DATA SHEET

1. PRODUCT NAME (strength pharmaceutical form)

ALKERAN (Melphalan Tablets 2mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2mg melphalan

3. PHARMACEUTICAL FORM

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ALKERAN tablets are indicated in the treatment of:
Multiple myeloma;

Advanced ovarian adenocarcinoma;

ALKERAN tablets may be used in the treatment of:
Breast carcinoma: ALKERAN either alone or in combination with other medicines has a significant therapeutic effect in a proportion of patients suffering from advanced breast carcinoma;

Polycythaemia rubra vera: ALKERAN is effective in the treatment of a proportion of patients suffering from polycythaemia vera.

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 Special Warnings and Special Precautions for Use).

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)

The absorption of ALKERAN after oral administration is variable. Dosage may need to be cautiously increased until myelosuppression is seen, in order to ensure that potentially therapeutic levels have been reached.

Multiple myeloma:
A typical oral dosage schedule is 0.15mg/kg bodyweight/day in divided doses for 4 days repeated at intervals of 6 weeks. Numerous regimens have, however, been used and the scientific literature should be consulted for details.
The administration of oral ALKERAN and prednisone may be more effective than ALKERAN alone. The combination is usually given on an intermittent basis.

Prolonging treatment beyond one year in responders does not appear to improve results.

Advanced ovarian adenocarcinoma:
A typical regimen is 0.2mg/kg bodyweight/day orally for 5 days. This is repeated every 4 to 8 weeks, or as soon as the peripheral blood count has recovered.

Carcinoma of the breast:
ALKERAN has been given orally at a dose of 0.15mg/kg bodyweight or 6mg/m^2 body surface area/day for 5 days and repeated every 6 weeks. The dose was decreased if bone marrow toxicity was observed.

Polycythaemia rubra vera:
For remission induction, doses of 6 to 10mg daily for 5 to 7 days have been used, after which 2 to 4mg daily were given until satisfactory disease control was achieved.
A dose of 2 to 6mg once per week has been used for maintenance therapy.

In view of the possibility of severe myelosuppression if ALKERAN is given on a continuous basis, it is essential that frequent blood counts are taken throughout therapy, with dosage adjustment or breaks in treatment, as appropriate, to maintain careful haematological control.

Use in children:
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.

Dosage in renal impairment:
(See also Special Warnings and Special Precautions for Use).

ALKERAN clearance, though variable, is decreased in renal impairment.

Currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction when administering ALKERAN tablets to patients with renal impairment, but it may be prudent to use a reduced dosage initially until tolerance is established.

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.

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

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:
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 Posology and Method of Administration), and these patients should be closely observed.

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

Mutagenicity:
Chromosome aberrations have been observed in patients being treated with the medicine.

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.
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.

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.

4.5 Interaction with other medicines and other forms of interaction

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

Simultaneous administration of nalidixic acid with melphalan should be avoided if possible. Nalidixic acid together with high dose intravenous melphalan has caused deaths in children due to haemorrhagic enterocolitis.

Ciclosporin and high dose melphalan is a potentially dangerous combination. A deterioration of renal function was associated with simultaneous use of these drugs, but not with melphalan alone.

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 bone marrow transplant patients who were conditioned with high-dose intravenous 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 the medicine.

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.

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)

Tabulated list of adverse reactions

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	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;[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*).

Haematologic: The most common side effect is bone marrow depression, 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, Carcinogenicity)

Gastrointestinal: Gastrointestinal effects such as nausea and vomiting have been reported in up to 30% of patients receiving conventional oral doses of ALKERAN. Hepatic disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice occur rarely. Diarrhoea is very common. Oral ulceration occurs infrequently.

Stomatitis occurs rarely following conventional doses of ALKERAN. At high doses stomatitis is very common.

Allergic reactions to ALKERAN such as urticaria, oedema, skin rashes and anaphylactic shock have been reported uncommonly following initial or subsequent dosing, particularly after intravenous administration. Maculopapular rashes and pruritus have occasionally been noted. 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 necrosis rarely requiring skin grafting, maculopapular rashes, pruritus, vasculitis, allergic reaction, and interstitial pneumonitis.
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.
Temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage.
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 has been commonly reported at conventional doses and occurs very commonly at high doses.

Myelodysplastic syndrome has also been reported.

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:

Overdoses resulting in death have been reported. Overdoses, including doses up to 290 mg/m2, have produced the following symptoms: severe nausea and vomiting, decreased consciousness, convulsions, muscular paralysis, and cholinomimetic effects. Damage to the gastrointestinal lining may also ensue. Severe mucositis, stomatitis, colitis, diarrhoea, and haemorrhage of the gastrointestinal tract occur at high doses (>100 mg/m2). Elevations in liver enzymes and veno occlusive disease occur infrequently. Significant hyponatremia caused by an associated inappropriate secretion of antidiuretic hormone (ADH) syndrome has been observed. Nephrotoxicity and adult respiratory distress syndrome have been reported rarely.

Management:

The principal toxic effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia. Haematologic parameters should be closely followed for at least 4 weeks following overdosage until there is evidence of recovery. An uncontrolled study suggests that administration of autologous bone marrow or haematopoietic growth factors (i.e. filgrastim) may shorten the period of pancytopenia. General supportive measures together with appropriate blood and platelet transfusions and antibiotics should be instituted as deemed necessary by the physician. This drug is not removed from plasma to any significant degree

by haemodialysis or haemoperfusion. A paediatric patient survived a 254 mg/m2 overdose treated with standard supportive care.

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mode 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. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumour cells.

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 the medicine 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 absolute bioavailability of melphalan was found to be 56 $\pm$ 27%. The plasma mean terminal elimination half-life was 90 $\pm$ 57 minutes with 11% of the medicine being recovered in the urine over 24 hours.

In a study of 18 patients administered melphalan 0.2 to 0.25mg/kg bodyweight orally, a maximum plasma concentration (range 87 to 350ng/mL) was reached within 0.5 to 2.0 hours. The mean elimination half-life was 1.12 $\pm$ 0.15 hours.

The administration of ALKERAN tablets immediately after food delayed the time to achieving peak plasma concentrations and reduced the area under the plasma concentration-time curves by between 39 and 45%.

5.3 Preclinical safety data

Melphalan is mutagenic in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:

Microcrystalline cellulose
Crospovidone
Colloidal anhydrous silica
Magnesium stearate
Tablet Film Coating:
Hypromellose
Titanium dioxide
Macrogol

6.2 Incompatibilities

None known

6.3 Shelf-life

36 months

6.4 Special precautions for storage

Store at 2°C to 8°C.

6.5 Nature and contents of container

ALKERAN are white to off-white film-coated, round, biconvex tablets engraved “GX EH3” on one side and “A” on the other, supplied in amber glass bottles with a child resistant closure. Each pack contains 25 tablets.

6.6 Special precautions for disposal

Safe handling of ALKERAN tablets:
The handling of ALKERAN tablets should follow guidelines for the handling of cytotoxic medicines according to prevailing local recommendations and/or regulations.
Provided the outer coating of the tablet is intact, there is no risk in handling ALKERAN Tablets.
ALKERAN tablets should not be divided. Do not break, crush or chew the tablets.

Disposal:
ALKERAN tablets should be destroyed in accordance with relevant local regulatory requirements concerning the disposal of cytotoxic medicines.

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

March 2017
29 July 2020
18 March 2020
28 September 2021
20 October 2023

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
4.3; 4.4; 4.5; 4.8; 4.9; 5.1; 6.6	Safety related changes
4.2	Thromboembolic events
6.3	Increase in shelf-life