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 mephalan

Each vial of solvent contains 10 ml of solvent

Excipients with known effect: ethanol, propylene glycol

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion

Powder: White to pale yellow lyophilized powder

Solvent: A clear colourless solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Melphalan Injection is indicated in the treatment of multiple myeloma before hematopoietic stem cell transplantation.
- Melphalan Injection is indicated in the treatment of multiple myeloma in palliative care patients whose oral medication is ineffective.

4.2 Posology and method of administration

Parenteral administration:

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

For intravenous administration, it is recommended that Melphalan Injection 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 Injection 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 intravenous infusion 0.9% w/v is used.

When further diluted in an infusion solution, Melphalan has reduced stability and the rate of degradation increases rapidly with rise in temperature. If 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 Injection 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.

Multiple myeloma: Melphalan Injection 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 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 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 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.

Use in Children

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

High dose Melphalan Injection, 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.

Use in the 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 Injection in elderly patients.

Dosage in renal impairment

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 Tablets to patients with renal impairment, but it may be prudent to use a reduced dosage initially until tolerance is established.

When Melphalan Injection 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 Injection 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.

4.3 Contraindications

Melphalan should not be given to patients have demonstrated a previous hypersensitivity to

the active substance (melphalan hydrochloride), or to any of the excipients listed in section

6.1

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.

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

Melphalan Injection solution 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 Injection solution 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 Injection should be confined to specialist centres, with the appropriate facilities and only be conducted by experienced clinicians.

In patients receiving high dose Melphalan Injection, 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 Injection. Melphalan Injection should not be given without haematopoietic stem cell rescue at doses of above 140 mg/m2.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be practised when either partner is receiving Melphalan.

Safe handling of Melphalan

The handling of Melphalan formulations should follow guidelines for the handling of cytotoxic drugs according to the Royal Pharmaceutical Society of Great Britain Working Party on the handling of cytotoxic drugs.

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.

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 Posology and Method of Administration). See Undesirable Effects for elevation of blood urea.

Mutagenicity

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

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.

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.

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.

The label for the product will contain the following statements:

Keep out of the reach of children.

Store below 30° C

Do not refrigerate.

Protect from light

4.5 Interaction with other medicinal products and other forms of interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see Warnings and Precautions).

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

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 Pregnancy and lactation

The teratogenic potential of Melphalan has not been studied. In view of its mutagenic properties and structural similarity to known teratogenic compounds, it is possible that melphalan could cause congenital defects in the offspring of patients treated with the drug.

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.

Mothers receiving Melphalan should not breastfeed.

4.7 Effects on ability to drive and use machines

None known.

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 utilised for the classification of frequency:- Very common $\geq$1/10, common $\geq$1/100, <1/10, uncommon $\geq$1/1000 and <1/100, rare $\geq$1/10,000 and <1/1000, very rare <1/10,000.

Blood and Lymphatic System Disorders

Very common: bone marrow depression leading to leucopenia, thrombocytopenia and anaemia

Rare: haemolytic anaemia

Immune System Disorders

Rare: allergic reactions (see Skin and Subcutaneous Tissue Disorders)

Allergic reactions to melphalan such as urticaria, oedema, skin rashes and anaphylactic shock have been reported uncommonly following initial or subsequent dosing, particularly after intravenous administration. Cardiac arrest has also been reported rarely in association with such events.

Respiratory, Thoracic and Mediastinal Disorders

Rare: interstitial pneumonitis and pulmonary fibrosis (including fatal reports)

Gastrointestinal Disorders

Very common: nausea, vomiting and diarrhoea; stomatitis at high dose

Rare: stomatitis at conventional dose

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.

Hepatobiliary Disorders

Rare: hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice; veno-occlusive disease following high dose treatment

Skin and Subcutaneous Tissue Disorders

Very common: alopecia at high dose

Common: alopecia at conventional dose

Rare: maculopapular rashes and pruritus (see Immune System Disorders)

Musculoskeletal and Connective Tissue Disorders

Injection**,** following isolated limb perfusion:

Very common: muscle atrophy, muscle fibrosis, myalgia, blood creatine phosphokinase increased.

Common: compartment syndrome

Not known: muscle necrosis, rhabdomyolysis

Renal and Urinary Disorders

Common: temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage

General Disorders and Administration Site Conditions

Very common: subjective and transient sensation of warmth and/or tingling

4.9 Overdose

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.

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 overdosage until there is evidence of recovery.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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.

Metabolism

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 Dosage and Administration - Renal impairment and Warnings and Precautions - Renal impairment).

• Elderly

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

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6. Pharmaceutical particulars

6.1 List of excipients

Powder

Povidone

Hydrochloric Acid (for pH adjustment)

Solvent

Sodium citrate dihydrate

Propylene Glycol

Ethanol (96%)

Water for Injection

6.2 Incompatibilities

Melphalan 50 mg Powder and Solvent for Solution for Infusion is not compatible with infusion solutions containing dextrose and it is recommended that ONLY Sodium Chloride Intravenous Infusion 0.9% w/v is used.

6.3 Shelf life

Unopened powder and solvent: 3 years

Reconstituted Solution: Once reconstituted the product should be used immediately. Any unused portion should be discarded.

Reconstituted and further diluted solution for infusion: The total time from the preparation of reconstituted solution at the completion of the dilution for infusion should not exceed one hour and a half.

6.4 Special precautions for storage

Store below 30°C. Protect from light. Protect from moisture.

6.5 Nature and contents of container

Powder: Clear type I moulded glass vial sealed with bromobutyl rubber stopper and flip off aluminium seal having dark red colour polypropylene button. Pack size: 50 mg per vial

Solvent: Clear type I moulded glass vial sealed with bromobutyl rubber stopper and flip off aluminium seal having blue polypropylene button. Pack size: 10 ml vial

6.6 Special precautions for disposal and other handling

<u>Preparation of Melphalan Injection Solution:</u>

Melphalan Injection 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 Injection 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.

7. MARKETING AUTHORISATION HOLDER

Importer by

Alliance Pharma Co., Ltd.

Bangkok, Thailand

Manufactured by

Emcure Pharmaceuticals Ltd.

Plot No. P1 and P.2, I.T.B.T.Park,

Phase-II, M.I.D.C., Hinjawadi,

Pune 411057, Maharashtra State, India.

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT