

## PRODUCT MONOGRAPH

**Pr ALKERAN<sup>®</sup>**

Melphalan

Tablets, 2 mg  
Injection, 50 mg/vial

Antineoplastic (Alkylating) Agent

ATC Code: L01AA03

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Pr **ALKERAN**<sup>®</sup>

Melphalan

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Oral	Tablets/ 2 mg	Not applicable.*
Intravenous Perfusion	Injection/ 50 mg/vial	ethanol*

\*For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.

**INDICATIONS AND CLINICAL USE**

ALKERAN<sup>®</sup> (melphalan) is indicated for:

- the palliative treatment of multiple myeloma
- the palliation of nonresectable epithelial carcinoma of the ovary.
- ALKERAN<sup>®</sup> for injection has been administered by hyperthermic isolated limb perfusion as an adjuvant to surgery in the treatment of malignant melanoma. However, there have been no prospective controlled or uncontrolled trials evaluating dose and its relationship to disease response and/or toxicity.

**CONTRAINDICATIONS**

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- ALKERAN<sup>®</sup> (melphalan) should not be used in patients whose disease has demonstrated a prior resistance to this agent. Patients who have demonstrated hypersensitivity to melphalan should not be given the drug. There may be cross-sensitivity (skin rash) between melphalan and chlorambucil (LEUKERAN<sup>®</sup>).

- Melphalan should not be given if other similar chemotherapeutic agents or radiotherapy have been administered to the patient recently, or if neutrophil and/or platelet counts are depressed.
- Melphalan should not be administered concurrently with radiotherapy.

## WARNINGS AND PRECAUTIONS

### **Serious Warnings and Precautions**

ALKERAN<sup>®</sup> (melphalan) should be administered in carefully adjusted dosages by or under the supervision of experienced physicians who are familiar with the drug's actions and the possible complications of its use.

The major acute toxicities associated with melphalan are:

- Hypersensitivity reactions including anaphylaxis (See Immune)
- Bone marrow suppression (See Hematologic)
- Pulmonary toxicity (See Respiratory and OVERDOSAGE)
- Infertility (See Sexual Function / Reproduction)
- Secondary malignancies (See Carcinogenesis and Mutagenesis)
- Mutagenicity and teratogenicity (See Carcinogenesis and Mutagenesis)

### **General**

ALKERAN<sup>®</sup> should be administered in carefully adjusted dosages by or under the supervision of experienced physicians who are familiar with the drug's actions and the possible complications of its use. The drug should not be administered by hyperthermic isolated limb perfusion unless the clinician is experienced and well-trained in this technique.

In all instances where the use of ALKERAN<sup>®</sup> for injection is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risk of adverse events. Melphalan 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. Dose reduction should be considered in patients with renal insufficiency receiving IV melphalan (See Hematologic and Renal).

### **Carcinogenesis and Mutagenesis**

Secondary malignancies, including acute nonlymphocytic leukemia, 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 leukemia, myeloproliferative syndrome or carcinoma is not possible. Published reports

of leukemia in patients who have received melphalan (and other alkylating agents) suggest that the risk of leukemogenesis increases with chronicity of treatment and with cumulative dose. In one study, the 10-year cumulative risk of developing acute leukemia or myeloproliferative syndrome after melphalan therapy was 19.5% for cumulative doses ranging from 730 mg to 9652 mg. In this same study, as well as in an additional study, the 10-year cumulative risk of developing acute leukemia or myeloproliferative syndrome after melphalan therapy was less than 2% for cumulative doses under 600 mg. This does not mean that there is a cumulative dose below which there is no risk of the induction of secondary malignancy. The potential benefits from melphalan therapy must be weighed on an individual basis against the possible risk of the induction of a second malignancy.

Melphalan has been shown to cause chromatid or chromosome damage in man.

### **Hematologic**

As with other nitrogen mustard drugs, excessive dosage will produce marked bone marrow suppression. Bone marrow suppression is the most significant toxicity associated with ALKERAN<sup>®</sup> for injection in most patients. Therefore, the following tests should be performed at the start of therapy and prior to each subsequent dose of ALKERAN<sup>®</sup>: platelet count, hemoglobin, white blood cell count and differential. The occurrence of a platelet count below  $50 \times 10^9/L$  or an absolute neutrophil count below  $0.5 \times 10^9/L$  is an indication to withhold further therapy until the blood counts have sufficiently recovered. Frequent blood counts are essential to determine optimal dosage and to avoid toxicity.

If the leukocyte count falls below  $3 \times 10^9/L$ , or the platelet count below  $100 \times 10^9/L$ , the drug should be discontinued until the blood picture has had a chance to recover.

Blood counts may continue to fall for 6-8 weeks after initiation of treatment. So, at the first sign of abnormally large fall in leukocyte or platelet counts, treatment should be temporarily interrupted.

In one trial by Cornwell *et al.* (1982), melphalan administered intravenously without adjustment for renal failure increased incidence rates for severe leucopenia and thrombocytopenia by 35% in patients with renal insufficiency (BUN  $\geq 30$ mg/dL).

### **Immune**

Acute hypersensitivity reactions, including anaphylaxis, have occurred infrequently (see ADVERSE REACTIONS). Treatment is symptomatic. The infusion should be terminated immediately, followed by the administration of volume expanders, pressor agents, corticosteroids, or antihistamines at the discretion of the physician.

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

### **Renal**

Systemic exposure of melphalan was positively correlated to the degree of renal insufficiency following either route of administration. In one trial by Cornwell *et al.* (1982), increased incidence rate of bone marrow suppression has been associated with impaired renal function in patients with intravenous administration without dose adjustment for renal failure. Dose adjustments should be considered for patients with significant renal dysfunction (BUN  $\geq$  30mg/dL) and these patients should be closely monitored for toxicity.

### **Respiratory**

Rare reports of pulmonary fibrosis or interstitial pneumonitis (including fatal reports) have been seen in patients treated with ALKERAN<sup>®</sup>.

### **Sexual Function / Reproduction**

Melphalan causes suppression of ovarian function in premenopausal women, resulting in amenorrhea in a significant number of patients.

Reversible and irreversible testicular suppression have also been reported. There is evidence from some animal studies that melphalan can have an adverse effect on spermatogenesis.

### **Special Populations**

**Pregnant Women:** Safe use of melphalan has not been established with respect to adverse effects on fetal development. Therefore, it should be used in women of childbearing potential and particularly during early pregnancy only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

**Nursing Women:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from melphalan, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatrics:** The safety and effectiveness in children have not been established.

**Geriatrics:** Clinical experience with ALKERAN<sup>®</sup> has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### **Monitoring and Laboratory Tests**

Periodic complete blood counts with differentials should be performed during the course of treatment with melphalan. At least one determination should be obtained prior to each dose. Patients should be observed closely for consequences of bone marrow suppression, which include severe infections, bleeding, and symptomatic anemia.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The following information on adverse reactions is based on data from both oral and intravenous administration of ALKERAN<sup>®</sup> (melphalan) as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

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.

**Gastrointestinal:** Gastrointestinal effects such as nausea and vomiting occur in up to 30% of patients receiving conventional oral doses of ALKERAN<sup>®</sup> and in up to 50% of patients receiving intravenous doses of ALKERAN<sup>®</sup>. Diarrhea is noted to occur one week post high dose melphalan therapy. Oral ulceration and hepatic toxicity including veno-occlusive disease have been reported.

The incidence of diarrhea, vomiting and stomatitis becomes the dose-limiting toxicity in patients given high intravenous doses of melphalan in association with autologous bone marrow transplantation. Cyclophosphamide pretreatment appears to reduce the severity of gastrointestinal damage induced by high-dose melphalan and the literature should be consulted for details. Stomatitis at conventional doses is rare.

**Hematologic:** The most common side effect is bone marrow suppression leading to leukopenia, thrombocytopenia and anemia. Neutropenia and hemolytic anemia were also observed. Irreversible bone marrow failure has been reported. Bone marrow suppression is uncommon after limb perfusion.

Frequencies of severe myelosuppression and infections including fatal cases secondary to myelosuppression were much higher in patients with renal insufficiency (BUN  $\geq$  30mg/dL) than those with normal renal function who were treated with intravenous melphalan (See WARNINGS AND PRECAUTIONS, Renal)

**Hepatic:** 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 following high-dose intravenous treatment.

Elevation in liver function enzymes is usually mild.

**Hyperthermic Isolated Limb Perfusion:** Adverse reactions may be attributable to the surgical procedure as well as the heated perfusion with ALKERAN<sup>®</sup> for Injection.

The local toxicity of hyperthermic perfusion appears to increase with increasing drug dose, duration of perfusion, and temperature. Muscle atrophy, muscle fibrosis, myalgia and increase in blood creatine phosphokinase were very commonly observed. Compartment syndrome has been commonly observed. Muscle necrosis and rhabdomyolysis have been seen at an unknown frequency. Severe nerve or muscle damage, severe skin or soft tissue reaction, or arterial thrombosis requiring amputation are rare, occurring in less than 1% of patients.

Systemic complications are uncommon, with reversible bone marrow suppression occurring in < 5% of patients. Wound complications, such as delayed healing or infection, occur in 5 to 10% of patients.

**Hypersensitivity:** Acute hypersensitivity reactions, including anaphylaxis, were reported in 2.4% of 425 patients receiving ALKERAN<sup>®</sup> for injection for myeloma (see WARNINGS AND PRECAUTIONS). These reactions were characterized by urticaria, pruritus, edema, skin rashes and in some patients, tachycardia, bronchospasm, dyspnea, and hypotension. Cardiac arrest had also been rarely reported in association with such events. These patients appeared to respond to antihistamine and corticosteroid therapy. Treatment with melphalan should be discontinued if a hypersensitivity reaction occurs.

**Local Reactions:** Mild pain and/or irritation at, or near, the site of injection occurred after approximately half of the infusions, resolving within few hours after the end of the injection, without a need for treatment. Skin ulceration at injection site and flushing were reported as well as subjective and transient sensation of warmth and/or tingling.

**Miscellaneous:** Other reported adverse reactions include: skin hypersensitivity, vasculitis, alopecia, allergic reaction, pulmonary fibrosis, stomatitis, maculopapular rashes and interstitial pneumonitis. Fatal reports of pulmonary fibrosis have been received. Flushing sensations were reported at high doses of melphalan.

**Renal:** Temporary significant elevation of the blood urea has been seen in the early stages of melphalan therapy in myeloma patients with renal damage. An increase in creatinine levels has been observed.

## DRUG INTERACTIONS

### Drug-Drug Interactions

**Table 1- Established or Potential Drug-Drug Interactions**

<b>ALKERAN®</b>	<b>Effect</b>	<b>Clinical comment</b>
Nalidixic acid	Hemorrhagic enterocolitis	Nalidixic acid together with high-dose intravenous melphalan has caused deaths in children due to hemorrhagic enterocolitis.
Cyclosporine	Impaired renal function	In bone marrow transplant patients who were conditioned with high-dose intravenous melphalan and who subsequently received cyclosporine to prevent graft-versus-host disease.
Live Viral Vaccines	Potential to cause infection in immunocompromised hosts	Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (See WARNINGS AND PRECAUTIONS).

### Drug-Food Interactions

The oral administration of melphalan 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% (See ACTION AND CLINICAL PHARMACOLOGY).

## DOSAGE AND ADMINISTRATION

### Recommended Dose

#### **Oral**

##### ***Multiple Myeloma:***

The usual oral dose is 6 mg (3 tablets) daily. The entire daily dose may be given at one time. It is adjusted, as required, on the basis of blood counts done at approximately weekly intervals. After 2-3 weeks of treatment, the drug should be discontinued for up to 4 weeks, during which time the blood count should be followed carefully. When the white blood cell and platelet counts are rising, a maintenance dose of 2 mg daily may be instituted. Because of the patient-to-patient variation in melphalan plasma levels following oral administration of the drug, several investigators have recommended that melphalan dosage be cautiously escalated until some myelosuppression is observed, in order to assure that potentially therapeutic levels of the drug have been reached.

Other dosage regimens have been used by various investigators. Osserman and Takatsuki have used an initial course of 10 mg/day for 7-10 days. They report that maximal suppression of the leukocyte and platelet counts occurs within 3-5 weeks and recovery within 4-8 weeks. Continuous maintenance therapy with 2 mg/day is instituted when the white blood cell count is greater than  $4 \times 10^9/L$  and the platelet count is greater than  $100 \times 10^9/L$ . Dosage is adjusted to between 1 and 3 mg/day depending upon the hematological response. It is desirable to try to maintain a significant degree of bone marrow depression so as to keep the leukocyte count in the range of 3 to  $3.5 \times 10^9/L$ . Hoogstraten et al. have started treatment with 0.15 mg/kg/day for 7 days. This is followed by a rest period of at least 14 days, but it may be as long as 5-6 weeks. Maintenance therapy is started when the white blood cell and platelet counts are rising. The maintenance dose is 0.05 mg/kg/day or less and is adjusted according to the blood count.

Available evidence suggests that about one-third to one-half of the patients with multiple myeloma show a favorable response to oral administration of the drug.

It is to be emphasized that response may be very gradual over many months; it is important that repeated courses or continuous therapy be given since improvement may continue slowly over many months and the maximum benefit may be missed if treatment is abandoned too soon.

#### ***Epithelial Ovarian Cancer:***

One commonly employed regimen for the treatment of ovarian carcinoma has been to administer melphalan at a dose of 0.2 mg/kg P.O. daily for 5 days as a single course. Courses are repeated every 4-5 weeks depending upon hematologic tolerance.

#### **Intravenous**

##### ***Multiple Myeloma:***

The usual intravenous dose is  $16 \text{ mg/m}^2$ . Dosage reduction of up to 50% should be considered in patients with renal insufficiency ( $\text{BUN} \geq 10.71 \text{ mmol/L}$  [ $30 \text{ mg/dL}$ ]). The drug is administered in one dose and the length of infusion should be from 15 to 90 minutes. Melphalan is repeated at 2-week intervals initially for 4 doses, then at 4-week intervals after adequate recovery from toxicity. Available evidence suggests about one-third to one-half of the patients with multiple myeloma show a favorable response to the drug. Experience with oral melphalan suggests that repeated courses should be given since improvement may continue slowly over many months, and the maximum benefit may be missed if treatment is abandoned prematurely. Dose adjustment on the basis of blood cell counts at the nadir prior to each dose should be considered.

#### **Perfusion Method**

##### ***Malignant Melanoma:***

Only physicians experienced and well-trained in hyperthermic isolated limb perfusion should administer the drug in this fashion.

## **Administration**

### **Preparation for Administration/Stability:**

#### ***Intravenous:***

1. Reconstitute ALKERAN<sup>®</sup> for injection, as directed, with 10 mL of the supplied diluent. This provides a 5 mg/mL solution of melphalan.
2. Immediately dilute the dose to be administered in 0.9% sodium chloride injection, USP, to a concentration not greater than 0.45 mg/mL.
3. Administer the diluted product over a minimum of 15 minutes.
4. Complete administration within 50 minutes of reconstitution.
5. Discard any reconstituted and diluted solutions remaining after 50 minutes of reconstitution.

The reconstituted product is stable for up to 2 hours at 30°C. A precipitate forms if the solution is stored at 5°C. **Do not refrigerate.**

Solutions diluted to a concentration of 0.1 mg/mL to 0.45 mg/mL in 0.9% sodium chloride injection are stable for up to 50 minutes at 30°C and 3 hours at 20°C.

**Reconstitution:** ALKERAN<sup>®</sup> for injection must be reconstituted, at room temperature, by rapidly transferring 10 mL of the supplied solvent-diluent directly into the vial of lyophilized powder using a sterile needle (20 gauge or larger needle diameter) and syringe. Immediately shake vial vigorously until a clear solution is obtained. Rapid addition of the diluent followed by immediate vigorous shaking is important for proper dissolution. The pH of resulting solution is approximately 6.5.

<b>Vial Size</b>	<b>Volume of Diluent to be Added to Vial</b>	<b>Approximate Available Volume</b>	<b>Nominal Concentration per mL</b>
50 mg	10 mL	10 mL	5 mg/mL

ALKERAN<sup>®</sup> injection solution has limited stability and should be prepared immediately before use. Any unused solution should be discarded. The reconstituted solution should be used immediately and should not be refrigerated as this will cause precipitation. It is stable for up to 2 hours at 30°C.

ALKERAN<sup>®</sup> injection solution has reduced stability when further diluted in an infusion solution and the rate of degradation increases rapidly with rise in temperature. In that case, only sodium chloride infusion, 0.9% w/v should be used. Solutions diluted to a concentration of 0.1 mg/mL to 0.45 mg/mL in 0.9% sodium chloride infusion should be used immediately and are stable for up to 50 minutes at 30°C and 3 hours at 20°C.

#### **Parenteral Products:**

Parenteral drug products should usually be inspected for particulate matter and discoloration prior to administration whenever solution and container permit. If either occurs, do not use this product.

## **OVERDOSAGE**

Overdose as high as 290 mg/m<sup>2</sup> resulting in death has been reported. It has also been reported that a pediatric patient survived a 254 mg/m<sup>2</sup> overdose treated with standard supportive care. The immediate effects are severe nausea and vomiting. Decreased consciousness, convulsions, muscular paralysis and cholinomimetic effects are less frequently seen. Severe mucositis, stomatitis, colitis, diarrhea, and hemorrhage of the gastrointestinal tract occur at high doses (>100 mg/m<sup>2</sup>). Elevations in liver enzymes and veno-occlusive disease occur infrequently. Nephrotoxicity and adult respiratory distress syndrome have been reported rarely. The principal toxic effect is bone marrow suppression leading to leucopenia, thrombocytopenia and anemia. Hematologic parameters should be closely followed for 3 to 6 weeks. Administration of autologous bone marrow or hematopoietic growth factors (i.e., sargramostim, filgrastim) may shorten the period of pancytopenia. General supportive measures together with appropriate blood transfusions and antibiotics should be instituted as deemed necessary by the physician. This drug is not removed from plasma to any significant degree by hemodialysis or hemoperfusion.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

ALKERAN<sup>®</sup> (melphalan) is an alkylating agent of the bischloroethylamine type. As a result, its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N<sup>7</sup> position of guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.

### **Pharmacokinetics**

#### **Absorption**

The absorption of oral melphalan is highly variable with respect to both the time to first appearance of the drug in plasma and peak plasma concentration. In studies of the absolute bioavailability of melphalan the mean absolute bioavailability ranged from 56 to 85%.

Mean ( $\pm$ SD) peak melphalan plasma concentrations in myeloma patients given melphalan intravenously at doses of 10 or 20 mg/m<sup>2</sup> were  $1.2 \pm 0.4$  and  $2.8 \pm 1.9$   $\mu$ g/mL, respectively. Studies in children as young as 1 year showed results similar to adults.

The oral administration of melphalan 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% (See DRUG INTERACTIONS).

### **Distribution**

The steady-state volume of distribution of melphalan is 0.5 L/kg and approximates total body water. Penetration into cerebrospinal fluid (CSF) is low. The extent of melphalan binding to plasma proteins is ranging from 69% to 78%. There is evidence that the protein binding is linear in the range of plasma concentrations usually achieved at standard dose therapy, but that the binding may become concentration-dependent at the concentrations observed at high dose therapy. Serum albumin is the major binding protein, accounting for about 55% to 60% of the plasma protein binding, and 20% is bound to  $\alpha_1$ -acid glycoprotein. In addition, melphalan binding studies have revealed the existence of an irreversible component attributable to the alkylation reaction with plasma proteins. Interactions with immunoglobulins have been found to be negligible.

Melphalan displays limited penetration of the blood-brain barrier. Melphalan was found at concentrations of approximately 10% of the corresponding plasma concentration in the cerebrospinal fluid samples following high-dose intravenous melphalan in two studies.

### **Metabolism**

Melphalan is eliminated from plasma primarily by chemical hydrolysis to monohydroxy- and dihydroxy-melphalan. Aside from these hydrolysis products, no other melphalan metabolites have been observed in man.

### **Elimination**

Following injection, drug plasma concentrations declined rapidly in a biexponential manner with distribution phase and terminal elimination phase half-lives of approximately 10 and 70 minutes, respectively. Estimates of average total body clearance varied among studies, but typical values of approximately 7 to 9 mL/min/kg (250 to 325 mL/min/m<sup>2</sup>) were observed.

Melphalan clearance may be decreased in renal impairment. An increase in AUC (i.e. melphalan systemic exposure) was observed in patients with renal impairment when melphalan was administered by either route. One study noted an increase in the occurrence of severe leukopenia in patients with elevated BUN after 10 weeks of therapy (see WARNINGS AND PRECAUTIONS, Hematologic).

The pharmacokinetics of melphalan administered by closed circuit limb perfusion have been studied by several investigators. Melphalan concentrations declined rapidly and biexponentially from circulating perfusate with average terminal half-lives reported from 26 min (n=4) to 53 min (n=48). Systemic exposure to melphalan during limb perfusion is generally very low. Peak melphalan concentrations in the closed circuit perfusate are typically 10 to 100 times greater than peak concentrations in plasma observed following standard dose systemic intravenous therapy for multiple myeloma.

## **STORAGE AND STABILITY**

Tablets: Store in a refrigerator, 2°C - 8°C (36°F - 46°F).

Injection: Store at controlled room temperature (15°C – 30°C). Protect from light.

## **SPECIAL HANDLING INSTRUCTIONS**

As with other toxic compounds, caution should be exercised when handling and preparing the solution of ALKERAN<sup>®</sup>. Skin reactions associated with accidental exposure may occur. The use of gloves is recommended. If the solution of ALKERAN<sup>®</sup> contacts the skin or mucosa, immediately wash the skin or mucosa thoroughly with soap and water.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **Dosage Forms**

#### **ALKERAN<sup>®</sup> (melphalan) for injection (freeze-dried) 50 mg:**

Vial of 50 mg melphalan as the hydrochloride.

#### **Solvent-diluent for ALKERAN<sup>®</sup> for injection:**

Vial of 10 mL.

#### **Tablets**

2 mg, white to off-white, round, biconvex, film-coated imprinted with "A" on one side and on the other side "GX EH3". ALKERAN<sup>®</sup> tablets are available in bottles of 50.

### **Composition**

#### **Tablets:**

Each white to off-white, round, biconvex, film-coated tablet is imprinted with "A" on one side and on the other side "GX EH3", and contains 2 mg melphalan. It also contains the following non-medicinal ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400 and titanium dioxide.

**Injection:**

ALKERAN<sup>®</sup> for injection is supplied as a 2-component pack comprising a vial containing a freeze-dried powder and a vial of solvent-diluent. Each ALKERAN<sup>®</sup> vial contains the equivalent of 50 mg of melphalan, in the form of the hydrochloride, as a sterile, white to cream-coloured, freeze-dried powder and povidone, 20 mg. Each vial of solvent-diluent provides 10 mL of buffer solution containing sodium citrate 0.20 g, ethanol 0.52 mL, propylene glycol 6.00 mL, and water for injection, q.s.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

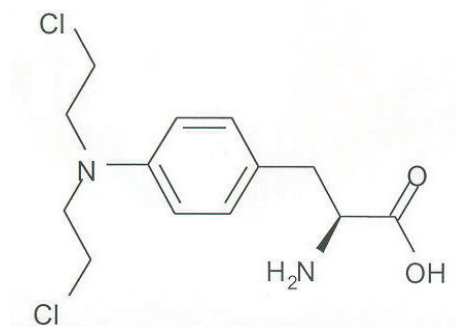
#### Drug Substance

Proper name: melphalan

Chemical name: 4-[bis(2-chloroethyl)amino]-L-Phenylalanine

Molecular formula and molecular mass:  $C_{13}H_{18}Cl_2N_2O_2$ , 305.20

Structural formula:



Physicochemical properties: A white to cream-coloured powder which melts with decomposition at about 175°C. Soluble in ethanol and propylene glycol. Practically insoluble in water.

### DETAILED PHARMACOLOGY

#### Metabolism

##### In vivo Studies

Alberts et al. found that plasma melphalan levels are highly variable after oral dosing, both with respect to the time of the first appearance of melphalan in plasma and to the peak concentrations achieved. Whether this results from incomplete gastrointestinal absorption or a variable "first pass" hepatic metabolism is unknown. Five patients were studied after both oral and intravenous dosing with 0.6 mg/kg as a single bolus dose by each route. The areas under the plasma concentration-time curves after oral administration averaged  $61 \pm 26\%$  ( $\pm$  standard deviation; range 25-89%) of those following intravenous administration. In 10 patients given a single, oral dose of 0.6 mg/kg of melphalan, the terminal plasma half-disappearance time of parent drug was  $101 \pm 63$  minutes. The 24-hour urinary excretion of parent drug in these patients was  $10 \pm 6\%$ , suggesting that renal clearance is not a major route of elimination of parent drug.

Tattersall et al. using universally labelled  $^{14}\text{C}$ -melphalan, found substantially less radioactivity in the urine of those given it intravenously (35-65% in 7 days). Following either oral or intravenous administration, the pattern of label recovery was similar, with the majority being recovered in the first 24 hours. Following oral administration, peak radioactivity occurred in plasma at 2 hours and then disappeared with a half-life of approximately 160 hours. In one patient where parent drug (rather than just radiolabel) was determined, the melphalan half-disappearance time was 67 minutes.

#### **In vitro Studies - Protein Binding and Dialysis**

After incubating  $^{14}\text{C}$ -melphalan in human plasma at  $37^\circ\text{C}$  for 8 hours, Chang et al. found that only 70% of the carbon-14 label was removed by methanol extraction. Almost none of the methanol-extractable  $^{14}\text{C}$ -melphalan was in the form of parent drug at that time.

Equilibrium dialysis of  $^{14}\text{C}$ -melphalan in human plasma at  $37^\circ\text{C}$  (30  $\mu\text{g}$  of melphalan per mL plasma) against 0.05 M phosphate buffer, pH 7.4, demonstrated that 30% of the carbon-14 remained undialyzable after equilibrium had been reached at 8 hours. These observations may indicate alkylation of plasma proteins by melphalan.

## **MICROBIOLOGY**

Not available.

## **TOXICOLOGY**

### **Animals**

<b>Species</b>	<b>LD<sub>50</sub></b>
Mouse	21 mg/kg P.O.
Mouse	10 mg/kg I.P.
Rat	4 mg/kg I.P.

No information is available on the acute effects of ALKERAN<sup>®</sup>(melphalan). However, chronic administration (by I.P. injection) produced lymphosarcomas and dose-related increase in lung tumours in mice and peritoneal tumours in rats.

## REFERENCES

1. Alberts DS, Chang SY, Chen HS, Evans TL, Moon TE. Oral melphalan kinetics. *Clin Pharmacol Ther* 1979 Dec; 26(6):737-45.
2. Ardiet C, Trachand B, Biron P, Rebattu P, Philip T. Pharmacokinetics of high-dose intravenous melphalan in children and adults with forced diuresis. Report in 26 cases. *Cancer Chemother Pharmacol* 1986; 16(3):300-305.
3. Benckhuijsen C, Varossieau FJ, Hart AAM, Wieberdink J, Norrdhoek J. Pharmacokinetics of melphalan in isolated perfusion of the limbs. *J Pharmacol Exp Ther* 1986; 237(2):538-588.
4. Bosanquet AG, Gilby ED. Pharmacokinetics of oral and intravenous melphalan during routine treatment of multiple myeloma. *Eur J Cancer Clin Oncol* 1982; 18(4):355-362.
5. Briele HA, Djuric M, Jung DT, Mortell T, Patel MK, Das Gupta TK. Pharmacokinetics of melphalan in clinical isolation perfusion of the extremities. *Cancer Res* 1985; 45(4):1885-1889.
6. Brox L, Birkett I, Belch A. Pharmacology of intravenous melphalan in patients with multiple myeloma. *Cancer Treat Rev* 1979; 6 Suppl:27-32.
7. Chang SY, Alberts DS, Farquhar D, Melnick LR, Walson PD, Salmon SE. Hydrolysis and protein binding of melphalan. *J Pharm Sci* 1978; 67(5):682-684.
8. Cornwell GG III, Pajak TF, McIntyre OR. Hypersensitivity reactions to I.V. melphalan during treatment of multiple myeloma: Cancer and Leukemia Group B experience. *Cancer Treat Rep* 1979; 63(3):399-403.
9. Cornwell GG, Pajak TF, McIntyre OR, Kochwa S, Dosik H. Influence of renal failure on myelosuppressive effects of melphalan: Cancer and Leukemia Group B experience. *Cancer Treat Rep* 1982; 66(3):475-481.
10. Ehrsson H, Lönroth U. Degradation of melphalan in aqueous solutions - influence of human albumin binding. *J Pharm Sci* 1982; 71(7):826-827.
11. Fisher B, Carbone P, Economou SG, Frelick R, Glass A, Lerner H et al. L-Phenylalanine mustard (L-PAM) in the management of primary breast cancer. *New Engl J Med* 1975; 292(3):117-122.
12. Fisher B, Glass A, Redmond C, Fisher ER, Barton B, Such E, et al. L-phenylalanine mustard (L-PAM) in the management of primary breast cancer. An update of earlier findings and a comparison with those utilizing L-PAM plus 5-fluorouracil (5-FU). *Cancer* 1977 Jun;39(6 Suppl):2883-903.

13. Gera S, Musch E, Osterheld HK, Loos U. Relevance of the hydrolysis and protein binding of melphalan to the treatment of multiple myeloma. *Cancer Chemother Pharmacol* 1989; 23(2):76-80.
14. Ghussen F, Nagel K, Groth W, Muller JM, Stutzer H. A prospective randomised study of regional extremity perfusion in patients with malignant melanoma. *Ann Surg* 1984; 200(6):764-768.
15. Gouyette A, Hartmann O, Pico JL. Pharmacokinetics of high-dose melphalan in children and adults. *Cancer Chemother Pharmacol* 1986; 16(2):184-189.
16. Greig NH, Sweeney DJ, Rapoport SI. Melphalan concentration dependent plasma protein binding in healthy humans and rats. *Eur J Clin Pharmacol* 1987; 32(2):179-185.
17. Hafstrom L, Hugander A, Jönsson PE, Westling H, Ehrsson H. Blood leakage and melphalan leakage from the perfusion circuit during regional hyperthermic perfusion for malignant melanoma. *Cancer Treat Rep* 1984; 68(6):867-872.
18. Hersh MR, Ludden TM, Kuhn JG, Knoght WA, III. Pharmacokinetics of high-dose melphalan. *Invest New Drugs* 1983; 1(4):331-334.
19. Hoogstraten B, Sheehe PR, Cuttner J, Cooper T, Kyle RA, Oberfield RA et al. Melphalan in multiple myeloma. *Blood* 1967; 30(1):74-83.
20. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to man. Some aziridines, N-, S- & O- mustards and selenium. *IARC Monogr Eval Carcinog Risk Chem Man* 1975;9:167-180.
21. Kohn DW. Molecular mechanisms of cross-linking by alkylating agents and platinum complexes. In: *Molecular Actions and Targets for Cancer Chemotherapeutic Agents* 1981:3-16.
22. Lawrence BV. Anaphylaxis due to oral melphalan. *Cancer Treat Rep* 1980 Apr; 64(4-5):731-2.
23. Lazarus HM, Herzig RH, Graham-Pole J, Wolff SN, Phillips GL, Strandjord S et al. Intensive melphalan chemotherapy and cryopreserved autologous bone marrow transplantation for the treatment of refractory cancer. *J Clin Oncol* 1983; 1(6):359-367.
24. Loos U, Musch E, Engel M, Hartlapp JH, Hügl E, Dengler HJ. The pharmacokinetics of melphalan during intermittent therapy of multiple myeloma. *Eur J Clin Pharmacol* 1988; 35(2):187-193.

25. Minor DR, Allen RE, Alberts D, Peng YM, Tardelli G, Hutchinson J. A clinical and pharmacokinetic study of isolated limb perfusion with heat and melphalan for melanoma. *Cancer* 1985; 55(11):2638-2644.
26. Osserman EF and Takatsuki K. Plasma cell myeloma: gamma globulin synthesis and structure. A review of biochemical and clinical data, with the description of a newly-recognized and related syndrome, "H-Gamma-2-Chain (Franklin's) Disease. *Medicine (Baltimore)* 1963; 42:357.
27. Osserman EF. Therapy of plasma cell myeloma with melphalan (1- phenylalanine mustard). *Proc Am Assoc Cancer Res*; 4:50 Apr 1963.
28. Reece PA, Hill HS, Green RM, Morris RG, Dale BM, Kotasek D et al. Renal clearance and protein binding of melphalan in patients with cancer. *Cancer Chemother Pharmacol* 1988; 22(4):348-352.
29. Sears ME, Haut A, Eckles N. Melphalan (NSC-8806) in advanced breast cancer. *Cancer Chemother Rep* 1966; 50(5):271-279.
30. Smith JP and Rutledge F. Chemotherapy in the treatment of cancer of the ovary. *Am J Obstet Gynecol* 1970; 107(5):691-703.
31. Tattersall MHN, Jarman M, Newlands ES, Holyhead L, Milstead RA, Weinberg A. Pharmacokinetics of melphalan following oral or intravenous administration in patients with malignant disease. *Eur J Cancer* 1978; 14(5):507-513.
32. Waldenstrom J. Melphalan therapy in myelomatosis. *Br Med J* 1964; 1:859-865.
33. Woodhouse KW, Hamilton P, Lennard A, Rawlins MD. The pharmacokinetics of melphalan in patients with multiple myeloma: An intravenous/oral study using a conventional dose regimen. *Eur J Clin Pharmacol* 1983; 24(2):283-285.
34. Young RC, Canellos GP, Chabner BA, Schein PS, Hubbard SP, De Vita VT, Jr. Chemotherapy of advanced ovarian carcinoma: a prospective randomized comparison of phenylalanine mustard and high dose cyclophosphamide. *Gynecol Oncol* 1974; 2(4):489-497.
35. Young RC, Chabner BA, Hubbard SP, Fisher RI, Bender RA, Anderson T et al. Advanced ovarian adenocarcinoma. A prospective clinical trial of melphalan (L-PAM) versus combination chemotherapy. *N Eng J Med* 1978; 299(23):1261-1266.
36. Zucchetti M, D'Incalci M, Willems Y, Cavalli F, Sessa C. Lack of effect of cisplatin on I.V. L-PAM plasma pharmacokinetics in ovarian cancer patients. *Cancer Chemother Pharmacol* 1988; 22(1):87-89.

**PART III: CONSUMER INFORMATION****Pr ALKERAN®  
Melphalan**

This leaflet is part III of a three-part "Product Monograph" published for ALKERAN®, approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ALKERAN®. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

ALKERAN® (melphalan) is indicated:

- to relieve symptoms caused by multiple myeloma (a form of cancer that affects plasma cells produced in the bone marrow).
- to relieve symptoms caused by nonresectable epithelial carcinoma of the ovary (cancer that begins in the cells of the ovary).

**What it does:**

ALKERAN® belongs to a group of chemotherapy drugs called antineoplastic alkylating agents. ALKERAN® interferes with the growth of cancer cells which eventually are killed. Normal cells may also be affected which may lead to side effects.

**When it should not be used:**

Do not take ALKERAN® if:

- You are allergic to melphalan or chlorambucil.
- You are allergic to any ingredients of the drug or any component of the container.
- Your disease has not responded to ALKERAN® treatment.
- You are currently receiving or have recently received radiotherapy or chemotherapy.
- You have been recently treated with medicines similar to ALKERAN®.
- You have low neutrophil or platelet count (neutrophil and platelets are blood cells).

**What the medicinal ingredient is:**

The medicinal ingredient for ALKERAN® is melphalan.

**What the important nonmedicinal ingredients are:****ALKERAN® tablets:**

The important nonmedicinal ingredients are: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol 400 and titanium dioxide.

**What dosage forms it comes in:**

ALKERAN® is available as 2 mg tablets.

**WARNINGS AND PRECAUTIONS****Serious Warnings and Precautions**

- Only take this drug as prescribed by a qualified doctor.
- ALKERAN® can lower your blood counts. Your blood counts should be measured regularly.
- ALKERAN® may cause an allergic reaction.
- ALKERAN® may cause abdominal upset and may harm your lungs.
- ALKERAN® may harm an unborn fetus.
- ALKERAN® may cause secondary cancers.

BEFORE you use ALKERAN® talk to your doctor or pharmacist if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient in ALKERAN®.
- you are pregnant or likely to become pregnant.
- you are breastfeeding a baby.
- you have been vaccinated, or planning to be vaccinated with a live vaccine.
- you are currently receiving, or have recently had radiotherapy or chemotherapy.
- you have kidney disease.

ALKERAN® has been reported to cause cancers in some patients who have been treated with the drug.

If you need surgery, tell the doctor/anaesthetist that you are taking ALKERAN®.

**INTERACTIONS WITH THIS MEDICATION**

It is important that your doctor know about all your medications so that you get the best possible treatment. Tell your doctor about all the medicines you are taking including those you have bought yourself. Nalidixic acid or cyclosporine should not be taken while you are taking, or soon after taking ALKERAN®.

Vaccination with live vaccines is not recommended.

**PROPER USE OF THIS MEDICATION**

It is important to take your medicine at the right times. You must take it in the way your doctor has told you to. The label on your pack will tell you how many tablets to take and how often to take them. If the label doesn't say or if you are not sure, ask your doctor or pharmacist.

**Usual dose:**

The dosage is very variable and it may be changed from time to time by your doctor. If you are unsure or the dosage on the label has changed for no apparent reason, ask your doctor. Your doctor will tell you how long to take your tablets.

Swallow your tablets whole with a little water. Do not break, crush or chew the tablets.

From time to time while you are taking ALKERAN<sup>®</sup>, your doctor will want you to have a blood test. This is to check your blood cell count. Depending on the blood cell count, your dose may need to be changed.

**Overdose:**

If you take too much ALKERAN<sup>®</sup> or if someone else takes your medicine by mistake, do not delay; ask your doctor what to do immediately or contact your nearest hospital emergency department.

**Missed Dose:**

If you forget to take a dose tell your doctor. **Do not** double your next dose.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

ALKERAN<sup>®</sup> may cause side effects in some people.

Production of bone marrow cells may be reduced.

In women, periods may stop.

In men, sperm production may be reduced or stopped.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking ALKERAN<sup>®</sup>, **Stop** taking the tablets and tell your doctor immediately:

- sudden wheeziness, difficulty breathing, chest pain or chest tightness.
- swelling of eyelids, face, lips, mouth or tongue.
- lumpy skin rash or "hives" anywhere on the body.

Tell your doctor if any of the following happen to you while you are taking ALKERAN<sup>®</sup>:

- if you feel sick, lose your appetite, have diarrhea or vomit.
- if you develop mouth ulcers, a skin rash and/or itching.
- effects on the blood may occur. Your doctor will do regular blood tests, but you should tell him at once if you notice any signs of fever or infection, or any unexpected bruising or bleeding.
- if you notice any signs of jaundice (yellowing of the whites of the eyes or the skin) as this may be due to hepatitis (inflammation/infection of the liver). If you have any blood tests to check how your liver is working, this medicine may affect the results.

- if you notice that you are gradually becoming more breathless than usual.
- you may notice some hair loss, especially if you are on a high dose of ALKERAN<sup>®</sup>.

Tell your pharmacist or doctor if you notice any other symptoms that you do not understand which are not mentioned here.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Frequency	Side Effect/ Symptom	Talk with your Doctor or Pharmacist	Stop taking drug and call your doctor or pharmacist immediately
Very Common	Any sign of fever or infection, or any unexpected bruising or bleeding	X	
Rare	Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate		X
	Jaundice (yellowing of the whites of eyes or the skin)	X	
	Progressively increasing shortness of breath	X	

*This is not a complete list of side effects. For any unexpected effects while taking ALKERAN<sup>®</sup>, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Store ALKERAN<sup>®</sup> tablets in a refrigerator, between 2°C – 8°C (36°F - 46°F). Keep out of the reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax 866-678-6789

By email: [cadtmp@hc-sc.gc.ca](mailto:cadtmp@hc-sc.gc.ca)

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness  
Information Division

Marketed Health Products Directorate

Tunney's Pasture, AL 0701C

Ottawa ON K1A 0K9

*NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.*

**MORE INFORMATION**

**Remember:** This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

This leaflet does not contain the complete information about your medicine. If any questions remain unanswered or you are not sure about something, you should ask your doctor or pharmacist.

You may want to read this leaflet again. **Please Do Not Throw It Away** until you have finished your medicine.

This document plus the full product monograph, prepared for health professionals can be found at:  
<http://www.tritonpharma.ca> or by contacting the sponsor,

Triton Pharma Inc.  
665 Milway Avenue,  
Suite 31B  
Concord, Ontario  
1.866.429.9707

This leaflet was prepared by Triton Pharma Inc.

Last revised: November 29, 2010

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**PART III: CONSUMER INFORMATION****Pr ALKERAN<sup>®</sup> Injection  
Melphalan**

This leaflet is part III of a three-part "Product Monograph" published for ALKERAN<sup>®</sup>, approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ALKERAN<sup>®</sup>. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

ALKERAN<sup>®</sup> (melphalan) is indicated:

- to relieve symptoms caused by multiple myeloma (a form of cancer that affects plasma cells produced in the bone marrow).
- to relieve symptoms caused by nonresectable epithelial carcinoma of the ovary (cancer that begins in the cell in the ovary).

**What it does:**

ALKERAN<sup>®</sup> belongs to a group of chemotherapy drugs called antineoplastic alkylating agents. ALKERAN<sup>®</sup> interferes with the growth of cancer cells which eventually are killed. Normal cells may also be affected which may lead to side effects.

**When it should not be used:**

Do not take ALKERAN<sup>®</sup> if:

- You are allergic to melphalan or chlorambucil.
- You are allergic to any ingredients of the drug or any component of the container.
- Your disease has not responded to ALKERAN<sup>®</sup> treatment.
- You are currently receiving or have recently received radiotherapy or chemotherapy.
- You have been recently treated with medicines similar to ALKERAN<sup>®</sup>.
- You have low neutrophil or platelet count (neutrophil and platelets are blood cells).

**What the medicinal ingredient is:**

The medicinal ingredient for ALKERAN<sup>®</sup> is melphalan.

**What the important nonmedicinal ingredients are:****ALKERAN<sup>®</sup> injection:**

Each vial contains 10 mL buffer solution contains the following important non-medicinal ingredients: sodium citrate 0.20g, ethanol 0.52 mL, propylene glycol 6.00 mL, and water for injection.

**What dosage forms it comes in:**

ALKERAN<sup>®</sup> is available as a 50 mg/vial injection.

**WARNINGS AND PRECAUTIONS****Serious Warnings and Precautions**

- Only take this drug as prescribed by a qualified doctor.
- ALKERAN<sup>®</sup> can lower your blood counts. Your blood counts should be measured regularly.
- ALKERAN<sup>®</sup> may cause an allergic reaction.
- ALKERAN<sup>®</sup> may cause abdominal upset and may harm your lungs.
- ALKERAN<sup>®</sup> may harm an unborn fetus.
- ALKERAN<sup>®</sup> may cause secondary cancers.

BEFORE you use ALKERAN<sup>®</sup> talk to your doctor or pharmacist if:

- you have a history of hypersensitivity (an allergic reaction) to any ingredient in ALKERAN<sup>®</sup>.
- you are pregnant or likely to become pregnant.
- you are breastfeeding a baby.
- you have been vaccinated, or planning to be vaccinated with a live vaccine.
- you are currently receiving, or have recently had radiotherapy or chemotherapy.
- you have kidney disease.

ALKERAN<sup>®</sup> has been reported to cause cancers in some patients who have been treated with the drug.

If you need surgery, tell the doctor/anaesthetist that you are taking ALKERAN<sup>®</sup>.

**INTERACTIONS WITH THIS MEDICATION**

It is important that your doctor know about all your medication so that you get the best possible treatment. Tell your doctor about all the medicines you are taking including those you have bought yourself. Nalidixic acid or cyclosporine should not be taken while you are taking, or soon after taking ALKERAN<sup>®</sup>.

Vaccination with live organism vaccines is not recommended.

**PROPER USE OF THIS MEDICATION**

You will receive this medicine under a doctor's care. It is infused through your blood.

Ask your doctor or pharmacist if you have any questions about how it is being given to you or what your dose is.

As with other toxic compounds, caution should be exercised

when handling and preparing the solution of ALKERAN®.

**Usual dose:**

The dosage is very variable and it may be changed from time to time by your doctor. If you have any questions, ask your doctor or pharmacist.

From time to time while you are taking ALKERAN® Injection, your doctor will want you to have a blood test. This is to check your blood cell count and to change your dose if necessary.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

ALKERAN® may cause side-effects in some people.

Production of bone marrow cells may be reduced.

In women, periods may stop.

In men, sperm production may be reduced or stopped.

Some people can be allergic to medicines. If you have any of the following symptoms soon after taking ALKERAN®, **Stop** taking the medicine and tell your doctor immediately:

- sudden wheeziness, difficulty breathing, chest pain or chest tightness.
- swelling of eyelids, face, lips, mouth or tongue.
- lumpy skin rash or "hives" anywhere on the body.

Tell your doctor if any of the following happen to you while you are taking ALKERAN®:

- if you feel sick, lose your appetite, have diarrhoea or vomit.
- if you develop mouth ulcers, a skin rash and/or itching.
- effects on the blood may occur. Your doctor will do regular blood tests, but you should tell him at once if you notice any signs of fever or infection, or any unexpected bruising or bleeding.
- if you notice any signs of jaundice (yellowing of the whites of the eyes or the skin) as this may be due to hepatitis (inflammation/infection of the liver). If you have any blood tests to check how your liver is working, this medicine may affect the results.
- if you notice that you are gradually becoming more breathless than usual.
- you may notice some hair loss, especially if you are on a high dose of ALKERAN®.

Tell your pharmacist or doctor if you notice any other symptoms that you do not understand which are not mentioned here.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Frequency	Side Effect/ Symptom	Talk with your Doctor or Pharmacist	Stop taking drug and call your doctor or pharmacist immediately
Very Common	Any sign of fever or infection, or any unexpected bruising or bleeding	X	
Rare	Immediate allergic reaction and symptoms such as swelling of the mouth, throat, difficulty in breathing, rash, hives, increased heart rate		X
	Jaundice (yellowing of the whites of eyes or the skin)	X	
	Progressively increasing shortness of breath	X	

*This is not a complete list of side effects. For any unexpected effects while taking ALKERAN®, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Store ALKERAN® Injection at controlled room temperature (15°C-30°C). Protect from light. Keep out of the reach of children.

**REPORTING SUSPECTED SIDE EFFECTS**

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax 866-678-6789

By email: [cadrmp@hc-sc.gc.ca](mailto:cadrmp@hc-sc.gc.ca)

By regular mail:  
National AR Centre  
Marketed Health Products Safety and Effectiveness  
Information Division  
Marketed Health Products Directorate  
Tunney's Pasture, AL 0701C  
Ottawa ON K1A 0K9

*NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.*

**MORE INFORMATION**

**Remember:** This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are the same as yours.

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This document plus the full product monograph, prepared for health professionals can be found at <http://www.tritonpharma.ca> or by contacting the sponsor:

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