1.3.1. SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Melfalan Eugia 50 mg, poeder en oplosmiddel voor oplossing voor injectie of infusie

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains melphalan hydrochloride equivalent to 50 mg melphalan.

Excipients with known effect:
Each vial of solvent contains 53 mg of Sodium, 0.52 ml (0.4 g) ethanol and 6.0 ml propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion.

Powder for injection/infusion: White to off-white lyophilized cake or powder.

Solvent for solution for powder for injection/infusion: Clear colorless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melfalan Eugia 50 mg, at conventional intravenous dosage, is indicated in the treatment of multiple myeloma and advanced ovarian cancer.

Melfalan Eugia 50 mg, at high intravenous dosage, is indicated, with or without haematopoietic stem cell transplantation, for the treatment of multiple myeloma and childhood neuroblastoma.

Melfalan Eugia 50 mg, administered by regional arterial perfusion, is indicated in the treatment of localized malignant melanoma of the extremities and localized soft tissue sarcoma of the extremities.

In the above indications, Melfalan Eugia 50 mg may be used alone or in combination with other cytotoxic drugs.

4.2 Posology and method of administration

Treatment with melphalan should be supervised by a physician experienced in the use of anticancer therapies.

General information
Melfalan Eugia 50 mg is for intravenous use and regional arterial perfusion only. Melfalan Eugia 50 mg should not be given without haematopoietic stem cell rescue at doses of above 140 mg/m2.

Thromboembolic events
Patients treated with Melfalan Eugia 50 mg in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone, have an increased risk of thromboembolic events (see section 4.8). Especially in patients with additional thrombotic risk factors antithrombotic prophylactic measures should be considered (see sections 4.4 and 4.8).

Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors (see sections 4.4 and 4.8).

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone may be restarted at the original dose dependent upon a benefit-risk assessment. The patient should continue anticoagulation therapy during the course of melphalan treatment.

Posology

Multiple myeloma
Conventional dose
Melfalan Eugia 50 mg is administered on an intermittent basis alone, or in combination with other cytotoxic drugs. Administration of prednisone has also been included in a number of regimens.

When used as a single agent, a typical intravenous melphalan dosage schedule is 0.4 mg/kg body weight (16 mg/m2 body surface area) repeated at appropriate intervals (e.g. once every 4 weeks), provided there has been recovery of the peripheral blood count during this period.

High dose
High dose regimens generally employ single intravenous doses of between 100 and 200 mg/m2 body surface area (approximately 2.5 to 5.0 mg/kg body weight), but haematopoietic stem cell rescue becomes essential following doses in excess of 140 mg/m2 body surface area.

Ovarian adenocarcinoma
When used intravenously as a single agent, a dose of 1 mg/kg body weight (approximately 40 mg/m2 body surface area) given at intervals of 4 weeks has often been used.

When combined with other cytotoxic drugs, intravenous doses of between 0.3 and 0.4 mg/kg body weight (12 to 16 mg/m2 body surface area) have been used at intervals of 4 to 6 weeks.

Advanced neuroblastoma
Doses of between 100 and 240 mg/m2 body surface area (sometimes divided equally over 3 consecutive days) together with haematopoietic stem cell rescue, have been used either alone or in combination with radiotherapy and/or other cytotoxic drugs.

Malignant melanoma
Hyperthermic regional perfusion with melphalan has been used as an adjuvant to surgery for early malignant melanoma and as palliative treatment for advanced but localized disease. The scientific literature should be consulted for details of perfusion technique and dosage used. A typical dose range for upper extremity perfusions is 0.6-1.0 mg/kg, whereas for lower extremity perfusions, dose ranges of 0.8-1.5 mg/kg are typically used.

Soft tissue sarcoma

Hyperthermic regional perfusion with melphalan has been used in the management of all stages of localized soft tissue sarcoma, usually in combination with surgery. A typical dose range for upper extremity perfusions is 0.6-1.0 mg/kg body weight, whereas for lower extremity perfusions, dose ranges of 1-1.4 mg/kg body weight are typically used.

Special populations

Paediatric population

Melfalan Eugia 50 mg at conventional dosage, is only rarely indicated in children and dosage guidelines cannot be stated.

High dose Melfalan Eugia 50 mg in association with haematopoietic stem cell rescue, has been used in childhood neuroblastoma and dosage guidelines based on body surface area may be used.

Elderly

Although Melfalan Eugia 50 mg is frequently used at conventional dosage in the elderly, there is no specific information available relating to its administration to this patient sub-group. Experience in the use of high dose Melfalan Eugia 50 mg in elderly patients is limited. Consideration should therefore be given to ensure adequate performance status and organ function, before using high dose Melfalan Eugia 50 mg in elderly patients.

Patients with impaired renal function

Melphalan clearance, though variable, may be decreased in renal impairment.

Currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction when administering melphalan to patients with renal impairment, but it may be prudent to use a reduced dosage initially until tolerance is established. When melphalan is used at conventional intravenous dosage (8-40 mg/m2 body surface area), it is recommended that the initial dose should be reduced by 50% and subsequent dosage determined according to the degree of haematological suppression.

For high intravenous doses of melphalan (100 to 240 mg/m2 body surface area), the need for dose reduction depends upon the degree of renal impairment, whether haematopoietic stem cells are reinfused, and therapeutic need. As a guide, for high dose melphalan treatment without haematopoietic stem cell rescue in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min) a dose reduction of 50% is usual.

High dose melphalan with haematopoietic stem cell rescue has been used successfully even in dialysis dependent patients with end-stage renal failure. The relevant literature should be consulted for details. Patients with renal impairment should be closely monitored, as they may also have bone marrow depression as a result of uraemia. Lowering the dose may then become necessary.

A transient significant increase in blood urea levels has been seen in myeloma patients with kidney damage at the start of treatment with melphalan.

Method of administration

For intravenous administration, it is recommended that melphalan is injected slowly into a fast-running infusion solution via a swabbed injection port. If direct injection into a fast-running infusion is not appropriate, melphalan may be administered diluted in an infusion bag.

Care should be taken to avoid possible extravasation of melphalan and in cases of poor peripheral venous access, consideration should be given to use of a central venous line.

If high dose melphalan is administered with or without autologous bone marrow transplantation, administration via a central venous line is recommended. In view of the hazards involved and the level of supportive care required (see section 4.4), the administration of high dose melphalan should be confined to specialist centres, with the appropriate facilities and only be conducted by experienced clinicians.

For regional arterial perfusion, the literature should be consulted for detailed methodology.

Protect the patient during intravenous administration against external contact with the melphalan solution for injection/infusion (see section 4.4).

Injection/infusion
For instructions on reconstitution, and if applicable dilution, of the medicinal product before administration, see section 6.6.
After reconstitution the appearance of the medicinal product should be a clear solution, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Melphalan is a cytotoxic drug, which falls into the general class of alkylating agents. It should be prescribed only by physicians experienced in the management of malignant disease with such agents. As with all high dose chemotherapy, precautions should be taken to prevent tumour lysis syndrome.

Immunization using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunizations with live organism vaccines are not recommended.

The eyes, skin and the mucous membranes of patients need to be protected against contact with the melphalan solution for injection/infusion or reconstituted solution.

Since melphalan is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary.

Melphalan can cause local tissue damage, should extravasation occur and consequently, it should not be administered by direct injection into a peripheral vein.

In patients receiving high dose melphalan, consideration should be given to the prophylactic administration of anti-infective agents and the administration of blood products as required. Consideration should be given to ensure adequate performance status and organ function before using high dose melphalan.

Melphalan should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity. It is recommended that Melphalan Injection solution is administered by injecting slowly into a fast-running intravenous infusion via a swabbed injection port, or via a central venous line.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be practiced when either partner is receiving melphalan up to three months after end of treatment. For ovarian cancer, non-hormonal contraceptive methods are advised.

Monitoring
Since melphalan is a potent myelosuppressive agent, it is essential that careful attention should be paid to the monitoring of blood counts, to avoid the possibility of excessive myelosuppression and the risk of irreversible bone marrow aplasia. Blood counts may continue to fall after treatment is stopped,

so at the first sign of an abnormally large fall in leukocyte or platelet counts, treatment should be temporarily interrupted.

Melphalan should be given with caution to patients, who have recently been treated with radiotherapy or other cytotoxic agents, due to the risk of increased toxicity in the bone marrow.

Since melphalan can strongly inhibit bone marrow, frequent complete blood counts (determinations of haemoglobin, leukocyte count and platelet count) should be performed during treatment and the dosage should be delayed or reduced if necessary (see section 4.2). The incidence of diarrhoea, vomiting and stomatitis becomes the dose-limiting toxicity in patients given high intravenous doses of melphalan in association with autologous bone marrow transplantation. Cyclophosphamide pretreatment appears to reduce the severity of gastro-intestinal damage induced by high-dose melphalan and the literature should be consulted for details.

Renal Impairment
Melphalan clearance may be reduced in patients with renal impairment who may also have uraemic marrow suppression. Dose reduction may therefore be necessary (see section 4.2). See section 4.8 for undesirable effects for elevation of blood urea. Patients with renal impairment should be closely monitored for signs/signals of overdose.
Temporary significant elevation of blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage.

Thromboembolic events
Patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone, have an increased risk of thromboembolic events (see section 4.8). Especially in patients with additional thrombotic risk factors antithrombotic prophylactic measures should be considered (see sections 4.2 and 4.8).

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

Carcinogenicity
Melphalan has been reported to be leukaemogenic, especially in older patients after long combination therapy and radiotherapy. 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.

A comparison of patients with ovarian cancer who received alkylating agents with those who did not, showed that the use of alkylating agents, including melphalan, significantly increased the incidence of acute leukaemia.

Before the start of the treatment, the leukaemogenic risk (acute myeloid leukaemia and myelodysplastic syndromes) must be balanced against the potential therapeutic benefit, especially if the use of melphalan in combination with thalidomide or lenalidomide and prednisone is considered, as it has been shown that these combinations may increase the leukaemogenic risk.
Before, during and after treatment, doctors must therefore examine the patient at all times by usual measurements to ensure the early detection of cancer and initiate treatment if necessary.
Use of alkylating agents has been linked with the development of a second primary malignancy (SPM). In particular, melphalan in combination with lenalidomide and prednisone and, to a lesser extent, thalidomide and prednisone, has been associated with the increased risk of solid SPM in elderly newly diagnosed multiple myeloma patients.
Other risk factors, such as patient characteristics (e.g. radiation therapy, transplantation), as well as environmental risk factors (e.g. tobacco use) of the individual patient should be carefully evaluated prior to melphalan administration.

Excipients with known effect
This medicinal product contains 2,3 mmol (53 mg) sodium per vial of solvent equivalent to 2.7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

5% Ethanol (alcohol)
This medicinal product contains 5% ethanol (alcohol), i.e. up to 0.4g per vial of solvent equivalent to 10 ml beer or 4.2 ml wine. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

Propylene glycol
This medicinal product contains 6.0 ml propylene glycol per vial of solvent.
Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce 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.

4.5 Interaction with other medicinal products and other forms of interaction

Vaccination with live organism vaccines
Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.4).

Nalidixic acid
Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to haemorrhagic entercolitis. Combined treatment of melphalan with nalidixic acid should be avoided.

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

Cyclosporin
Impaired renal function has been described in bone marrow transplant patients who received high dose intravenous melphalan and who subsequently received ciclosporin to prevent graft-versus-host disease.

4.6 Fertility, pregnancy and lactation

Contraception for men and women of childbearing potential
As with all cytotoxic treatments, male patients who use melphalan hydrochloride should use effective and reliable contraceptive methods up until three months after cessation of treatment and female patients who use melphalan hydrochloride should use effective and reliable contraceptive methods up until six months after cessation of treatment.
The use of hormonal contraceptives should be avoided in ovarian cancer.

Pregnancy
There are no or limited amount of data from the use of melphalan hydrochloride in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Risk for human is not known, but due to the mutagenic properties and structural similarity of melphalan hydrochloride with known

teratogenic compounds, it is possible that melphalan can induce congenital malformations in offspring of treated patients.melphalan hydrochloride should not be used during pregnancy unless the clinical condition of the woman requires treatment with melphalan.

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

Fertility
Melphalan hydrochloride causes suppression of ovary function in premenopausal women, resulting in amenorrhea in a large number of patients.
Studies in animals have shown melphalan hydrochloride can have adverse effects on spermatogenesis (see section 5.3). Therefore it is possible that melphalan hydrochloride may cause temporary or permanent adverse effects on male fertility. It is recommended that men who are receiving treatment with melphalan not father a child during treatment and up to 3 months afterwards. Cryopreservation of semen before treatment is advised.

4.7 Effects on ability to drive and use machines

There are no data regarding the effect of melphalan hydrochloride treatment on the ability to drive and use machines.
Based on the pharmacological profile such an effect is not anticipated. When advising patients treated for malignant disease it is recommended to consider their general health status.

4.8 Undesirable effects

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication and dose received and also when given in combination with other therapeutic agents.

The following convention has been utilized for the classification of frequency: very common ≥1/10, common ≥1/100 and <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000, not known (cannot be estimated from the available data).

Body system	**Frequency**	**Side effects**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Not known	secondary acute myeloid leukaemia and myelodysplastic syndrome (see section 4.4), second primary malignancy (see section 4.4)
Blood and lymphatic system disorders	Very often	bone marrow depression leading to neutropenia, thrombocytopenia and anaemia
	Rare	haemolytic anaemia
Immune system disorders	Rare	hypersensitivity[1] (see also Skin and subcutaneous disorders)

Respiratory, thoracic and mediastinal disorders	Rare	interstitial lung disease and pulmonary fibrosis (including fatal reports)
Gastrointestinal disorders[2]	Very often	nausea, vomiting and diarrhea, stomatitis after high dosage
	Rare	stomatitis after conventional dosing
Hepatobiliary disorders	Rare	liver disorders ranging from abnormal liver function test result to clinical manifestations such as hepatitis, jaundice, veno-occlusive disease after high dose treatment[3]
Skin and subcutaneous tissue disorders	Very common	alopecia at high doses
	Often	alopecia with conventional dosing
	Rare	rash maculo-papular and pruritus (see also Immune system disorders)
Skeletalmuscle system and connective tissue[4] disorders[4]	Very often	muscle atrophy, muscle fibrosis, myalgia, blood creatine phosphokinase increased
	Often	compartmentsyndroom
	Not known	muscle necrosis, rhabdomyolysis
Renal and urinary disorders	Common	blood urea increased[5]
Reproductive system and breast disorders	Not known	azoospermia, amenorrhoea
Vascular Disorders[6]	Not known	deep vein thrombosis and pulmonary embolism
General disorders and administration site conditions	Very often	subjective and transient: feeling hot and/or administration site paresthesia[3], pyrexia

1. Allergic reactions to melphalan such as urticaria, edema, skin rashes and anaphylactic shock have been reported uncommonly after initial or subsequent dosing, particularly after intravenous administration. Rare cases of cardiac arrest have been reported under these conditions.
2. Gastrointestinal complaints, such as nausea and vomiting, occur in up to approximately 30% of patients taking melphalan at conventional oral doses.
3. Only with melphalan infusion.
4. Only with melphalan infusion after administration of regional perfusion in the leg or arm.
5. A temporary significant increase in blood urea levels has been observed in the early phases of melphalan therapy in myeloma patients with kidney damage.

6. The clinically relevant adverse reactions associated with the use of melphalan in combination with thalidomide and prednisone or dexamethasone and to a lesser extend melphalan with lenalidomide and prednisone are: deep vein thrombosis and pulmonary embolism (see sections 4.2 and 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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, vomiting and diarrhoea are the most likely signs of acute oral overdosage. The immediate effects of acute intravenous overdosage are nausea and vomiting. Damage to the gastro-intestinal mucosa may also ensue and diarrhoea, sometimes haemorrhagic, has been reported after overdosage. The principal toxic effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia.

Treatment
General supportive measures, together with appropriate blood and platelet transfusions, should be instituted if necessary and consideration given to hospitalization, antibiotic cover, the use of haematological growth factors.

There is no specific antidote. The blood count should be closely monitored for at least four weeks following overdosage until there is evidence of recovery.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineplastic agents, alkalating agents, nitrogen mustard analogues, ATC code: L01AA03.

Mechanism of action
Melphalan is a bifunctional alkylating agent. 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.

5.2 Pharmacokinetic properties

Absorption
The absorption of oral melphalan is highly variable with respect to both the time to first appearance of the drug 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 moderately bound to plasma proteins with reported percent 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.

Following administration of a two-minute infusion of doses ranging from 5 to 23 mg/m2 body surface area (approximately 0.1 to 0.6 mg/kg bodyweight) to 10 patients with ovarian cancer or multiple myeloma, the mean volumes of distribution at steady state and central compartment were 29.1 ± 13.6 litres and 12.2 ± 6.5 litres, respectively.

In 28 patients with various malignancies who were given doses of between 70 and 200 mg/m2 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 drug. Low concentrations (~10% of that in plasma) were observed in a single high-dose study in children.

Biotransformation

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

Elimination

In 13 patients given oral melphalan at 0.6 mg/kg bodyweight, the plasma mean terminal elimination half-life was 90 ± 57 min with 11% of the drug being recovered in the urine over 24 h.

In 8 patients given a single bolus dose of 0.5 to 0.6 mg/kg bodyweight, the composite initial and terminal half-lives were reported to be 7.7 ± 3.3 min and 108 ± 20.8 min, respectively. Following injection of melphalan, monohydroxymelphalan and dihydroxymelphalan were detected in the patients' plasma, reaching peak levels at approximately 60 min and 105 min, respectively. A similar half-life of 126 ± 6 min was seen when melphalan was added to the patients' serum *in vitro* (37°C), suggesting that spontaneous degradation rather than enzymic metabolism may be the major determinant of the drug's half-life in man.

Following administration of a two-minute infusion of doses ranging from 5 to 23 mg/m2 body surface area (approximately 0.1 to 0.6 mg/kg bodyweight) to 10 patients with ovarian cancer or multiple myeloma, the pooled initial and terminal half-lives were, respectively, 8.1 ± 6.6 min and 76.9 ± 40.7 min. A mean clearance of 342.7 ± 96.8 ml/min was recorded.

In 15 children and 11 adults given high-dose i.v. melphalan (140 mg/m2 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/m2 body surface area as a 2- to 20-min infusion. The mean clearance was 564.6 ± 159.1 ml/min.

Following hyperthermic (39°C) perfusion of the lower limb with 1.75 mg/kg bodyweight, mean initial and terminal half-lives of 3.6 ± 1.5 min and 46.5 ± 17.2 min, respectively, were recorded in 11 patients with advanced malignant melanoma. A mean clearance of 55.0 ± 9.4 ml/min was recorded.

Special patient populations

Renal impairment

Melphalan clearance may be decreased in renal impairment (see section 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 is a cytostatic agent and mutagenicity has therefore not been thoroughly investigated in pre-clinical studies. Melphalan was mutagenic in vivo causing chromosomal aberrations. Clinical information on potential toxicity of melphalan is provided in sections 4.4 and 4.6.

Reproductive toxicity and fertility
Melphalan was teratogenic in rat after single dose exposure in reproductive toxicity studies. In repeated dose reproductive toxicity studies, melphalan was maternal toxic and induced congenital malformations, intra-uterine death, growth retardation and disrupted development.

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 for injection/infusion:
Hydrochloric acid
Povidone K12

Solvent for solution for powder for injection/infusion:
Sodium Citrate
Propylene Glycol
Ethanol (96%)
Water for Injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Powder: Keep the vials in outer carton in order to protect from light.

Solvent: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Powder: Melphalan 50mg powder and solvent for solution for injection/infusion is packed in tubular Type-I clear glass vials with bromobutyl rubber stoppers and sealed with aluminum seals having polypropylene disc. The glass vials will be supplied with a package leaflet.

Pack size: 1 vial containing 50 mg melphalan

Solvent: Solvent for solution for melphalan powder for injection/infusion is packed in Type-I tubular clear glass vial with bromobutyl rubber stoppers and sealed with aluminium seals having polypropylene discs. The glass vials will be supplied with a package leaflet. The glass vials will be further placed in a suitable carton.

Pack size: 1 vial containing 10 ml

Each pack contains 1 vial with powder and 1 vial with solvent.

6.6 Special precautions for disposal and other handling

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

7 HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Eugia Pharma (Malta) Limited
Valletta Waterfront 14 Vault 2 Level
FRN 1914 Floriana
Malta

8 NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 131386

9 DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum eerste verlening van de vergunning: 9 oktober 2024

10 DATE OF REVISION OF THE TEXT