1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINE FOR HUMAN USE

SCHEDULING STATUS

S4 ALKERAN 50

S3 ALKERAN SD

1. NAME OF THE MEDICINE

ALKERAN 50 powder for injection

ALKERAN SD solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Sugar free.

For the full list of excipients, see section 6.1.

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

Contains alcohol: Ethanol 4,99 % *v/v.*

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ALKERAN 50:

Powder for injection.

White to off-white freeze-dried powder.

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

ALKERAN SD:

Solution for injection.

Clear colourless solution, practically free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic 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 haematopoietic stem cell rescue, either as first line treatment or to consolidate a response to conventional cytoreductive chemotherapy.

Neuroblastoma in childhood: High-dose ALKERAN 50 with haematopoietic stem cell rescue has been used either alone, or combined with radiotherapy and/or other cytotoxic medicines, to consolidate a response to conventional treatment (see section 4.5).

ALKERAN 50, administered by regional arterial perfusion, is indicated in the treatment of:

- Localised malignant melanoma of the extremities (see section 4.2: Advanced malignant melanoma).
- Localised soft tissue sarcoma of the extremities (see section 4.2: Soft tissue sarcoma).

4.2. Posology and method of administration

Posology

General

ALKERAN 50 is a cytotoxic medicine, which falls into the general class of alkylating medicines. It should be prescribed only by healthcare professionals experienced in the management of malignant disease with such medicines. Since ALKERAN 50 is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be adjusted if necessary (see section 4.4).

Thromboembolic events

ALKERAN 50, in combination with lenalidomide and prednisone or in combination with thalidomide and prednisone or dexamethasone is associated with an increased risk of venous thromboembolism. 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 section 4.4).

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 50 in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone may be restarted at the original dose. The patient should continue anticoagulation therapy during the course of ALKERAN 50 treatment.

Multiple myeloma

ALKERAN 50 has been used on an intermittent basis alone, or in combination with other cytotoxic medicines, at doses varying between 8 mg/m^2 body surface area and 30 mg/m^2 body

surface area, given at intervals of between 2 to 6 weeks. The literature should be consulted for details.

When used as a single medicine, a typical intravenous dosage schedule is 0,4 mg/kg body mass (16 mg/m^2 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 and 200 mg/m^2 body surface area (approximately 2,5 to 5,0 mg/kg body mass). Haematopoietic stem cell rescue becomes essential following doses in excess of 140 mg/m^2 body surface area. In cases of renal impairment, the dose should be reduced by 50 %. In view of the severe myelosuppression induced by high-dose ALKERAN 50, treatment should be confined to specialist centres, with the appropriate facilities, and only be administered by experienced medical practitioners (see section 4.4).

Advanced ovarian adenocarcinoma

When used intravenously as a single medicine, a dose of 1 mg/kg body mass (approximately 40 mg/m^2 body surface area) given at intervals of 4 weeks has often been used.

When combined with other cytotoxic medicines, intravenous doses of between 0,3 and 0,4 mg/kg body mass (12 to 16 mg/m^2 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.

Soft tissue sarcoma

Hyperthermic regional perfusion with ALKERAN 50 has been used in the management of all stages of localised soft tissue sarcoma, usually in combination with surgery.

A typical dose range for upper extremity perfusions is 0,6 to 1,0 mg/kg body weight and for lower extremity perfusions is 1,0 to 1,4 mg/kg body weight.

ALKERAN 50 has also been given with actinomycin D, and the scientific literature should be consulted for details of dosage regimens.

Advanced neuroblastoma

Doses of between 100 and 240 mg/m^2 body surface area (sometimes divided equally over three consecutive days) together with haematopoietic stem cells, have been used either alone or in combination with radiotherapy and/or other cytotoxic medicines.

Paediatric population

High-dose ALKERAN 50, in association with haematopoietic stem cell rescue, has been administered to children and dosage guidelines based on body surface area, as for adults, may be used (see section 4.5).

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 ALKERAN 50 in elderly patients is limited. Consideration should be given to ensure adequate performance status and organ function, before using high-dose ALKERAN 50 in elderly patients (see section 4.4).

The pharmacokinetics of ALKERAN 50 has not shown a correlation between age and melphalan clearance or with melphalan terminal elimination half-life. The limited data available do not support specific dosage adjustment recommendations for elderly patients receiving ALKERAN 50 and suggested that current practice of dosage adjustment based upon the general condition of the geriatric patient and the degree of myelosuppression incurred during therapy should be continued (see section 5.2: Elderly patients).

Dosage in renal impairment

ALKERAN 50 clearance, though variable, is decreased in renal impairment (see section 5.2: Renal impairment). When ALKERAN 50 is used at conventional intravenous dosage (8 to 40 mg/m^2 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 haematological suppression.

For high intravenous doses of ALKERAN 50 (100 to 240 mg/m^2), the need for dose reduction depends upon the degree of renal impairment, whether haematopoietic stem cells are reinfused, and therapeutic need. As a guide, for high dose ALKERAN 50 treatment without haematopoietic stem cell rescue in patients with moderate renal impairment (creatinine clearance 30 to 50 mLl/min) a dose reduction of 50 % is usual. High-dose ALKERAN 50 without haematopoietic stem cell rescue is not recommended in patients with more severe renal impairment.

High dose ALKERAN 50 with haematopoietic stem cell rescue has been used successfully even in dialysis dependent patients with end-stage renal failure. The relevant literature should be consulted for details.

Method of administration

For instructions on dilution of ALKERAN 50 before administration, see section 6.6.

Parenteral administration (see section 4.4).

Except in cases where regional arterial perfusion is indicated, ALKERAN 50 is for intravenous use only. It is recommended that ALKERAN 50 injection solution 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 injection solution 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 % *w/v* is used.

When further diluted in an infusion solution, ALKERAN 50 has 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 (see section 4.4).

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.

4.3. Contraindications

ALKERAN 50 is contraindicated in:

- Patients with hypersensitivity to melphalan or to any of the excipients in ALKERAN 50 (see section 6.1 and section 4.8).
- Pregnancy and lactation (see section 4.6).
- Immunisation with live attenuated organism vaccines.

4.4. Special warnings and precautions for use

ALKERAN 50 IS AN ACTIVE CYTOTOXIC MEDICINE FOR USE ONLY UNDER THE DIRECTION OF HEALTHCARE PROFESSIONALS EXPERIENCED IN THE ADMINISTRATION OF SUCH MEDICINES.

Immunisation with live organism vaccines

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are contraindicated (see section 4.3 and section 4.5).

Renal Impairment

Patients with renal impairment should be closely observed, as they may have uraemic marrow suppression. Dosage reduction may be necessary (see section 4.2).

A fifty percent dosage reduction is essential in patients with impaired renal function who are given high-dose ALKERAN 50 (see section 4.2 and section 4.8).

Monitoring

Since ALKERAN 50 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 50 should be used with caution in patients who have undergone recent radiotherapy or chemotherapy in view of increased bone marrow toxicity.

Mutagenicity

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

Carcinogenicity

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

ALKERAN 50 may be leukaemogenic, especially in elderly patients after long combination therapy and radiotherapy. There have been reports of acute leukaemia occurring after prolonged ALKERAN 50 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 medicines with those who did not, showed that the use of alkylating medicines, including ALKERAN 50, significantly increased the incidence of acute leukaemia.

Before the start of the treatment, the leukaemogenic risk (AML and MDS) must be balanced against the potential therapeutic benefit, especially if the use of ALKERAN 50 in combination with thalidomide 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 patient at all times by usual measurements to ensure the early detection of cancer and initiate treatment if necessary.

Male infertility

Men who are receiving treatment with ALKERAN 50 should not father a child during treatment and for at least 12 months afterwards and they should have a consultation on sperm preservation before treatment due to the possibility of irreversible infertility as a result of ALKERAN 50 treatment (see section 4.6).

Parenteral administration

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 healthcare professionals.

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.

Elderly patients

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

Administration

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 solution is administered by injecting slowly into a fast-running i.v. infusion via a swabbed injection port, or via a central venous line (see section 4.2*: Parenteral administration*).

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

Solid tumours

Use of alkylating medicines, such as ALKERAN 50, has been linked with the development of second primary malignancy (SPM). In particular, ALKERAN 50 in combination with lenalidomide and prednisone and, 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 50 administration.

Contraception

Due to an increased risk of venous thromboembolism in patients undergoing treatment with ALKERAN 50 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 to 6 weeks after discontinuing combined oral contraception (see section 4.2: Thromboembolic events).

Highly effective contraceptive precautions should be advised when either partner is receiving ALKERAN 50 and for at least a year after cessation of treatment (see section 4.3).

4.5. Interaction with other medicines and other forms of interaction

Live organism vaccines: Vaccinations with live organism vaccines are contraindicated in immunocompromised individuals (see section 4.3 and section 4.4).

Nalidixic acid: Nalidixic acid together with high-dose intravenous ALKERAN 50 has caused deaths in children due to haemorrhagic enterocolitis (see section 4.1).

Busulfan: In paediatric population, for the busulfan-melphalan regimen it has been reported that the administration of melphalan less than 24 hours after the last oral busulfan administration may influence the development of toxicities.

Ciclosporin: Impaired renal function has been described in haemopoietic stem cell rescue patients who were preconditioned with high dose intravenous ALKERAN 50 and who subsequently received ciclosporin to prevent graft-versus-host disease.

4.6. Fertility, pregnancy and lactation

See section 4.3 and section 4.4: *Contraception*.

Pregnancy

The use of ALKERAN 50 is contraindicated during pregnancy, as mutagenicity has been documented in animals (see section 4.3).

Breastfeeding

Mothers receiving ALKERAN 50 should not breastfeed (see section 4.3).

Teratogenicity

In view of its mutagenic properties and structural similarity to known teratogenic compounds, ALKERAN 50 could cause congenital defects in the offspring of patients treated with the medicine.

Highly effective contraceptive precautions should be advised when either partner is receiving ALKERAN 50 and for at least a year after cessation of treatment (see section 4.3).

Fertility

ALKERAN 50 causes suppression of ovarian function in premenopausal women resulting in amenorrhoea in a significant number of patients. ALKERAN 50 may cause temporary or permanent sterility in male patients (see section 4.4).

Male infertility

Men who are receiving treatment with ALKERAN 50 should not father a child during treatment and for at least 12 months afterwards and they should have a consultation on sperm preservation before treatment due to the possibility of irreversible infertility as a result of ALKERAN 50 treatment (see section 4.4).

4.7. Effects on ability to drive and use machines

ALKERAN 50 has no or negligible influence on the ability to drive and use machines.

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that ALKERAN 50 does not adversely affect their ability to do so safely (see section 4.8).

4.8. 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 medicines.

a) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Secondary acute myeloid leukaemia, myelodysplastic syndrome
Blood and the lymphatic system disorders	Bone marrow depression leading to leucopaenia and thrombocytopaenia, anaemia	Haemolytic anaemia	
Immune system disorders		Allergic reactions	
Vascular disorders		Deep vein thrombosis, pulmonary embolism	
Respiratory, thoracic and mediastinal disorders		Interstitial lung disease, pulmonary fibrosis (including fatal reports)	
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, stomatitis (at high dose)	Stomatitis (at conventional dose)	
Hepato-biliary disorders		Hepatic disorders, ranging from abnormal liver function tests to clinical manifestations such as hepatitis and jaundice, veno-occlusive disease has been reported following high dose treatment	

Skin and subcutaneous tissue disorders	Alopecia (at high and conventional dose)	Maculopapular rashes, pruritus	
Musculoskeletal and connective tissue disorders	Muscle atrophy, muscle fibrosis, myalgia, increased blood creatine phosphokinase, compartment syndrome (injection, following isolated limb perfusion)		Muscle necrosis, rhabdomyolysis (injection, following isolated limb perfusion)
Reproductive system and breast disorders			Azoospermia, amenorrhoea
General disorders and administrative site conditions	A subjective and transient sensation of warmth and/or tingling		
Investigations	Temporary significant elevation of the blood urea has been seen in the early stages of ALKERAN 50 therapy in myeloma patients with renal damage		

b) Description of selected adverse reactions

Allergic reactions

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.

Gastrointestinal disorders

The incidence of diarrhoea, vomiting and stomatitis becomes the dose-limiting toxicity in patients given high i.v. doses of ALKERAN 50 in association with haemopoietic stem cell rescue. Cyclophosphamide pre-treatment has been shown to reduce the severity of the gastrointestinal damage induced by high-dose ALKERAN 50; the literature should be consulted for details.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification: A. 26. Cytostatic agents

Mechanism of action

Melphalan is a bifunctional alkylating medicine. 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.

5.2. Pharmacokinetic properties

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 % of 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.

Following administration of a two-minute infusion of doses ranging from 5 to 23 mg/m^2 body surface area (approximately 0,1 to 0,6 mg/kg bodyweight) to 10 patients with ovarian cancer or

multiple myeloma, the mean volumes of distribution at steady state and central compartment were 29,1 ± 13,6 litres and 12,2 ± 6,5 litres, respectively.

In 28 patients with various malignancies who were given doses of between 70 and 200 mg/m^2 body surface area as a 2- to 20-min infusion, the mean volumes of distribution at steady state and central compartment were, respectively, 40,2 ± 18,3 litres and 18,2 ± 11,7 litres.

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

Biotransformation

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

Elimination

In 8 patients given a single bolus dose of 0,5 to 0,6 mg/kg bodyweight, the composite initial and terminal half-lives were reported to be 7,7 ± 3,3 min and 108 ± 20,8 min, respectively. Following injection of melphalan, monohydroxymelphalan and dihydroxymelphalan were detected in the patients' plasma, reaching peak levels at approximately 60 min and 105 min, respectively. A similar half-life of 126 ± 6 min was seen when melphalan was added to the patients' serum *in vitro* (37°C), suggesting that spontaneous degradation rather than enzymic metabolism may be the major determinant of the medicine’s half-life in man.

Following administration of a two-minute infusion of doses ranging from 5 to 23 mg/m^2 body surface area (approximately 0,1 to 0,6 mg/kg bodyweight) to 10 patients with ovarian cancer or multiple myeloma, the pooled initial and terminal half-lives were, respectively, 8,1 ± 6,6 min and 76,9 ± 40,7 min. A mean clearance of 342,7 ± 96,8 mL/min was recorded.

In 15 children and 11 adults given high-dose i.v. melphalan (140 mg/m^2 body surface area) with forced diuresis, the mean initial and terminal half-lives were found to be 6,5 ± 3,6 min and 41,4 ± 16,5 min, respectively. Mean initial and terminal half-lives of 8,8 ± 6,6 min and 73,1 ± 45,9 min, respectively, were recorded in 28 patients with various malignancies who were given doses of between 70 and 200 mg/m^2 body surface area as a 2- to 20-min infusion. The mean clearance was 564,6 ± 159,1 mL/min.

Following hyperthermic (39°C) perfusion of the lower limb with 1,75 mg/kg bodyweight, mean initial and terminal half-lives of 3,6 ± 1,5 min and 46,5 ± 17,2 min, respectively, were recorded in 11 patients with advanced malignant melanoma. A mean clearance of 55,0 ± 9,4 mL/min was recorded.

Special Populations

Renal impairment

Melphalan clearance, though variable, is decreased in renal impairment (see section 4.2: Dosage in renal impairment).

Elderly patients

No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Povidine

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

ALKERAN 50: 24 months

ALKERAN SD: 36 months

6.4. Special precautions for storage

Store at or below 30 °C.

Protect from light.

Keep in original packaging until required for use.

6.5. Nature and contents of container

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.

6.6. Special precautions for disposal and other handling

Preparation of ALKERAN 50 solution

ALKERAN 50 should be prepared, AT ROOM TEMPERATURE, by reconstituting the freeze-dried powder with 10 ml of the ALKERAN SD provided.

If the ALKERAN SD is used at cold temperature, ALKERAN 50 powder may not reconstitute properly and undissolved particles may be observed.

10 ml of the vehicle should be added quickly, as a single quantity into the vial containing the freeze-dried powder, and immediately shaken VIGOROUSLY (for at least 50 seconds) until a clear solution, without visible particles, is obtained. Each vial must be reconstituted individually in this manner. Slow diluents addition and delaying the shaking may lead to the formation of insoluble particles.

It should be also noticed that the shaking process creates a considerable amount of very small air bubbles. These bubbles may persist and may take further 2 or 3 minutes to clear, as the resulting solution is quite viscous. This could make difficult the evaluation on solution clearness.

The resulting solution contains the equivalent of 5 mg per ml anhydrous melphalan at approximately pH 6,5.

ALKERAN 50 injection solution has limited stability and should be prepared immediately before use.

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

Any unused solution should be disposed of in accordance with local requirements (see section 4.4).

Safe handling of ALKERAN 50

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBERS

ALKERAN 50: 27/26/0506

ALKERAN SD: 27/34/0507

9. DATE OF FIRST AUTHORISATION

29 December 1993

10. DATE OF REVISION OF TEXT

10 June 2020

Botswana: B9317235 S2

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