SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Melphalan 50 mg powder and solvent for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder contains melphalan hydrochloride equivalent to 50 mg melphalan.
Each vial of solvent contains 10 ml of solvent.
Each ml of the reconstituted solution contains 5 mg melphalan.

Excipients with known effect:
Each vial of solvent contains 0.4 g ethanol and 6.3 g propylene glycol.
Each vial of solvent contains 47 mg sodium (2.04 mmol).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion
Powder: white to off-white powder
Solvent: clear colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Melphalan, at conventional intravenous dosage, is indicated in the treatment of multiple myeloma and advanced ovarian cancer.
- Melphalan, at high intravenous dosage, is indicated, with or without haematopoietic stem cell transplantation, for the treatment of multiple myeloma and childhood neuroblastoma.
- Melphalan, administered by regional arterial perfusion, is indicated in the treatment of localised malignant melanoma of the extremities and localised soft tissue sarcoma of the extremities.

In the above indications, Melphalan may be used alone or in combination with other cytotoxic medicinal products.

4.2 Posology and method of administration

Melphalan should only be prescribed for patients by a specialist doctor who is experienced in management of malignant disease.

As melphalan is a myelosuppressive agent, it is necessary to perform blood count test during therapy. If necessary, discontinue administration or adjust dose. The use of Melphalan should only be performed with careful haematological control. If the leukocyte or platelet count drops unusually, the treatment should be temporarily interrupted (see section 4.4).

Posology

Parenteral administration:
Melphalan is for intravenous use and regional arterial perfusion only. Melphalan should not be given without haematopoietic stem cell rescue at doses of above 140 mg/m2.

Multiple myeloma: Melphalan is administered on an intermittent basis alone, or in combination with other cytotoxic medicinal products. 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 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. Hydration and forced diuresis are also recommended.

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 medicinal products, intravenous doses of between 0.3 and 0.4 mg/kg body weight (12 to 16 mg/m2body 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 medicinal products.

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 localised 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 bodyweight and for lower extremity perfusions is 0.8-1.5 mg/kg body weight.

Soft tissue sarcoma: Hyperthermic regional perfusion with melphalan has been used in the management of all stages of localised 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 and for lower extremity perfusions is 1 - 1.4 mg/kg body weight.

Paediatric population

Melphalan, at conventional dosage, is only rarely indicated in the paediatric population and dosage guidelines cannot be stated.

High dose melphalan, in association with haematopoietic stem cell rescue, has been used in childhood neuroblastoma and dosage guidelines based on body surface area, as for adults, may be used.

Elderly

Although melphalan 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 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. The pharmacokinetics of intravenous melphalan did not show a correlation between age and melphalan clearance or terminal elimination half-life of melphalan.

The limited data available does not support specific recommendations for dose adjustment in elderly patients receiving melphalan intravenously. It is recommended that the current practice of dose adjustment be continued based on the general condition of the elderly and the degree of myelosuppression during therapy.

Renal impairment

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

When Melphalan is used at conventional intravenous dosage (16-40 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 re-infused, and therapeutic need. Melphalan should not be given without haematopoietic stem cell rescue at doses of above 140 mg/m2.

As a guide, for high dose Melphalan treatment without haematopoietic stem cell rescue in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min) a dose reduction of 50% is usual. High dose Melphalan (above 140 mg/m2) without haematopoietic stem cell rescue should not be used in patients with more severe renal impairment.

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.

Thromboembolic events

Patients undergoing melphalan therapy in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone should receive a

thrombosis prophylaxis at least during the first 5 months of treatment due to an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), especially if there are other thrombogenic risk factors. The decision to use drugs for thrombosis prophylaxis should be made after a careful assessment of the underlying risk factors (see sections 4.4 and 4.8) for each patient.
If a thromboembolic event occurs, therapy should be terminated and one should start a standard anticoagulation therapy. Once the condition of the patient has stabilized under the anticoagulation therapy and any complications of thromboembolic event has been treated, Melphalan therapy in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone may be resumed at the original dose only after an assessment of the risk benefit ratio. The patient should continue anticoagulation therapy during melphalan therapy.

Method of administration
Injection/infusion
For intravenous administration, it is recommended that Melphalan solution 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 solution may be administered diluted in an infusion bag.
Melphalan is not compatible with infusion solutions containing dextrose and it is recommended that only sodium chloride 9 mg/ml (0.9%) solution for injection is used. For instructions on reconstitution and dilution before administration, see section 6.6
When further diluted in an infusion solution, Melphalan has reduced stability and the rate of degradation increases rapidly with rise in temperature. When Melphalan is infused at a room temperature of approximately 25°C, the total time from preparation of the injection solution to the completion of infusion should not exceed 1.5 hours.
Should any visible turbidity or crystallisation appear in the reconstituted or diluted solutions, the preparation must be discarded.
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.
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)

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Breastfeeding (see section 4.6)

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.

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

Melphalan can cause local tissue damage, should extravasation occur and consequently, it should not be administered by direct injection into a peripheral vein. It is recommended that Melphalan is administered by injecting slowly into a fast-running intravenous infusion via a swabbed injection port, or via a central venous line.
In view of the hazards involved and the level of supportive care required, the administration of high dose Melphalan should be confined to specialist centres, with the appropriate facilities and only be conducted by experienced clinicians.
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 injections should not be given without haematopoietic stem cell rescue at doses of above 140 mg/m2.
As with any cytotoxic chemotherapy, adequate contraceptive precautions should be practiced when either partner is receiving Melphalan up to six months after end of treatment. For ovarian cancer, non-hormonal contraceptive methods are advised.

Safe handling of Melphalan
The handling of melphalan formulations should follow guidelines for the handling of cytotoxic drugs. 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.

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

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.

Neutropenia and thrombocytopenia
Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in elderly patients newly diagnosed with multiple myeloma, treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone. Patients and physicians are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxes, especially in patients receiving combination drug regimens described (section 4.8).

Venous thromboembolic events
Patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone, have an increased risk of deep vein thrombosis and pulmonary embolism (see section 4.8). The risk appears to be greatest during the first 5 months of therapy, especially in patients with additional thrombotic risk factors (e.g. smoking, hypertension, hyperlipidaemia and history of thrombosis). These patients should be closely monitored and actions to minimize all modifiable risk factors should be undertaken. Thromboprophylaxis and dosing/anticoagulation therapy recommendations are provided in section 4.2.
Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. If a patient experiences any thromboembolic events, discontinue the treatment immediately and initiate the standard anticoagulation therapy. 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 throughout the course of treatment.

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 elevation of blood urea. Patients with renal impairment should be closely monitored for signs/signals of overdose.

Paediatric population
There is no adequate experience for children. Dose recommendations cannot be given (see section 4.2).

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

Carcinogenicity (Second primary malignancy)
Acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS)
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 amyloidosis, 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.
The leukaemogenic risk must be balanced against the potential therapeutic benefit when considering the use of melphalan, 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.

Solid tumours
Use of alkylating agents has been linked with the development of 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.
Patient characteristics (e.g. age, ethnicity), primary indication and treatment modalities (e.g. radiation therapy, transplantation), as well as environmental risk factors (e.g. tobacco use) should be evaluated prior to melphalan administration.

Contraception
Due to an increased risk of venous thromboembolism in patients undergoing treatment with melphalan in combination with lenalidomide and prednisone or in combination with thalidomide and prednisone or dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception, she should switch to other reliable contraceptive methods (i.e. ovulation inhibitory progesterone-only pills such as desogestrel, barrier method, etc). The risk of venous thromboembolism continues for 4-6 weeks after discontinuing combined oral contraception.

Effects on fertility
Melphalan causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients.
There is evidence from some animal studies that melphalan can have an adverse effect on spermatogenesis. Therefore, it is possible that melphalan may cause temporary or permanent sterility in male patients.

Excipients with known effects

This medicinal product contains 2.04 mmol (47 mg) sodium per vial of solvent, equivalent to 2.4% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicinal product contains 5 % ethanol (alcohol), i.e. up to 0.4 g 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.

This medicinal product contains 6.3 g 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

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

Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to haemorrhagic enterocolitis.

In children and adolescents, treated with busulfan-melphalan regimen, there were reports that the administration of melphalan within 24 hours after the last oral administration of busulfan may have an influence on the development of toxicities.

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 women of childbearing potential

As with all cytotoxic treatments, female patients who use melphalan 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 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 with known teratogenic compounds, it is

possible that melphalan can cause congenital malformations in the offspring of treated patients.

The use of melphalan should be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case, the potential hazard to the foetus must be balanced against the expected benefit to the mother.

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

Fertility
Melphalan causes suppression of ovary function in premenopausal women resulting in amenorrhoea in a large number of patients.

There is evidence from some 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.

It is recommended that men who are receiving treatment with melphalan do not father a child during treatment and up to 3 months afterwards and that they have a consultation on sperm preservation before treatment due to the possibility of irreversible infertility as a result of melphalan treatment.

4.7 Effects on ability to drive and use machines

There are no data regarding the effect of melphalan 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 medicinal 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.
Adverse reactions are listed below by system organ class and frequency grouping. The frequencies are defined as follows: 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), not known (cannot be estimated from the available data).

MedDRA system organ class	Frequency	Adverse events
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Not known	Secondary acute Myeloid Leukaemia (AML) and myelodysplastic syndromes (MDS), second primary malignancy (see section 4.4)
Blood and lymphatic system disorders	Very common	Bone marrow depression, which manifests as leukocytopenia, thrombocytopenia and anaemia.
	Rare	Hemolytic Anaemia[1]
Immune system disorders	Rare	Allergic reactions (see also skin and subcutaneous tissue disorders)[2].
Respiratory, thoracic and mediastinal disorders	Rare	Interstitial pneumonitis and pulmonary fibrosis (including fatal cases).
Gastrointestinal disorders	Very commo	nausea, diarrhoea and vomiting, stomatitis at high doses.
	Rare	Stomatitis with conventional dose.
Hepatobiliary disorders	Rare	Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice; veno-occlusive disease after high-dose therapy.
Skin and subcutaneous tissue disorders	Very commo	Alopecia at high dose.
	Common	Alopecia at conventional dose
	Rare	Maculopapular exanthemia and pruritus (see also immune system disorders).
Musculoskeletal and connective tissue disorders (after parenteral administration for regional perfusion of the extremities)	Very commo n	Muscular atrophy, muscle fibrosis, myalgia, increase in creatine phosphokinase in the blood.
	Common	Compartment Syndrome
	Not known	Muscle necrosis, rhabdomyolysis.
Renal and urinary disorders	Common	blood urea increased[3]
Reproductive System and breast disorders	Not known	Azoospermia and Amenorrhoea (see section 4.4)
Vascular disorders	Not known	Deep vein thrombosis, pulmonary embolism
General disorders and administration site conditions	Very commo	Subjective and transient heat sensation and/or tingling

1 Since melphalan is a strongly myelosuppressive agent, careful monitoring of the blood values is imperative to avoid excessive bone marrow depression and the risk of irreversible bone marrow aplasia. Since the blood values can continue to drop even after termination of the therapy, the treatment should be interrupted at the first sign of an unusually severe drop in leukocyte or platelet values.

2 Allergic reactions such as urticaria, edema, rashes, and anaphylactic shock occur in the initial and follow-up treatment, especially in the case of intravenous melphalan treatment. Cardiac arrest has been reported in rare cases in connection with the allergic reactions.

3 Temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The immediate effects of acute intravenous overdose are nausea and vomiting. Damage to the gastro-intestinal mucosa may also ensue and diarrhoea, sometimes haemorrhagic, has been reported after overdose. The principal toxic effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia.
General supportive measures, together with appropriate blood and platelet transfusions, should be instituted if necessary and consideration given to hospitalisation, antibiotic cover, the use of haematological growth factors. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, Antineoplastic agents. Alkylating agents. Nitrogen mustard analogues; ATC code: L01AA03

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.
After hyperthermic (39 °C) lower limb perfusion with melphalan at 1.75 mg / kg body weight in 11 patients with another tumor disease (advanced malignant melanoma), mean volumes for steady state and central compartment distribution were 2.87 ± 0.8 liters and 1.01 ± 0.28 liters, respectively.
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 intravenous 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

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

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

5.3 Preclinical safety data

Mutagenicity
Melphalan is mutagenic in animals.

Reproductive toxicity
Reproduction studies in rats using a single intraperitoneal injection of melphalan at a dose of 0.48 times the Maximum Recommended Human Dose (MRHD) revealed embryolethal and teratogenic effects. Congenital anomalies included those of the brain (underdevelopment, deformation, meningocele, and encephalocele), eye (anophthalmia and micropthalmos), reduction of the mandible and tail, and hepatocele. High foetal losses occurred and foetal abnormalities were observed after exposure to a minimum dose of 0.48 times the MRHD and 0.81 times the MRHD on Days 6 and 9, respectively. Single dose of 2.42 times the MRHD on Days 12 to 14 resulted in embryolethality (30%) but not foetal abnormalities (see section 4.6).

Fertility Studies
In mice, melphalan administered intraperitoneally at a dose of 7.5 mg/kg, showed reproductive effects attributable to cytotoxicity in specific male germ cell stages and induced dominant lethal mutations and heritable translocations in post-meiotic germ cells, particularly in mid to late stage spermatids.
Females received melphalan at clinically relevant exposure levels and were then housed with an untreated male for most of their reproductive life span. A pronounced reduction in litter size occurred within the first post-treatment interval, followed by an almost complete recovery. Thereafter, a gradual decline in litter size occurred. This was simultaneous with a reduction in the proportion of productive females, a finding associated with an induced reduction in the number of small follicles (see section 4.6).

Genotoxicity

Melphalan has been tested for genotoxicity in a number of short-term assays, both in vitro and in vivo.

In mice, intraperitoneal administration of melphalan at doses of 0.10-3.25 times the MRHD increased frequencies of dominant lethal mutations, chromosomal aberrations, sister chromatic exchange, micronuclei and DNA strand breaks.

The observed mutations originated primarily from large deletions in the postspermatogonial cells whereas other types of mutagenic mechanisms predominated in the spermatogonial cells.

This in vivo data is supported by in vitro studies showing that cell culture treatment with melphalan (at concentrations ranging from 0.1 to 25 μM) also induced DNA damage.

In addition, it induced aneuploidy and sex-linked recessive lethal mutations in Drosophila, and mutation in bacteria. It was positive with all strains in the Ames test at concentrations of 200 μg/plate and above. The mutagenic activity of melphalan was increased 3-fold in the presence of liver S9 metabolising preparations, which is unexpected since melphalan is not considered to need liver activation to produce a cytotoxic effect.

Carcinogenicity

Melphalan is a direct-acting alkylating agent that is carcinogenic via a genotoxic mechanism, which is sufficiently supported by animal studies.

Development of neoplastic tumours in rats was reported following intraperitoneal administration of melphalan at doses of 0.15-1.61 times the MRHD; in mice, the carcinogenic potential was observed at doses of 0.02-1.39 times the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Povidone

Hydrochloric acid (for pH adjustment)

Solvent

Sodium citrate dihydrate

Propylene glycol

Ethanol

Water for injections

6.2 Incompatibilities

Melphalan is not compatible with infusion solutions containing dextrose and it is recommended that ONLY sodium chloride 9 mg/ml (0.9%) solution for injection is used.

6.3 Shelf life

Unopened vial: 2 years
Reconstituted solution: Once reconstituted, the medicinal product should be used immediately. Any unused portion of reconstitution solution should be discarded. The reconstituted solution should not be kept in the refrigerator since the active substance may precipitate. Melphalan has a limited shelf life and the rate of decomposition increases rapidly as the temperature increases.
Reconstituted and further diluted solution for infusion: The total time from preparation of the injection solution to the completion of infusion should not exceed 1.5 hours.
From a microbiological point of view, the reconstituted and diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store below 25ºC. Keep the vial in the outer carton, in order to protect from light. Do not refrigerate. For storage conditions of the medicinal product after reconstitution and dilution, see section 6.3

6.5 Nature and contents of container

Clear type I glass vial sealed with chlorobutyl rubber stopper and flip off aluminium seal.
Pack size:
Each pack contains 1 vial with powder and 1 vial with solvent.
The vial with powder contains 50 mg of melphalan.
The vial with solvent contains 10 ml of solvent to reconstitute the powder.

6.6 Special precautions for disposal

MELPHALAN IS AN ACTIVE CYTOTOXIC AGENT FOR USE UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS.
Procedures for proper handling and disposal of cytotoxic medicinal products should be observed:

- The employees are to be instructed in the reconstitution of the drug.
- Pregnant women should be excluded from handling this medicine.
- The personnel should wear suitable protective clothing with face masks, safety goggles and gloves when reconstituting the preparation.
- Any items used for administration or cleaning, including gloves, should be disposed of in waste containers for contaminated material to high-temperature combustion. Liquid waste can be discharged with plenty of water.

In case of accidental eye contact with Melphalan immediately rinse with sodium chloride eyewash or plenty of water and immediately consult a doctor.

In case of skin contact, immediately wash the affected areas with soap and plenty of cold water and consult a doctor immediately. The spilled solution should be immediately wiped with a damp paper towel, which must then be disposed of safely. The contaminated surfaces must be washed with plenty of water.

Preparation of Melphalan powder and solvent for solution for injection/infusion:

Melphalan powder and solvent for solution for injection/infusion should be prepared at room temperature (approximately 25°C), by reconstituting the freeze-dried powder with the solvent-diluent provided.

It is important that both the freeze-dried powder and the solvent provided are at room temperature before starting reconstitution. Warming the diluent in the hand may aid reconstitution. 10 ml of this vehicle should be added quickly, as a single quantity into the vial containing the freeze-dried powder, and immediately shaken vigorously (for approximately 1 minute) until a clear solution, without visible particles, is obtained. Each vial must be reconstituted individually in this manner. The resulting solution contains the equivalent of 5 mg per ml anhydrous melphalan and has a pH of approximately 6.5.

Melphalan solution has limited stability and should be prepared immediately before use. Any solution unused after one hour should be discarded according to standard guidelines for handling and disposal of cytotoxic drugs.

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

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

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

7 MARKETING AUTHORISATION HOLDER

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