

1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4 ALKERAN 50

S3 ALKERAN SD

PROPRIETARY NAME AND DOSAGE FORM

ALKERAN 50 (powder for injection)

ALKERAN SD (solution for injection)

COMPOSITION

Each vial of ALKERAN 50 contains 50 mg melphalan (anhydrous) hydrochloride.

Excipient:

Povidine

Sugar free

Each vial of ALKERAN SD contains ethanol, propylene glycol, water for injection.

Contains alcohol: Ethanol 4,99 % v/v

Sugar free

CATEGORY AND CLASS

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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 50, at conventional intravenous dosage, may be used in the treatment of:

Multiple myeloma: ALKERAN 50, either alone or in combination with other cytotoxic medicines.

Ovarian cancer: ALKERAN 50, either alone or in combination with other cytotoxic medicines.

ALKERAN 50, at high intravenous dosage, may be used in the treatment of:

Multiple myeloma: With or without autologous bone marrow rescue, either as first line treatment or to consolidate a response to conventional cytoreductive chemotherapy.

Neuroblastoma in childhood: High-dose ALKERAN 50 with autologous bone marrow rescue has been used either alone or combined with radiotherapy and/or other cytotoxic medicines, to consolidate a response to conventional treatment.

CONTRAINDICATIONS

ALKERAN 50 should not be given to patients who have suffered a previous allergic reaction to melphalan.

Lactation:

Mothers receiving ALKERAN 50 should not breastfeed.

Pregnancy:

The use of ALKERAN 50 is contraindicated during pregnancy, as mutagenicity has been documented in animals.

WARNINGS AND SPECIAL PRECAUTIONS

ALKERAN 50 IS AN ACTIVE CYTOTOXIC AGENT FOR USE ONLY UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS.

Safe handling of ALKERAN 50 formulations should follow guidelines for the handling of cytotoxic medicines according to prevailing local recommendations and/or regulations.

It is essential that careful attention should be paid to the monitoring of blood counts.

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

Adequate contraceptive precautions should be advised when either partner is receiving ALKERAN 50 and for at least a year after cessation of treatment.

Cyclophosphamide pretreatment has been shown to reduce the severity of the gastrointestinal damage induced by high-dose ALKERAN 50; the literature should be

consulted for details.

ALKERAN 50 solution can cause local tissue damage should extravasation occur and consequently it should not be administered by direct injection into a peripheral vein. It is recommended that ALKERAN 50 is administered by injecting slowly into a fast-running intravenous infusion via a swabbed injection port, or via a central venous line.

In view of the hazards involved and the level of supportive care required, the administration of high-dose ALKERAN 50 should be confined to specialist centres, with the appropriate facilities and only be conducted by experienced clinicians.

In patients receiving high-dose ALKERAN 50, consideration should be given to the prophylactic administration of anti-infective medicines, the administration of blood products as required and the maintenance of a high renal output during the period immediately following the administration of ALKERAN 50 by the use of hydration and forced diuresis.

Consideration should be given to ensure adequate performance status and organ function, before using high-dose ALKERAN 50 in elderly patients.

ALKERAN 50 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.

A fifty percent dosage reduction is essential in patients with impaired renal function who are given high-dose ALKERAN 50.

Monitoring

Since ALKERAN 50 is 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.

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 50 is mutagenic in animals and chromosome aberrations have been observed in patients being treated with the medicine.

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 50 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.

Effects on fertility

ALKERAN 50 causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients.

It is possible that ALKERAN 50 may cause temporary or permanent sterility in male patients.

INTERACTIONS

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

HUMAN REPRODUCTION

Lactation:

Mothers receiving ALKERAN 50 should not breastfeed.

Pregnancy:

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

Teratogenicity:

The teratogenic potential of ALKERAN 50 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.

Effects on fertility:

ALKERAN 50 causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients.

It is possible that ALKERAN 50 may cause temporary or permanent sterility in male patients.

DOSAGE AND DIRECTIONS FOR USE

General

ALKERAN 50 is 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 agents.

Since ALKERAN 50 is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be adjusted if necessary (see WARNINGS AND SPECIAL PRECAUTIONS).

Multiple myeloma

ALKERAN 50 has been used on an intermittent basis alone, or in combination with other cytotoxic agents, at doses varying between 8 mg/m² body surface area and 30 mg/m² body surface area, given at intervals of between 2 to 6 weeks. The literature should be consulted for details.

When used as a single agent, a typical intravenous dosage schedule is 0,4 mg/kg body mass (16 mg/m² body surface area) repeated at appropriate intervals (e.g. once every 4 weeks), provided there has been recovery of the peripheral blood count during this period.

High-dose regimens generally employ single intravenous doses of between 100 mg/m² and 200 mg/m² body surface area (approximately 2,5 mg/kg to 5,0 mg/kg body mass), but autologous bone marrow rescue becomes essential following doses in excess of 140 mg/m² body surface area. In cases of renal impairment, the dose should be reduced by fifty percent. In view of the severe myelosuppression induced by high-dose ALKERAN 50, treatment should be confined to specialist centers, with the appropriate facilities, and only be administered by experienced clinicians (see WARNINGS AND SPECIAL PRECAUTIONS).

Advanced ovarian adenocarcinoma

When used intravenously as a single agent, a dose of 1 mg/kg body mass (approximately 40 mg/m² body surface area) given at intervals of 4 weeks has often been used.

When combined with other cytotoxic agents, intravenous doses of between 0,3 mg/kg and 0,4 mg/kg body mass (12 mg/m² to 16 mg/m² body surface area) have been used at intervals of 4 to 6 weeks.

Advanced malignant melanoma

Hyperthermic regional perfusion with ALKERAN 50 has been used as palliative treatment for advanced but localised disease.

The scientific literature should be consulted for details of perfusion technique and dosage used.

Advanced neuroblastoma

Doses of between 100 and 240 mg/m² body surface area (sometimes divided equally over 3 consecutive days) together with autologous bone marrow rescue, have been used either alone or in combination with radiotherapy and/or other cytotoxic medicines.

Use in Children

High-dose ALKERAN 50, in association with bone marrow rescue, has been administered to children and dosage guidelines based on body surface area, as for adults, may be used.

Use in the elderly

Although ALKERAN 50 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 50 in elderly patients is limited.

Consideration should therefore be given to ensure adequate performance status and organ function before using high-dose ALKERAN 50 in elderly patients.

Dosage in renal impairment

ALKERAN 50 clearance, though variable, is decreased in renal impairment.

When ALKERAN 50 is used at conventional intravenous dosage (8 mg/m² to 40 mg/m² body surface area), it is recommended that the initial dose should be reduced by 50 % in patients with moderate to severe renal impairment and subsequent dosage determined according to the degree of hematological suppression.

For high intravenous doses of ALKERAN 50 (100 mg/m² to 240 mg/m²), the need for dose reduction depends upon the degree of renal impairment, whether autologous bone marrow stem cells are reinfused, and therapeutic need. As a guide, for moderate to severe impairment (EDTA clearance 30 ml/min to 50 ml/min) a dose reduction of 50 % is usual. Adequate hydration and forced diuresis are also necessary. High-dose ALKERAN 50 is not recommended in patients with more severe renal impairment (EDTA clearance less than 30 ml/min).

Preparation of ALKERAN 50

ALKERAN 50 should be prepared, at room temperature, by reconstituting the freeze-dried powder with 10 ml of the Solvent-Diluent provided as a single quantity, and the vial shaken vigorously until solution is complete. The resulting solution contains the equivalent of 5 mg per ml anhydrous melphalan at approximately pH 6,5.

ALKERAN 50 solution has limited stability and should be prepared immediately before use. Any unused solution should be discarded.

The reconstituted solution should not be refrigerated as this will cause precipitation.

Parenteral administration

Except in cases where regional arterial perfusion is indicated, ALKERAN 50 is for intravenous use only.

It is recommended that ALKERAN 50 is injected slowly into a fast-running infusion solution via a swabbed injection port.

If direct injection into a fast-running infusion is not appropriate, ALKERAN 50 may be

administered diluted in an infusion bag.

ALKERAN 50 is not compatible with infusion solutions containing dextrose and it is recommended that only Sodium Chloride Intravenous Infusion 0,9 % *m/v* is used.

When further diluted in an infusion solution, ALKERAN 50 had reduced stability and the rate of degradation increases rapidly with increasing temperature. If ALKERAN 50 is infused at a room temperature of approximately 25 °C, the total time from preparation of the Injection solution to the completion of infusion should not exceed 1,5 hours.

Should any visible turbidity or crystallization appear in the reconstituted or diluted solutions the preparation must be discarded.

Care should be taken to avoid possible extravasation of ALKERAN 50 and in cases of poor peripheral venous access, consideration should be given to use of a central venous line.

If high-dose ALKERAN 50 is administered with or without autologous bone marrow transplantation, administration via a central venous line is recommended.

For regional arterial perfusion, the literature should be consulted for detailed methodology.

SIDE EFFECTS

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

Stomatitis occurs rarely following conventional doses of ALKERAN 50.

The incidence of diarrhoea, vomiting and stomatitis becomes dose-limiting in patients given high intravenous doses of ALKERAN 50 in association with autologous bone marrow transplantation.

Allergic reactions of ALKERAN 50 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 cases.

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.

A subjective and transient sensation of warmth and/or tingling was described in

approximately two thirds of patients with haematological malignancy who were given high-dose ALKERAN 50 via a central line.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

The immediate effects of acute intravenous overdosage are nausea and vomiting. Damage to the gastrointestinal mucosa may also ensue, and diarrhoea, sometimes haemorrhagic, has been reported after 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

ALKERAN 50: White to off-white freeze-dried powder.

When dissolved in 10 ml of ALKERAN SD is practically free from visible particles.

ALKERAN SD: Clear colourless solution, practically free from visible particles.

PRESENTATION

ALKERAN 50:

50 mg freeze-dried powder is packed in a clear, neutral glass vial of nominal capacity of 17 ml, and closed with a bromobutyl rubber stopper and aluminium collar with a plastic flip-

top cover.

ALKERAN SD:

10 ml is packed in a clear, neutral glass vial and closed with a chlorobutyl stopper and an aluminium collar with a plastic flip-top cover.

A vial of ALKERAN 50 is packed together with a vial of ALKERAN SD into a cardboard box with a leaflet.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Protect from light.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

ALKERAN 50: 27/26/0506

ALKERAN SD: 27/34/0507

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

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

**DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES
FOR HUMAN USE**

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Authority: 22 March 1994

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