinal products.

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