Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Alkeran 50mg, Powder and Solvent for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Alkeran Injection is supplied as a unit pack comprising of a vial of powder containing 50 mg sterile, anhydrous melphalan, with a vial of solvent containing 10 ml of solvent.

Where a pack is reconstituted with 10 ml of the solvent, the resultant solution contains 5 mg/ml anhydrous melphalan.

Excipients: When reconstituted each vial contains 53.24 mg of Sodium, 0.52 ml (0.4 g) of Ethanol and 6.0 ml of Propylene Glycol (E1520).

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for infusion
Powder: A white to off-white freeze-dried powder.
Solvent: A clear, colourless solution (10ml)
The pH of the reconstituted solution is 6.5.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alkeran Injection, 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.

Alkeran Injection may be used alone or in combination with other cytotoxic drugs in the therapy of advanced ovarian carcinoma, multiple myeloma and stage IV neuroblastoma.

Alkeran Injection may be used alone or in combination with other cytotoxic drugs in high-dose therapy for patients with multiple myeloma. Where oral melphalan is not appropriate, intravenous melphalan may be used at conventional doses for treatment of multiple myeloma.

4.2 Posology and method of administration

General

Alkeran 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. 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 (see section 4.4).

Since Alkeran is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary (see section 4.4).

Thromboembolic events
Melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism). 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.

Preparation of Alkeran Injection Solution (see section 6.6).

Posology

Adults

Intravenous
Except in cases where regional arterial perfusion is indicated, Alkeran Injection is for intravenous use only.

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.

Alkeran Injection 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 hour.

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 Alkeran and in cases of poor peripheral venous access, consideration should be given to use of a central venous line.

If high-dose Alkeran Injection is administered with or without transplantation (autologous bone marrow, allogenic or haematopoietic stem cell), administration via a central venous line is recommended as extravasation and subsequent local tissue damage may occur if peripheral administration is used (see section 4.4).

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

Multiple myeloma

Conventional dose

Alkeran Injection has been used on an intermittent basis alone, or in combination with other cytotoxic drugs, at doses varying between 8 mg/m^2 body surface area and 30 mg/m^2 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.

When used as a single agent, a typical intravenous dosage schedule is 0.4 mg/kg bodyweight (16 mg/m^2 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 240 mg/m ^{2} body surface area (approximately 2.5 to 6.0 mg/kg bodyweight), but autologous bone marrow rescue becomes essential following doses in excess of 140 mg/m^2 body surface area. In cases of renal impairment, the dose should be reduced by 50%. 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 section 4.4).

Advanced ovarian carcinoma

When used intravenously as a single agent, a dose of 1 mg/kg bodyweight (approximately 40 mg/m^2 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 bodyweight (12 to 16 mg/m^2 body surface area) have been used at intervals of 4 to 6 weeks.

Perfusion

Malignant melanoma

Hyperthermic regional perfusion with Alkeran 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.

Soft tissue sarcoma

Hyperthermic regional perfusion with Alkeran has been used in the management of all stages of localised soft tissue sarcoma, usually in combination with surgery. Alkeran has also been given with actinomycin D, and the scientific literature should be consulted for details of dosage regimens.

Paediatric population

Alkeran, within the conventional dosage range, is only rarely indicated in the paediatric population and dosage guidelines cannot be stated. High dose Alkeran, in association with haematopoietic stem cell rescue, has been used in childhood neuroblastoma and dosage guidelines based on body surface area are used in this situation.

Stage IV neuroblastoma in childhood

High Dose: Doses of between 100 and 240 mg/m^2 body surface area (sometimes divided equally over 3 consecutive days) together with autologous bone marrow rescue, have been used either alone or in combination with radiotherapy and/or other cytotoxic drugs.

Elderly population
Although Alkeran is frequently used at conventional dosage in the older people, there is no specific information available relating to its administration to this patient sub-group.

Experience in the use of Alkeran in older patients is limited. Consideration should therefore be given to ensure adequate performance status and organ function before using high-dose Alkeran Injection in older patients. The pharmacokinetics of intravenous Alkeran has not shown a correlation between age and Alkeran clearance or with Alkeran terminal elimination half-life. The limited data available do not support specific dosage adjustment recommendations for older patients receiving intravenous Alkeran and suggested that current practice of dosage adjustment based upon the general condition of the older patient and the degree of myelosuppression incurred during therapy should be continued.

Renal impairment

Alkeran clearance, though variable, may be decreased in renal impairment (see section 4.4).

When Alkeran Injection is used at conventional intravenous dosage (8 to 40 mg/m^2 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 Alkeran (100 to 240 mg/m^2 body surface area), the need for dose reduction depends upon the degree of renal impairment, whether autologous bone marrow stem cells are reinfused, and therapeutic need.

As a guide, for high-dose Alkeran treatment without haematopoietic stem cell rescue in patient with moderate renal impairment (creatinine clearance 30 to 50 ml/min) an initial dose reduction of 50% is usual.

High-dose Alkeran without haematopoietic stem cell rescue is not recommended in patients with more severe renal impairment.

High-dose Alkeran 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.

Method of administration

Injection / infusion

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

After reconstitution the appearance of the product should be a clear solution, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Melphalan should be administered under the direction of a specialist oncology service having the facilities for a regular monitoring of clinical biochemical and haematological effects during and after administration.

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

In view of the hazards involved and the level of supportive care required, the administration of high-dose Alkeran Injection should only be conducted by experienced clinicians.

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

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

Monitoring

Bone marrow depression, with leucopenia and thrombocytopenia, is the main side effect. The time of maximum depression is variable, and careful attention should be paid to the monitoring of blood counts, both during and after treatment, to avoid the possibility of excessive myelosuppression and 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.

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

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.

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.

Neutropenia and thrombocytopenia
Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in newly diagnosed elderly multiple myeloma in patients 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).

Mutagenicity
Melphalan has been shown to be mutagenic in animals and chromosome aberrations have been observed in patients being treated with the drug. Melphalan has also been shown to be carcinogenic in animals (section 5.3), and the possibility of a similar effect should be borne in mind when designing the long-term management of the patient.

Suppression of ovarian function with resultant amenorrhoea occurs in a significant number of pre-menopausal patients. There is evidence from some animal studies that Alkeran can have an adverse effect on spermatogensis. Therefore, it is possible that Alkeran may cause temporary or permanent sterility in male patients.

Carcinogenicity (Second primary malignancy)

Acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS)

Melphalan, in common with other alkylating agents, has been reported to be leukaemogenic in man, especially in older patients after long combination therapy and radiotherapy.

There have been reports of acute leukaemia occurring after treatment for disease such as amyloidosis, malignant melanoma, multiple myeloma, macroglobulinaemia, cold agglutinin syndrome and there has been a significant increase in patients with 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 (AML and MDS) 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.

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 another reliable contraceptive method (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.

Renal Impairment

In patients with moderate to severe renal impairment the initial dose of the intravenous preparation should be reduced by 50% being determined thereafter according to haematological response. Such patients should be closely observed for uraemic marrow suppression. Temporary significant elevation of blood urea has been seen in the early stages of treatment in myeloma patients with renal damage.

Excipients with known effects

Sodium: Alkeran contains 53.24 mg sodium per vial, equivalent to 2.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult."

Ethanol: Alkeran contains 416 mg of alcohol (ethanol) in each vial, which is equivalent to 41.6mg/ml (4% w/v). The amount in each vial of this medicine is equivalent to less than 11 ml beer or 5 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

Propylene Glycol: 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

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 the paediatric population due to haemorrhagic enterocolitis.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of melphalan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). In view of its mutagenic properties and structural similarity to known teratogenic compounds, it is possible that Alkeran could cause congenital defects in the offspring of patients treated with the drug.
Alkeran should be not be used during pregnancy and particularly during the first trimester, unless considered absolutely essential by the physician. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother.

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

Breast-feeding

Mothers receiving Alkeran should not breast-feed (see section 4.3).

Fertility
Melphalan causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of premenopausal 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 not father a child during treatment and up to 6 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

Effects on the ability to drive and operate machinery in patients taking this medicine have not been studied.

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 ≥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)
Blood and Lymphatic System Disorders	Very common	bone marrow depression leading to leucopenia, thrombocytopenia, neutropenia[1] and anaemia
	Rare	haemolytic anaemia
Immune System Disorders	Rare	hypersensitivity[2] (see Skin and Subcutaneous Tissue Disorders)
Respiratory, Thoracic and Mediastinal Disorders	Rare	interstitial lung disease and pulmonary fibrosis (including fatal reports)
Gastrointestinal Disorders	Very common	at high dose[3]: nausea, vomiting and diarrhoea; stomatitis
	Rare	stomatitis at conventional dose
Hepatobiliary Disorders	Rare	liver disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice; venoocclusive disease following high dose treatment
Skin and Subcutaneous Tissue Disorders	Very Common	alopecia at high dose
	Common	alopecia at conventional dose
	Rare	rash maculo-papular and pruritus (see Immune System Disorders)
Musculoskeletal and Connective Tissue Disorders[4]	Very common	muscle atrophy, muscle fibrosis, myalgia, blood creatine phosphokinase increased
	Common	compartment syndrome

	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 common	subjective and transient: feeling hot and/or application site paraesthesia, pyrexia

1. Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in newly diagnosed elderly multiple myeloma in patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone (see sections 4.4)
2. 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.
3. 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 pre-treatment appears to reduce the severity of gastro-intestinal damage induced by high-dose melphalan and the literature should be consulted for details.
4. Only with melphalan infusion after administration of regional perfusion in the limb.
5. Temporary significant elevation of the blood urea has been commonly seen in the early stages of melphalan therapy in myeloma patients with renal damage.
6. The clinically important 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 include: deep vein thrombosis and pulmonary embolism (see sections 4.2 and 4.4).

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:

HPRA Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

Symptoms and signs

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 hospitalisation, cover with anti-infective agents, and 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

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

Mechanism of Action
Melphalan is a bifunctional alkylating anti-neoplastic agent with some immunosuppressant properties. Formation of carbonium intermediates from each of the two bis-2-chloroethyl groups enables alkylation through covalent bonding with the 7-nitrogen of guanine on DNA, cross-linking 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 α_1-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/m ^{2} 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/m^2 body surface area as a 2- to 20-min infusion, the mean volumes of distribution at steady state and central compartment were, respectively, 40.2 ± 18.3 litres and 18.2 ± 11.7 litres.

Following hyperthermic (39°C) perfusion of the lower limb with melphalan at 1.75 mg/kg bodyweight in 11 patients with advanced malignant melanoma, mean volumes of distribution at steady state and central compartment were, respectively, 2.87 ± 0.8 litres and 1.01 ± 0.28 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 the paediatric population.

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/m^2 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/m^2 body surface area) with forced diuresis, the mean initial and terminal half- lives were found to be 6.5 ± 3.6 min and 41.4 ± 16.5 min, respectively. Mean initial and terminal half- lives of 8.8 ± 6.6 min and 73.1 ± 45.9 min, respectively, were recorded in 28 patients with various malignancies who were given doses of between 70 and 200 mg/m^2 body surface area as a 2- to 20- min infusion. The mean clearance was 564.6 ± 159.1 ml/min.

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 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 at clinically relevant exposure levels 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 levelsand 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

Freeze-dried powder
Povidone
Hydrochloric acid (for pH adjustment)

Solvent
Propylene glycol
Sodium citrate
Ethanol, (96 per cent)
Water for Injections

6.2 Incompatibilities

Alkeran Injection 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: 3 years.
Once reconstituted the product should be used immediately. Any unused portion should be discarded.

6.4 Special precautions for storage

Do not store above 30°C. Do not refrigerate.
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Powder: Clear, Type I glass vial with a bromobutyl rubber stopper and aluminium collar with a plastic flip-top cover. Pack Size: 50mg per vial.

Solvent: Clear, Type I glass vial with either a chlorobutyl rubber stopper or a grey fluoro-resin D film, B2 coated stopper and aluminium collar with a plastic flip-top cover. Pack Size: 10 ml per vial.

6.6 Special precautions for disposal and other handling

- **Safe Handling of Alkeran Injection**

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.

Refer to local cytotoxic guidelines before commencing. For instructions on administration, see section 4.2.

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.

Staff who are pregnant or trying to conceive should not handle Alkeran injection.

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.

Preparation of Alkeran Injection Solution
(see also above, Safe Handling of Alkeran).

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

If the solvent is used at cold temperature, the freeze-dried powder may not reconstitute properly and undissolved particles may be observed.

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 at least 50 seconds) until a clear colourless solution without visible particles, is obtained.

Each vial must be reconstituted individually in this manner. Slow solvent addition and delaying the shaking may lead to the formation of insoluble particles. It should also be noted that the shaking process creates a considerable amount of very small air bubbles. These bubbles may persist and may take a further 2 to 3 minutes to clear, as the resulting solution is quite viscous.

The resulting solution contains the equivalent of 5 mg/ml anhydrous melphalan and has a pH of approximately 6.5.

The reconstituted solution should be colourless, clear and practically free from visible particles.

Alkeran Injection solution has limited stability and should be prepared immediately before use. Any unused solution remaining after one hour should be discarded (see Disposal, above).

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 hour.

Alkeran Injection is not compatible with infusion solutions containing dextrose and it is recommended that ONLY Sodium Chloride Intravenous Infusion 0.9% w/v is used. (Please refer to section 4.2).

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

7 MARKETING AUTHORISATION HOLDER

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