DATA SHEET

1. PRODUCT NAME (strength pharmaceutical form)

ALKERAN (Melphalan Injection 50mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A vial containing 50mg sterile, anhydrous melphalan (as the hydrochloride) with one vial of 10mL solvent-diluent.

3. PHARMACEUTICAL FORM

Powder for Injection with solvents

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;
- Localised soft tissue sarcoma of the extremities.

ALKERAN Injection, at conventional intravenous dosage, may be used in the treatment of:

- Multiple myeloma: ALKERAN Injection, either alone or in combination with other cytotoxic agents, is as effective as the oral formulation in the treatment of multiple myeloma;
- Advanced ovarian cancer: ALKERAN injection produces an objective response in approximately 50% of the patients with advanced ovarian adenocarcinoma, when given alone, or in combination with other cytotoxic.

ALKERAN Injection, at high intravenous dosage, may be used in the treatment of:

- Multiple myeloma: complete remissions have been achieved in up to 50% of patients given high-dose ALKERAN Injection, with or without haematopoietic stem cell rescue, either as first-line treatment or to consolidate a response to conventional cytoreductive chemotherapy;
- Advanced neuroblastoma in childhood: high-dose ALKERAN Injection with haematopoietic stem cell rescue has been used either alone, or combined with radiotherapy and/or other cytotoxic agents, to consolidate a response to conventional treatment.

A significant increase in the duration of disease-free survival was demonstrated in a prospective randomised trial of high-dose ALKERAN injection versus no further treatment.

4.2 Dose and method of administration

General

ALKERAN is a cytotoxic medicine 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 ALKERAN is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary (see Warnings and Precautions).

Thromboembolic events

Melphalan in combination with lenalidomide and prednisone or in combination with thalidomide and prednisone or dexamethasone is associated with an increased risk of venous thromboembolism. 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 Special Warnings And Precautions For Use and Undesirable Effects 4.4 and section 4.8)

Multiple myeloma

ALKERAN Injection has been used on an intermittent basis alone, or in combination with other cytotoxic agents, at doses varying between 8mg/m^2 body surface area and 30mg/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 (16mg/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 regimens generally employ single intravenous doses of between 100 and 200mg/m^2 body surface area (approximately 2.5 to 5.0mg/kg bodyweight), but haematopoietic stem cell rescue becomes essential following doses in excess of 140mg/m^2 body surface area. In cases of renal impairment, the dose should be reduced by 50% (see Dosage in 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).

Advanced ovarian adenocarcinoma
When used intravenously as a single agent, a dose of 1mg/kg bodyweight (approximately 40mg/m^2 body surface area) given at intervals of 4 weeks has often been used.

When combined with other cytotoxic agents, intravenous doses of between 0.3 and 0.4mg/kg bodyweight (12 to 16mg/m^2 body surface area) have been used at intervals of 4 to 6 weeks.

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.

Advanced neuroblastoma in childhood
Doses of between 100 and 240mg/m^2 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 agents.

Preparation of ALKERAN Injection Solution (see Pharmaceutical Precautions).
ALKERAN Injection should be prepared, AT ROOM TEMPERATURE, by reconstituting the freeze-dried powder with the Solvent-Diluent provided.

10mL 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 5mg/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 Pharmaceutical Precautions).

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

Parenteral administration

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 1.5 hours.

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 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 autologous bone marrow transplantation, administration via a central venous line is recommended.

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

Use in children
High-dose ALKERAN Injection, in association with bone marrow rescue, has been used in childhood neuroblastoma and dosage guidelines based on body surface area are used in this situation (see Dosage in children, advanced neuroblastoma in childhood).

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

Use in the elderly
Although ALKERAN 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 ALKERAN 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.

Dosage in renal impairment (See Warnings and Precautions).
ALKERAN clearance, though variable, is decreased in renal impairment.

When ALKERAN Injection is used at conventional intravenous dosage (8 to 40mg/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 240mg/m^2 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 ALKERAN treatment without haematopoietic stem cell rescue in patients with moderate renal impairment (creatinine clearance 30 to 50mL/min) a 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

ALKERAN 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.

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.

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.

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.

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.

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. The recommended duration of contraception in females should be until the end of relevant systemic exposure or 6 months afterwards (See section 4.6).

Carcinogenicity (Second primary malignancy)
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.

Safe handling of ALKERAN: (Special precautions for disposal).

The handling of ALKERAN formulations should follow guidelines for the handling of cytotoxic medicines according to prevailing local recommendations and/or regulations (for example, Royal Pharmaceutical Society of Great Britain Working Party on the Handling of Cytotoxic Medicines).

Monitoring
Since ALKERAN 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 leucocyte 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.

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

The use of high dose melphalan has the potential to cause acute kidney injury in patients, especially those with underlying renal impairment.

Mutagenicity
Chromosome aberrations have been observed in patients being treated with ALKERAN.

Carcinogenicity
Melphalan, in common with other alkylating agents, has been reported to be leukaemogenic in man. 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.

4.5 Interaction with other medicines 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 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.

Ciclosporin:

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.

Cisplatin/Carmustine:

Cisplatin may affect melphalan kinetics by inducing renal dysfunction and subsequently altering melphalan clearance. IV melphalan may also reduce the threshold for Carmustine lung toxicity.

In a 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.

Impaired renal function has been described in haemopoietic stem cell rescue patients who were conditioned with high-dose i.v. melphalan and who subsequently received cyclosporin to prevent graft-versus-host disease.

4.6 Fertility, pregnancy and lactation

Teratogenicity

The teratogenic potential of ALKERAN 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 ALKERAN.

Effects on fertility

ALKERAN 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 ALKERAN can have an adverse effect on spermatogenesis. Therefore, it is possible that ALKERAN may cause temporary or permanent sterility in male patients.

Women of childbearing potential / Contraception in males and females

As with all cytotoxic treatments, male and female patients who use Melphalan should use effective and reliable contraceptive methods for a period of six months, following the cessation of treatment.

The final decision regarding the additional time period on contraception should be taken by the doctor and/or the patient (See section 4.4).

Pregnancy

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

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.

Lactation
Mothers receiving ALKERAN should not breast-feed.

4.7 Effects on ability to drive and use machines
No data

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, <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	Side Effects	
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Not known	Secondary acute myeloid leukaemia and myelodysplastic syndrome (*see Carcinogenicity)*
Blood and Lymphatic System Disorders	Very common	bone marrow depression leading to leucopenia, thrombocytopenia and anaemia
	Rare	haemolytic anaemia
Immune System Disorders	Rare	hypersensitivity[1] (*see Adverse Reactions - Skin and Subcutaneous Tissue Disorders*)
Respiratory, Thoracic and Mediastinal Disorders	Rare	interstitial lung disease and pulmonary fibrosis (including fatal reports)
Gastrointestinal Disorders[2]	Very common	nausea, vomiting and diarrhoea; stomatitis at high dose
	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[3]
Skin and Subcutaneous Tissue Disorders	Very common	alopecia at high dose
	common	alopecia at conventional dose
	Rare	rash maculo-papular and pruritus (*see Adverse Reactions - 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 Not known	blood urea increased[5] acute kidney injury – kidney failure (significant reduction of kidney function) that happens within a short time
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;[3] pyrexia

1. 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.
2. Gastrointestinal effects such as nausea and vomiting have been reported in up to 30% of patients receiving conventional oral doses of melphalan.
   The incidence of diarrhoea, vomiting and stomatitis becomes the dose-limiting toxicity in patients given high intravenous doses of melphalan in association with haemopoietic stem cell rescue. Cyclophosphamide pretreatment appears to reduce the severity of gastro-intestinal damage induced by high-dose melphalan and the literature should be consulted for details.
3. Only with Alkeran Infusion
4. Only with Alkeran 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 Dosage and Administration and Warnings and Precautions*).

The following information on adverse reactions is based on data from both oral and IV administration of melphalan as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Haematologic

The most common side effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia. White blood cell count and platelet count nadirs usually occur 2 to 3 weeks after treatment, with recovery in 4 to 5 weeks after treatment. Irreversible bone marrow failure has been reported. Acute leukaemia has also been reported (See Section 5.3 Preclinical Safety data).

Gastrointestinal

Gastrointestinal disturbances such as nausea, vomiting and diarrhoea are very common. At high doses of ALKERAN INJECTION, stomatitis is very common and rare at conventional doses. The incidence of diarrhoea, vomiting and stomatitis becomes the dose limiting toxicity in patients given high i.v. doses of ALKERAN INJECTION in association with hematopoietic stem cell rescue. Cyclophosphamide pre-treatment appears to reduce the severity of gastrointestinal damage induced by high-dose ALKERAN INJECTION and the literature should be consulted for details. Oral ulceration occurs infrequently. Hepatic toxicity, including veno-occlusive disease, has been reported.

Hypersensitivity

Acute hypersensitivity reactions including anaphylaxis were reported in 2.4% of 425 patients receiving ALKERAN INJECTION for myeloma (see Section 4.4 Special warnings and precautions for use). These reactions were characterised by urticaria, pruritus, skin rashes, oedema, and in some patients, tachycardia, bronchospasm, dyspnoea, and hypotension. These patients appeared to respond to antihistamine and corticosteroid therapy. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered since hypersensitivity reactions have also been reported with oral melphalan. Cardiac arrest has also been reported rarely in association with such events.

Miscellaneous

Other reported adverse reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis rarely requiring skin grafting, maculopapular rashes, pruritus, vasculitis, allergic reaction, and interstitial pneumonitis. A subjective and transient sensation of warmth and/or tingling is very common.

Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice have been reported. Veno-occlusive disease has been reported in association with these cases.

There have been case reports of interstitial pneumonitis and pulmonary fibrosis. There have also been case reports of fatal pulmonary fibrosis and haemolytic anaemia occurring after melphalan treatment.

Alopecia is very common at high doses and common at conventional doses.

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

Muscular atrophy, muscle fibrosis, myalgia and increases in blood creatine phosphokinase are very commonly observed following isolated limb perfusion, while compartment syndrome is commonly observed. The incidence of muscle necrosis and rhabdomyolysis are not known in this setting.

Myelodysplastic syndrome

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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 4 weeks following overdosage until there is evidence of recovery.

Immediately telephone your doctor or the National Poisons Information Centre (0800 POISON or 0800 764 766) for advice.

5 PHARMACOLOGICAL PROPERTIES

5.1Pharmacodynamic 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 two DNA strands and thereby preventing cell replication.

5.2 Pharmacokinetic Properties

The absorption of melphalan was found to be highly variable in 13 patients given 0.6mg/kg bodyweight orally, with respect to both the time to first appearance of melphalan in plasma

(range 0 to 336 minutes) and peak plasma concentration (range 70 to 630ng/mL). In 5 of the patients who were given an equivalent intravenous dose, the mean bioavailability of melphalan was found to be 56 ± 27%. The terminal plasma half-life was 90 ± 57 minutes with 11% of the agent being recovered in the urine over 24 hours.

The pharmacokinetics of intravenous ALKERAN given at both conventional and high doses are best described by a bi-exponential, 2-compartment model. In 8 patients given a single bolus dose of 0.5 to 0.6mg/kg bodyweight, the composite initial and terminal half-lives were reported to be 7.7 ± 3.3 minutes and 108 ± 20.8 minutes, respectively. Following injection of melphalan, monohydroxymelphalan and dihydroxymelphalan were detected in the patients' plasma, reaching peak levels at approximately 60 minutes and 105 minutes, respectively. A similar half-life of 126 ± 6 minutes 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 melphalan's half-life in man.

Following administration of a 2 minute infusion of doses ranging from 5 to 23 mg/m^2 body surface area (approximately 0.1 to 0.6mg/kg bodyweight) to 10 patients with ovarian cancer or multiple myeloma, the pooled initial and terminal half-lives were, respectively, 8.1 ± 6.6 minutes and 76.9 ± 40.7 minutes. In this study, the mean volumes of distribution at steady state and central compartment were 29.1 ± 13.6 litres and 12.2 ± 6.5 litres, respectively, and a mean clearance of 342.7 ± 96.8 mL/minute was recorded.

In 15 children and 11 adults given high-dose intravenous ALKERAN (140mg/m^2 body surface area) with forced diuresis, the mean initial and terminal half-lives were found to be 6.5 ± 3.6 minutes and 41.4 ± 16.5 minutes, respectively. Mean initial and terminal half-lives of 8.8 ± 6.6 minutes and 73.1 ± 45.9 minutes, respectively, were recorded in 28 patients with various malignancies who were given doses of between 70 and 200mg/m^2 body surface area as a 2 to 20 minute 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, and the mean clearance was 564.6 ± 159.1mL/minute.

Following hyperthermic (39°C) perfusion of the lower limb with 1.75mg/kg bodyweight, mean initial and terminal half-lives of 3.6 ± 1.5 minutes and 46.5 ± 17.2 minutes, respectively, were recorded 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, and a mean clearance of 55.0 ± 9.4mL/minute was recorded.

5.3 Preclinical safety data

Melphalan is mutagenic in animals.

6 PHARMACEUTICAL PARTICULARS

6.1List of excipients

None

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

36 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

Carton containing one vial freeze-dried melphalan 50mg and one vial 10mL solvent-diluent.

6.6 Special precautions for disposal

Instructions for Use/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.

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.

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 Injection).

ALKERAN Injection should be prepared, AT ROOM TEMPERATURE, by reconstituting the freeze-dried powder with the Solvent-Diluent provided.

10mL 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 5mg/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, 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 1.5 hours.

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

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Pharmacy Retailing Pty Ltd
Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

9 DATE OF FIRST APPROVAL

22 December 2006

10 DATE OF REVISION OF THE TEXT

29 July 2020
17 March 2021
28 September 2021
2 April 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
Format of Data sheet	As per new European SmPC style format
4.8	Myelodysplastic syndrome
4.4; 4.5; 4.8	Safety related changes
4.2	Thromboembolic events
4.4 & 4.8	Acute Kidney Injury
4.4 & 4.6	Effects on Fertility