

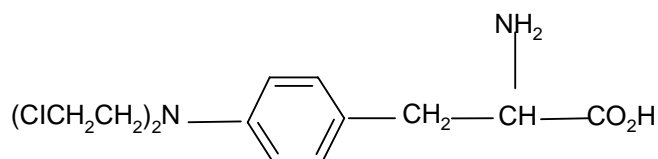
PRODUCT INFORMATION

ALKERAN[®] TABLETS

NAME OF THE DRUG:

Alkeran tablets contain 2mg melphalan.

Melphalan, also known as L-phenylalanine mustard, phenylalanine mustard, L-PAM, or L-sarcolysin, is a phenylalanine derivative of nitrogen mustard. Melphalan is a bifunctional alkylating agent that is active against selected human neoplastic diseases. The chemical name for melphalan, is 4-bis (2-chloroethyl) amino-L-phenylalanine, it has a molecular weight of 305.20, and its molecular formula is $C_{13}H_{18}Cl_2N_2O_2$, CAS No.: 148-82-3 and the chemical structure is:



DESCRIPTION:

Melphalan is a white to cream coloured powder. It is practically insoluble in water, chloroform and ether, slightly soluble in methanol and dissolves in dilute mineral acids. Each Alkeran tablet also contains microcrystalline cellulose, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide and macrogol 400.

PHARMACOLOGY:

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.

PHARMACOKINETICS:

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

The steady-state volume of distribution of melphalan is 0.5 L/kg. Penetration into cerebrospinal fluid (CSF) is low. The extent of melphalan binding to plasma proteins ranges from 60% to 90%. Serum albumin is the major binding protein, while α_1 -acid glycoprotein appears to account for about 20% of the plasma protein binding. Approximately 30% of the drug is (covalently) irreversibly bound to plasma proteins. Interactions with immunoglobulins have been found to be negligible.

Melphalan is eliminated from plasma primarily by chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan. Aside from these hydrolysis products, no other melphalan metabolites have been observed in humans. Although the contribution of renal elimination to melphalan clearance appears to be low, one study noted an increase in

the occurrence of severe leucopenia in patients with elevated blood urea nitrogen (BUN) after 10 weeks of therapy.

CLINICAL TRIALS

A randomised trial compared prednisone plus IV melphalan to prednisone plus oral melphalan in the treatment of myeloma. As discussed below, overall response rates at week 22 were comparable; however, because of changes in trial design, conclusions as to the relative activity of the two formulations after week 22 are impossible to make.

Both arms received oral prednisone starting at 0.8 mg/kg per day with doses tapered over 6 weeks. Melphalan doses in each arm were:

- Arm 1 Oral melphalan 0.15 mg/kg per day x 7 followed by 0.05 mg/kg per day when WBC began to rise.
Arm 2 IV melphalan 16 mg/m² once every 2 weeks x 4 (over 6 weeks) followed by the same dose every 4 weeks.

Doses of melphalan were adjusted according to the following criteria:

Table 1: Criteria for Dosage Adjustment in a Randomised Clinical Trial

WBC/mm ³	Platelets	Percent of Full Dose
≥4000	≥100,000	100
≥3000	≥75,000	75
≥2000	≥50,000	50
<2000	<50,000	0

One hundred and seven patients were randomised to the oral melphalan arm and 203 patients to the IV melphalan arm. More patients had a poor-risk classification (58% versus 44%) and high tumour load (51% versus 34%) on the oral compared to the IV arm ($P < 0.04$). Response rates at week 22 are shown in the following table:

Table 2: Response Rates at Week 22

Initial Arm	Evaluable Patients	Responders n (%)	<i>P</i>
Oral melphalan	100	44 (44%)	$P > 0.2$
IV melphalan	195	74 (38%)	

Because of changes in protocol design after week 22, other efficacy parameters such as response duration and survival cannot be compared.

Severe myelotoxicity (WBC ≤1000 and/or platelets ≤25,000) was more common in the IV melphalan arm (28%) than in the oral melphalan arm (11%).

An association was noted between poor renal function and myelosuppression; consequently, an amendment to the protocol required a 50% reduction in IV melphalan dose if the BUN was ≥30 mg/dl (≥10.71 mmol/L). The rate of severe leucopenia in the IV arm in the patients with BUN over 30 mg/dl (≥10.71 mmol/L) decreased from 50% (8/16) before protocol amendment to 11% (3/28) ($P = 0.01$) after the amendment.

Before the dosing amendment, there was a 10% (8/77) incidence of drug-related death in the IV arm. After the dosing amendment, this incidence was 3% (3/108). This compares to an overall 1% (1/100) incidence of drug-related death in the oral arm.

INDICATIONS:

Alkeran is indicated for the palliative treatment of multiple myeloma and advanced ovarian adenocarcinoma.

Alkeran has a significant therapeutic effect in a proportion of patients suffering from advanced breast carcinoma and may be used in the treatment of polycythaemia vera.

CONTRAINDICATIONS:

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

PRECAUTIONS AND WARNINGS:

ALKERAN IS AN ACTIVE CYTOTOXIC AGENT FOR USE ONLY 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.

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.

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. Therefore, the following tests should be performed at the start of therapy and prior to each subsequent course of ALKERAN: platelet count, haemoglobin, white blood cell count, and differential. Thrombocytopenia and/or leucopenia are indications to withhold further therapy until the blood counts have sufficiently recovered. Frequent blood counts are essential to determine optimal dosage and to avoid toxicity. Dose adjustment on the basis of blood counts at the nadir and day of treatment should be considered. See DOSAGE AND ADMINISTRATION.

Although controlled trials comparing intravenous (IV) to oral melphalan have shown more myelosuppression with the IV formulation, severe bone marrow suppression with resulting infection or bleeding may occur.

ALKERAN should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior irradiation or chemotherapy or whose marrow function is recovering from previous cytotoxic therapy.

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.

Mutagenicity and carcinogenicity: Alkeran is mutagenic in animals and chromosome aberrations have been observed in patients being treated with the drug.

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.

Secondary malignancies, including acute nonlymphocytic leukaemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with alkylating agents (including melphalan). Some patients also received other chemotherapeutic agents or radiation therapy. Precise quantitation of the risk of acute leukaemia, myeloproliferative syndrome, or carcinoma is not possible. Published reports of leukaemia in patients who have received melphalan (and other alkylating agents) suggest that the risk of leukaemogenesis increases with chronicity of treatment and with cumulative dose. The potential benefits from ALKERAN therapy must be weighed on an individual basis against the possible risk of the induction of a second malignancy.

Although adequate and well-controlled carcinogenicity studies have not been conducted in animals, there is clear evidence from animal studies that melphalan is carcinogenic. Intraperitoneal (IP) administration of melphalan in rats (5.4 or 10.8 mg/m²) and mice (2.25 or 4.5 mg/m²) three times per week for 6 months followed by a 12 months post-dose observation produced peritoneal sarcoma in rats, and lung tumors and lymphosarcomas (males) in mice. Lung tumours were also increased in two other studies in mice (total dose: 144 mg/m² dermal given as 10 injections over a period of 10 weeks; 3.2-51 mg/m² IP given as 12 injections over a period of 4 weeks) while in one of these studies (dermal), skin papillomas were increased although non-significantly.

Chromosome aberrations have been observed in patients being treated with Melphalan. Melphalan has been shown to cause chromatid and chromosome damage in human lymphocytes at a single dose of 20 mg IV (~10.6 mg/m², comparable to a therapeutic dose of 16 mg/m²) and in rat bone marrow cells at a single intramuscular dose of 6 mg/m². Melphalan also showed mutagenic effects on germ cells in male mice at 17.1-21.9 mg/m².

Effects on fertility: Alkeran causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients. Reversible and irreversible testicular suppression have also been reported.

No fertility studies have been conducted in animals. However, there is evidence from some animal studies that melphalan can have an adverse effect on spermatogenesis. Therefore, it is possible that ALKERAN may cause temporary or permanent sterility in male patients.

Use in Pregnancy: Category D.

As with other cytotoxic agents, Alkeran can produce spontaneous abortion, foetal loss and birth defects. 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 drug.

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

The use of Alkeran 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.

Melphalan has been shown to be teratogenic and embryogenic in animal studies. A single dose of 5 mg/kg IP (30 mg/m²) given on day 6 or day 9 of gestation in the rat was embryolethal and teratogenic, and a single dose of 3 mg/kg IP (18 mg/m²) was teratogenic when administered on day 6. Malformations resulting from melphalan administration included alterations of the brain (underdevelopment, deformation, meningocele and encephalocele) and eye (anophthalmia and microphthalmos), reduction of the mandible and tail, as well as exomphaly (umbilical hernia).

In a repeat-dose embryotoxicity study in rats, (0.33, 1 and 3 mg/kg/day PO on gestation days 7-17; total doses: 22, 66 and 198 mg/m² PO, respectively; cf. clinical dose of 16 mg/m² IV), all doses were maternotoxic (reduced weight gain, and mortality occurred at the high dose). Intrauterine deaths, reduced foetal and pup weights and pup weight gain over the lactation period were seen in the mid and high dose groups but pup survival over the lactation period was reduced at all doses. Melphalan showed a reduction in ossification at ≥ 1 mg/kg/day and an increased incidence of rib anomalies and impairment of pup development (delayed eruption of incisors, significantly different open-field behaviour) at the high dose.

No animal studies have been conducted to investigate the peri- and post-natal effects of melphalan.

Lactation: It is not known whether this drug is excreted in human milk. Mothers receiving Alkeran should not breast feed.

Interactions: 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.

Cyclosporin 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.

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (See PRECAUTIONS AND WARNINGS).

Adverse Reactions:

Haematologic: The most common side-effect is bone marrow depression leading to leucopenia, thrombocytopenia and anemia. 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 Mutagenicity and carcinogenicity).

Gastrointestinal: Gastro-intestinal effects such as nausea and vomiting occur in up to 30 per cent of patients receiving conventional oral doses of Alkeran. Diarrhoea is very common. Oral ulceration occurs infrequently.

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

Hypersensitivity: Acute hypersensitivity reactions including anaphylaxis were reported in 2.4% of 425 patients receiving ALKERAN for Injection for myeloma (see PRECAUTIONS AND WARNINGS). 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 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 is very common at high doses and common at conventional doses.

DOSAGE AND 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.

Since Alkeran is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be delayed or adjusted if necessary. At least one determination should be obtained prior to each course of treatment. Patients should be observed closely for consequences of bone marrow suppression, which include severe infections, bleeding, and symptomatic anaemia (see Precautions and Warnings).

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: The administration of Alkeran and prednisone is more effective than Alkeran alone. The combination is usually given on an intermittent basis.

A typical oral dosage schedule is 0.15 mg/kg bodyweight/day in divided doses for 4 days together with 40 mg prednisone daily for 4 days, repeated at intervals of six weeks. Numerous regimes have been used and the scientific literature should be consulted for details. Prolonging treatment beyond one year in responders does not appear to improve results.

Advanced ovarian adenocarcinoma: The usual regime is 0.2 mg/kg bodyweight/day, given orally in divided doses, three times daily, for 5 days. This is repeated every 4-8 weeks, provided the bone marrow has recovered.

Advanced carcinoma of the breast: Alkeran has been given orally at a dose of 0.15 mg/kg bodyweight daily or 5 mg/m² body surface area daily for 4-6 days and repeated every 6 weeks.

Polycythaemia vera: For remission induction the usual dose is 6 to 10 mg daily for 5 to 7 days, after which 2-4 mg daily is given until satisfactory disease control is achieved. The maintenance dose is 2 to 6 mg once per week. 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 haematological control.

Children: Safety and efficacy in children have not been established.

Elderly: Although Alkeran is frequently used at conventional dosage in the elderly, there is no specific information available relating to its administration in this patient sub-group. Clinical experience with ALKERAN has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment: See also Precautions and Warnings. Alkeran clearance, though variable, is decreased in renal impairment. Dosage reduction of up to 50% should be considered in patients with moderate to severe renal impairment and subsequent dosage determined according to the degree of haematological suppression. See PRECAUTIONS AND WARNINGS.

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 (ie. 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.

PRESENTATION:

Alkeran tablets 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. They each contain 2 mg melphalan and are supplied in bottles of 25 and 50* tablets.

(*not currently distributed in Australia)

Stored at 2°C to 8°C. (Refrigerate. Do not freeze).

SPONSOR NAME AND ADDRESS:

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards NSW 2065

Date of TGA approval: 03 April 2002

Date of most recent amendment: 31 July 2010

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