SOUTH AFRICAN PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

ALKERAN 2 mg (tablet)

COMPOSITION

Each ALKERAN 2 mg tablet contains 2 mg melphalan.

Excipients:

Colloidal anhydrous silica, crospovidone, hypromellose, macrogol, magnesium stearate, microcrystalline cellulose, titanium dioxide (CI. 77891)

Sugar free

CATEGORY AND CLASS

A 26. Cytostatic agents

PHARMACOLOGICAL ACTION

Melphalan is a bifunctional alkylating agent. Formation of carbonium intermediates from each of the two bis-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.

INDICATIONS

ALKERAN 2 mg tablets are indicated in the treatment of:

Multiple myeloma and advanced ovarian adenocarcinoma.

ALKERAN 2 mg tablets may be used in the treatment of:

Breast carcinoma: either alone or in combination with other medicines.

ALKERAN 2 mg has been used as an adjuvant to surgery in the management of breast carcinoma.

CONTRAINDICATIONS

ALKERAN 2 mg should not be given to patients who have suffered a previous allergic reaction to melphalan.

Lactation

Mothers receiving ALKERAN 2 mg should not breastfeed.

Pregnancy

The use of melphalan is contraindicated during pregnancy as mutagenicity has been demonstrated in animals.

WARNINGS AND SPECIAL PRECAUTIONS

ALKERAN 2 mg IS AN ACTIVE CYTOTOXIC AGENT FOR USE ONLY UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH MEDICINES.

Safe handling of ALKERAN 2 mg formulations should follow guidelines for the handling of cytotoxic medicine according to prevailing local recommendations and/or regulations.

Provided the outer coating of the tablet is intact, there is no risk in handling ALKERAN 2 mg tablets. ALKERAN 2 mg tablets should not be divided.

Monitoring

Since ALKERAN 2 mg is a potent myelosuppressive medicine, 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 leukocyte or platelet counts, treatment should be temporarily interrupted.

ALKERAN 2 mg should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity.

Patients with renal impairment should be closely observed as they may have uraemic marrow suppression (see SIDE EFFECTS). Dosage reduction may be necessary (refer to DOSAGE AND DIRECTIONS FOR USE - Dosage in renal impairment).

Adequate contraceptive precautions should be advised when either partner is receiving ALKERAN 2 mg and for at least a year after cessation of treatment (see HUMAN REPRODUCTION).

INTERACTIONS

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

Impaired renal function has been described in bone marrow transplant patients who were preconditioned with high dose intravenous melphalan and who subsequently received cyclosporin to prevent graft-versus-host disease.

Mutagenicity

ALKERAN 2 mg is mutagenic in animals and chromosome aberrations have been observed in patients being treated with the medicine (see HUMAN REPRODUCTION).

Carcinogenicity

Melphalan, in common with other alkylating agents, may be leukaemogenic in man. There have been reports of acute leukaemia occurring after prolonged 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.

Teratogenicity

The teratogenic potential of ALKERAN 2 mg has not been studied. In view of its mutagenic properties and structural similarity to known teratogenic compounds, melphalan could cause congenital defects in the offspring of patients treated with the medicine (see HUMAN REPRODUCTION).

Effects on fertility

ALKERAN 2 mg causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients (see HUMAN REPRODUCTION).

It is possible that ALKERAN 2 mg may cause temporary or permanent sterility in male patients (see HUMAN REPRODUCTION).

HUMAN REPRODUCTION

Lactation

Mothers receiving ALKERAN 2 mg should not breastfeed (see CONTRAINDICATIONS).

Pregnancy

The use of melphalan is contraindicated during pregnancy as mutagenicity has been demonstrated in animals (see CONTRAINDICATIONS).

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DOSAGE AND DIRECTIONS FOR USE

General

ALKERAN 2 mg is a cytotoxic agent, 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 medicines. Since ALKERAN 2 mg is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be adjusted if necessary (see SIDE EFFECTS). The absorption of ALKERAN 2 mg 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 body mass/day in divided doses for 4 days repeated at intervals of six weeks. Numerous regimens have been used and the scientific literature should be consulted for details.

The administration of oral ALKERAN 2 mg and prednisone may be more effective than ALKERAN 2 mg 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 Carcinoma

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 2 mg has been given orally at a dose of 6 mg/m^2 body surface area per day for advanced carcinoma of the breast and as 0,15 mg/kg body mass or 6 mg/m^2 body surface area per day as an adjuvant to surgery in primary breast cancer; in both cases treatment was for 5 days and repeated every 6 weeks. The dose was decreased if bone marrow toxicity was observed.

Use in children

ALKERAN 2 mg, at conventional dosage, is only rarely indicated in children and dosage guidelines cannot be stated.

Use in the elderly

Although ALKERAN 2 mg is frequently used at conventional dosage in the elderly, there is no specific information available relating to its administration to this patient sub-group.

Experience in the use of high dose ALKERAN 2 mg in elderly patients is limited.

Dosage in renal impairment

ALKERAN 2 mg clearance though variable, is decreased in renal impairment.

Currently available pharmacokinetic data do not justify an absolute recommendation on dosage reduction when administering ALKERAN 2 mg tablets to patients with renal impairment, but it may be prudent to use a reduced dosage initially until tolerance is established (see WARNINGS AND SPECIAL PRECAUTIONS).

SIDE EFFECTS

The most common side effect is bone marrow depression, leading to leucopaenia and thrombocytopaenia.

Gastrointestinal effects such as nausea and vomiting have been reported in up to 30 % of patients receiving conventional oral doses of ALKERAN 2 mg.

Stomatitis occurs rarely following conventional doses of ALKERAN 2 mg.

Allergic reactions of ALKERAN 2 mg such as urticaria, oedema, skin rashes and anaphylaxis have been reported following initial or subsequent dosing, particularly after intravenous administration in patients who were treated over several months. Cardiac arrest has occurred in association with such events.

Maculopapular rashes and pruritus have been noted.

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.

There have been case reports of interstitial pneumonitis and pulmonary fibrosis; fatal reports of pulmonary fibrosis have been received.

There have also been case reports of haemolytic anaemia occurring after melphalan treatment.

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

Alopecia has been reported.

Patients with renal impairment should be closely observed as they may have uraemic marrow suppression (see WARNINGS AND SPECIAL PRECAUTIONS).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms and signs

Gastrointestinal effects, including nausea, vomiting and diarrhoea are the most likely signs of acute oral overdosage. The principal toxic effect is bone marrow suppression, leading to leucopaenia, thrombocytopaenia and anaemia.

Treatment

General supportive measures, together with appropriate blood transfusion, should be instituted if necessary. There is no specific antidote. The blood picture should be closely

monitored for at least four weeks following overdosage until there is evidence of recovery and consideration given to hospitalisation, antibiotic cover, and the use of haematological growth factors.

IDENTIFICATION

White to off-white, round, biconvex film-coated tablets engraved “GX EH3” on one side and “A” on the other side.

PRESENTATION

Round, amber, glass bottles of 25 or 50 tablets, closed with child-resistant, polypropylene (inner) and high density polyethylene (outer) closures. Each bottle is packed in a pre-printed carton together with a leaflet.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store between 2 °C and 8 °C.

Keep dry.

Keep in the original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

H/26/2744

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

DATE OF PUBLICATION OF THIS PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration: 14 March 1994

Date of the most recent amendment to the professional information as approved by the Authority: 10 March 2003

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