10000000126041 **PRESCRIBING INFORMATION**

Alkeran Injection

TITLE

Melphalan

SCOPE

Trade Name

ALKERAN™ INJECTION

Formulation and Strength

Alkeran Injection 50 mg is supplied as a unit pack comprising a vial containing a freeze-dried powder and a vial of solvent-diluent. Each Alkeran Injection vial contains the equivalent of 50 mg of melphalan, in the form of the hydrochloride, as a sterile, white to off-white, freeze-dried powder which includes 20 mg povidone K12. Each vial of solvent-diluent provides 10 ml of buffer solution containing 60% w/v propylene glycol with sodium citrate and ethanol.

CLINICAL INFORMATION

Indications

For the palliative treatment of multiple myeloma and the palliation of non-resectable epithelial cancer of the ovary.

Dosage and Administration

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.

Since melphalan is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary (see *Warnings and Precautions–Monitoring*).

Preparation of Alkeran Injection Solution

(See also *Incompatibilities*).

Alkeran Injection should be prepared, AT ROOM TEMPERATURE, by reconstituting the freeze-dried powder with the solvent-diluent provided.

10 ml of this vehicle should be added, as a single quantity, and the vial immediately shaken vigorously until solution is complete. The resulting solution contains the equivalent of 5 mg/ml anhydrous melphalan and has a pH of approximately 6.5.

Alkeran Injection solution has limited stability and should be prepared immediately before use. Any unused solution should be discarded (see *Disposal*).

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

Parenteral administration (see also *Warnings and Precautions–Parenteral administration, Incompatibilities* and *Use and Handling*)

Except in cases where regional arterial perfusion is indicated, Alkeran Injection is for intravenous use only. For regional arterial perfusion, the literature should be consulted for detailed methodology.

For intravenous administration, it is recommended that Alkeran 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, Alkeran 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, Alkeran Injection has reduced stability and the rate of degradation increases rapidly with rise in temperature. If administration occurs 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 (see *Use and Handling–Preparation of Alkeran Injection solution*).

Should any visible turbidity or crystallization 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 (see *Warnings and Precautions –Parenteral administration*).

If high-dose Alkeran Injection is administered with or without haematopoietic stem cell rescue, administration via a central venous line is recommended.

Populations

• Adults

MULTIPLE MYELOMA

Alkeran Injection has been used on an intermittent basis alone, at doses varying between 8 mg/m² body surface area and 30 mg/m² body surface area, given at intervals of between 2 to 6 weeks. Additionally, administration of prednisone has been included in a number of regimens. The literature should be consulted for precise details on treatment protocols.

A typical intravenous dosage schedule is 0.4 mg/kg bodyweight (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 i.v. doses of between 100 and 200 mg/m² body surface area (approximately 2.5 to 5.0 mg/kg bodyweight), but haematopoietic stem cell rescue becomes essential following doses in excess of 140 mg/m² body surface area. In cases of renal impairment, the dose should be reduced by 50% (see *Dosage and Administration–Renal impairment*). In view of the severe myelosuppression induced by high-dose Alkeran Injection, treatment should be confined to specialist centres with the appropriate facilities, and only be administered by experienced clinicians (see *Warnings and Precautions*).

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.

• Children

Melphalan, within the conventional dosage range, is only rarely indicated in children and absolute dosage guidelines cannot be provided.

• 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 Alkeran Injection in elderly patients.

The pharmacokinetics of intravenous melphalan has not shown a correlation between age and melphalan clearance or with melphalan terminal elimination half-life. The limited data available do not support specific dosage adjustment recommendations for elderly patients receiving intravenous melphalan and suggested that current practice of dosage adjustment based upon the general condition of the geriatric patient and the degree of myelosuppression incurred during therapy should be continued.

• Renal impairment

Melphalan clearance, though variable, is decreased in renal impairment (see also *Warnings and Precautions–Renal impairment*).

When Alkeran Injection is used at conventional intravenous dosage (8 to 40 mg/m² body surface area), it is recommended that the initial dose should be reduced by 50% in patients with moderate to severe renal impairment 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 without haematopoietic stem cell rescue is not recommended 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.

Contraindications

Melphalan should not be given to patients who have suffered a previous hypersensitivity reaction to melphalan.

Warnings and Precautions (see also *Use and Handling*)

MELPHALAN IS AN ACTIVE CYTOTOXIC AGENT FOR USE UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS.

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

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.

Safe handling of melphalan

See also *Use and Handling*

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

Renal impairment

Melphalan clearance may be reduced in patients with renal impairment, who may also have uraemic bone marrow suppression. Dose reduction may therefore be necessary (see *Dosage and Administration-Renal impairment*), and these patients should be closely observed.

Mutagenicity

Chromosome aberrations have been observed in patients being treated with the drug.

Carcinogenicity

Melphalan, in common with other alkylating agents, may be leukaemogenic in man. There have been reports of acute leukaemia occurring after prolonged 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.

Parenteral administration

In view of the hazards involved and the level of supportive care required, the administration of high-dose Alkeran Injection should be confined to specialist centres, with the appropriate facilities, and only be conducted by experienced clinicians.

Consideration should be given to ensure adequate performance status and organ function before using high-dose Alkeran Injection.

In patients receiving high-dose Alkeran Injection, consideration should be given to the prophylactic administration of anti-infective agents and the administration of blood products as required.

Alkeran Injection solution may 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 Alkeran Injection solution is administered by injecting slowly into a fast-running intravenous infusion via a swabbed injection port, or via a central venous line (see *Dosage and Administration–Parenteral administration*).

Interactions

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 enterocolitis.

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

Use in Pregnancy and Lactation

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 melpha adverse effect on spermatogenesis. Therefore, it is possible may cause temporary or permanent sterility in male pa

Pregnancy

As with all cytotoxic chemotherapy, adequate contracep should be practiced when either partner is receiving m

The teratogenic potential of melphalan has not been stu its mutagenic properties and structural similarity to kno compounds, it is possible that melphalan could cause co in the offspring of patients treated with the drug.

The use of melphalan should be avoided whenever p pregnancy, particularly during the first trimester. In case the potential hazard to the foetus must be balan expected benefit to the mother.

Lactation

Mothers receiving melphalan should not breast-feed.

Ability to perform tasks that require judgeme cognitive skills

No data.

Adverse Reactions

For this product there is no modern clinical docume can be used as support for determining the frequency effects. Undesirable effects may vary in their incidenc the indication and dose received and also when given with other therapeutic agents.

The following convention has been utilised for the frequency: Very common ≥1/10, common ≥1/100, <1/ ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very not known (cannot be estimated from the available d

Blood and Lymphatic System Disorders

Very common: bone marrow depression leading thrombocytopenia and anaemia

Rare: haemolytic anaemia

Immune System Disorders

Rare: allergic reactions (see *Adverse Reactions–Skin an Tissue Disorders*)

Allergic reactions to melphalan such as urticaria, oedema anaphylactic shock have been reported uncommonly fo subsequent dosing, particularly after i.v. administratio has also been reported rarely in association with such

Respiratory, Thoracic and Mediastinal Disorders

Rare: interstitial pneumonitis and pulmonary fibrosis 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 i.v. doses of melphalan in association with haemopoietic stem cell rescue. Cyclophosphamide pretreatment appears to reduce the severity of gastrointestinal 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

Rare: 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 *Adverse Reactions–Immune System Disorders*)

Musculoskeletal and Connective Tissue Disorders *(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

Overdosage

Symptoms and signs

The immediate effects of acute intravenous overdosage are nausea and vomiting. Damage to the gastrointestinal 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 hospitalisation, antibiotic cover and the use of haematological growth factors.

There is no specific antidote. The blood picture should be closely monitored for at least 4 weeks following overdosage until there is evidence of recovery.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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 two DNA strands and thereby preventing cell replication.

Pharmacokinetics

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 (see *Pharmacokinetics-Elimination*).

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.

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*).

NON-CLINICAL INFORMATION

Carcinogenesis, mutagenesis

Melphalan is mutagenic in animals.

PHARMACEUTICAL INFORMATION

Shelf-Life

2 years.

Storage

Injection unit pack: Store below 25°C. Protect from light.

Nature and Contents of Container

Injection unit pack: vial of melphalan freeze-dried powder and vial of solvent-diluent.

Incompatibilities

Alkeran Injection is not compatible with infusion solutions containing dextrose, and it is recommended that ONLY Sodium Chloride i.v. Infusion 0.9% w/v is used (see *Use and Handling–Preparation of Alkeran Injection solution*).

Use and Handling

The handling of melphalan formulations should follow guidelines for the handling of cytotoxic drugs according to the prevailing local recommendations.

Safe handling

Alkeran Injection should be prepared for administration either by or under the direct supervision of a pharmacist who is familiar with its properties and safe handling requirements.

Alkeran Injection should be prepared for use in the aseptic unit of a pharmacy equipped with a suitable vertical laminar flow cabinet. Where such a facility is not available, a specially designated side room of a ward or clinic may be used.

Personnel preparing or handling Alkeran Injection should wear the following protective clothing:

- disposable gloves of surgical latex or polyvinylchloride of a suitable quality (rubber gloves are not adequate);
- surgical facemask of suitable quality;
- protective goggles or glasses which should be washed thoroughly with water after use;
- disposable apron.

In an aseptic facility, other suitable clothing will be required.

Any spillage should be dealt with immediately (by personnel wearing suitable protective clothing), by mopping with damp, disposable paper towels which are placed in a high-risk waste disposal bag after use and disposed of in compliance with relevant local legislation. Contaminated surfaces should be washed with copious quantities of water.

Should Alkeran Injection solution come into contact with the skin, wash immediately and thoroughly with soap and plenty of cold water. In such instances it may be prudent to seek medical advice.

In case of contact with eyes, IMMEDIATE irrigation with sodium chloride eye wash should be carried out and medical attention sought without delay. If sodium chloride solution is not available, large volumes of water may be used.

Preparation of Alkeran Injection solution

(See also *Incompatibilities*).

Alkeran Injection should be prepared, AT ROOM TEMPERATURE, by reconstituting the freeze-dried powder with the solvent-diluent provided.

10 ml of this vehicle should be added, as a single quantity, and the vial immediately shaken vigorously until solution is complete. The resulting solution contains the equivalent of 5 mg/ml anhydrous melphalan and has a pH of approximately 6.5

Alkeran Injection solution has limited stability and should be prepared immediately before use. Any unused solution should be discarded (see *Disposal*).

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

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

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

Disposal

Alkeran Injection solution should be disposed of in compliance with relevant local legislation. In the absence of such guidelines, the solution should be disposed of in a manner appropriate for toxic chemicals, for example, high-temperature incineration or deep burial.

Disposal of sharp objects, such as needles, syringes, administration sets and ampoules should be in rigid containers labelled with a suitable hazard warning seal. Personnel involved in disposal should be aware of the precautions to be observed, and the material should be destroyed by incineration if appropriate. All disposal must be in accordance with local regulatory requirements.

MANUFACTURER

GlaxoSmithKline Manufacturing SPA, Parma, Italy

LICENSE HOLDER

Perrigo Israel Agencies Ltd., Israel,
29 Lehi Street, Bnei Brak 51200

LICENSE NUMBER

65-79-28146-10

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in May 2007

4.2014