ALKERAN™ TABLETS

Melphalan

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg melphalan.

PHARMACEUTICAL FORM

Film-coated tablets.

CLINICAL PARTICULARS

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 drugs 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 rubra vera.

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 (*see Warnings and Precautions*).

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 0.15 mg/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 0.2 mg/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 0.15 mg/kg bodyweight or 6 mg/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 10 mg daily for 5 to 7 days have been used, after which 2 to 4 mg daily were given until satisfactory disease control was achieved.

A dose of 2 to 6 mg 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 Warnings and Precautions*).

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

Curently 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.

Contraindications

ALKERAN should not be given to patients who have suffered a previous hypersensitivity reaction to the active substance or to any of the excipients listed in section *LIST OF EXCIPIENTS*. Do not take *ALKERAN* if you are breastfeeding.

Warnings and Precautions

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:* (*See Instructions for Use/Handling*).

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.

Thromboembolic events

ALKERAN in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism). Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors (see *Warnings and Precautions* and *Adverse Reactions*).

If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, *ALKERAN* in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone may be restarted at the original dose dependent upon a benefit-risk assessment. The patient should continue anticoagulation therapy during the course of *ALKERAN* treatment.

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

Chromosome aberrations have been observed in patients being treated with the drug.

Carcinogenicity (Second primary malignancy)

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

ALKERAN, in common with other alkylating agents, has been reported to be leukaemogenic, especially in elderly patients after long combination therapy and radiotherapy. There have been reports of acute leukaemia occurring after *ALKERAN* treatment for diseases such as amyloidosis, 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 show that the use of alkylating agents, including *ALKERAN*, significantly increased the incidence of acute leukaemia.

The leukaemogenic risk must be balanced against the potential therapeutic benefit when considering the use of *ALKERAN*, especially if the use of *ALKERAN* in combination with thalidomide or lenalidomide and prednisone is considered, as it has been shown that these combinations increase the leukaemogenic risk. Before, during and after treatment, doctors must therefore examine the patients at all times by usual measurements to ensure the early detection of cancer and initiate treatment if necessary.

Contraception

Due to an increased risk of venous thromboembolism in patients undergoing treatment with *ALKERAN* 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.

Solid tumours

Use of alkylating agents has been linked with the development of second primary malignancy (SPM). In particular, *ALKERAN* in combination with lenalidomide and prednisone and, to a lesser extent, thalidomide and prednisone has been associated with the increased risk of solid SPM in elderly newly diagnosed multiple myeloma patients.

Patient characteristics (e.g. age, ethnicity), primary indication and treatment modalities (e.g. radiation therapy, transplantation), as well as environmental risk factors (e.g., tobacco use) should be evaluated prior to *ALKERAN* administration.

Interactions

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

Nalidixic acid together with high-dose intravenous *ALKERAN* has caused deaths in children due to haemorrhagic enterocolitis.

In paediatric population, for the Busulfan-Melphalan regimen it has been reported that the administration of *ALKERAN* 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 *ALKERAN* and who subsequently received cyclosporin to prevent graft-versus-host disease.

Pregnancy and Lactation

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.

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 (see Section Non-Clinical Information – Fertility studies). Therefore, it is possible that *ALKERAN* may cause temporary or permanent sterility in male patients.

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.

Mothers receiving *ALKERAN* should not breast-feed.

Effects on Ability to Drive and Use Machines

No data.

Adverse Reactions

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication and dose received and also when given in combination with other therapeutic agents.

The following convention has been utilised for the classification of frequency:

Very common: ≥1/10

Common: ≥1/100 and <1/10

Uncommon: ≥1/1000 and <1/100

Rare: ≥1/10,000 and <1/1000

Very rare: <1/10,000

Not known: (cannot be estimated from the available data)

Neoplasms benign, malignant and unspecified (including cysts and polyps)

Not *known:* Secondary acute myeloid leukaemia and myeloidysplastic 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: hypersensitivities (*see Skin and Subcutaneous Tissue Disorders*).

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.

Respiratory, Thoracic and Mediastinal Disorders

Rare: interstitial lung disease and pulmonary fibrosis (including fatal reports).

Gastrointestinal Disorders

Very common: nausea, vomiting and diarrhoea; stomatitis at high dose .

Rare: stomatitis at conventional dose.

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 *ALKERAN* in association with haemopoietic stem cell rescue. Cyclophosphamide pretreatment appears to reduce the severity of gastro-intestinal damage induced by high-dose *ALKERAN* and the literature should be consulted for details.

Hepatobilliary Disorders

Rare: liver disorders ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice.

Skin and Subcutaneous Tissue Disorders

Very common: alopecia at high dose.

Common: alopecia at conventional dose.

Rare: rash maculo-papular and pruritus (*see Immune System Disorders*).

Musculoskeletal and Connective Tissue Disorders

Very common: muscle atrophy, muscle fibrosis, myalgia, blood creatinine phosphokinase increased

Common: compartment syndrome

Not known: muscle necrosis, rhabdomyolysis

Renal and Urinary Disorders

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

Reproductive system and breasts disorders

Not known: azospermia, amenorrhoea

Vascular disorders

Not known: deep vein thrombosis and pulmonary embolism

The clinically important adverse reactions associated with the use of ALKERAN 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*).

General Disorders and Administration Site Conditions

Very common: subjective and transient feeling hot, pyrexia

Overdose

Gastrointestinal effects, including nausea, vomiting and diarrhoea are the most likely early signs of acute oral overdosage.

The principal toxic effect is bone marrow suppression, leading to leucopenia, thrombocytopenia and anaemia.

General supportive measures, together with appropriate blood and platelet transfusions should be instituted if necessary, and consideration given to hospitalisation, cover with anti-infective agents, and the use of haematological growth factors.

There is no specific antidote. The blood picture should be closely monitored for at least 4 weeks following overdosage until there is evidence of recovery.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group

antineoplastic and immunomodulating agents, antineoplastic agents, alkylating agents, nitrogen mustard analogues

ATC Code

L01AA03

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.

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%.

Intravenous administration can be used to avoid variability in absorption associated with myeloablative treatment.

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 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 54%.

Distribution

Melphalan is moderately bound to plasma proteins with reported percent binding ranging from 69% to 78%. There is evidence that the protein binding is linear in the range of plasma concentrations usually achieved in standard dose therapy, but that the binding may become concentration-dependent at the concentrations observed in high-dose therapy. Serum albumin is the major binding protein, accounting for about 55 to 60% the binding, and 20% is bound to α_1-acid glycoprotein. In addition, melphalan binding studies have revealed the existence of an irreversible component attributable to the alkylation reaction with plasma proteins.

Melphalan displays limited penetration of the blood-brain barrier. Several investigators have sampled cerebrospinal fluid and found no measurable drug. Low concentrations (~10% of that in plasma) were observed in a single high-dose study in children.

Metabolism

In vivo and *in vitro* data suggest that spontaneous degradation rather than enzymatic metabolism is the major determinant of the drugs half-life in man.

Elimination

In 13 patients given oral melphalan at 0.6 mg/kg bodyweight, the plasma mean terminal elimination half-life was 90 ± 57 min with 11 % of the drug being recovered in the urine over 24 h.

In 18 patients administered **melphalan** 0.2 to 0.25 mg/kg bodyweight orally, the mean elimination half-life was 1.12 ± 0.15 h.

Special Patient Populations

- **Renal impairment**

Melphalan clearance may be decreased in renal impairment (*see Dosage and Administration - Renal impairment and Warnings and Precautions - Renal impairment*).

- **Elderly**

No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life (*see Dosage and Administration*).

NON-CLINICAL INFORMATION

• Carcinogenesis, mutagenesis

ALKERAN is mutagenic in animals.

• Fertility Studies

In mice, *ALKERAN* administered intraperitoneally at a dose of 7.5 mg/kg, showed reproductive effects attributable to cytotoxicity in specific male germ cell stages and induced dominant lethal mutations and heritable translocations in post-meiotic germ cells, particularly in mid to late stage spermatids. A study was performed to measure the total reproductive capacity of *ALKERAN* in female mice. Females received a single intraperitoneal dose of 7.5mg/kg *ALKERAN* and were then housed with an untreated male for most of their reproductive life span (a minimum of 347 days post-treatment). A pronounced reduction in litter size occurred within the first post-treatment interval, followed by an almost complete recovery. Thereafter, a gradual decline in litter size occurred. This was simultaneous with a reduction in the proportion of productive females, a finding associated with an induced reduction in the number of small follicles (see section *Pregnancy and Lactation*).

Pre-clinical Safety Data

Melphalan is mutagenic in animals.

PHARMACEUTICAL PARTICULARS

List of Excipients

Tablet Core:

Microcrystalline cellulose

Crospovidone

Colloidal anhydrous silica

Magnesium stearate

Tablet Film Coating:

Hypromellose

Titanium dioxide

Macrogol

Incompatibilities

None known.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Store at 2°C to 8°C.

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 containing “X” (number) tablets as registered locally.

Instructions for Use/Handling

Safe handling of *ALKERAN* tablets:

The handling of *ALKERAN* tablets should follow guidelines for the handling of cytotoxic drug 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.

Disposal:

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

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