1.3.1.1 Proposed Professional Information for` Medicines for Human Use (clean copy)

SCHEDULING STATUS

S3

S4

1. NAME OF THE MEDICINE

ZALCAREN

STERILE DILUENT FOR ZALCAREN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZALCAREN:

Melphalan hydrochloride equivalent to 50 mg melphalan per vial.

Each 10 ml contains sodium citrate 0,2 g, propylene glycol – 6 mL, ethanol (96 %) 0,52 mL and water for injection.

ZALCAREN contains small amounts of ethanol (alcohol), 0,52 mL per 10 mL.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ZALCAREN:

MELPHALAN 50 mg POWDER FOR INJECTION/INFUSION

Before Reconstitution:

White to off-white Lyophilized cake or powder in clear glass vial stoppered with gray igloo lyo rubber stopper and sealed with aluminium seal having sky blue colour PP disc.

After Reconstitution (Reconstitution with 10 mL of Solvent for solution for Melphalan powder for injection/infusion)

A clear colourless to pale yellow coloured solution essentially free from visible particles.

SOLVENT FOR SOLUTION FOR MELPHALAN POWDER FOR INJECTION/INFUSION)

Clear colourless solution, essentially free from visible particles filled in clear glass vial stoppered with gray rubber stoppers and sealed with aluminium seal having sky blue colour pp disc.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

Multiple myeloma: ZALCAREN Injection, either alone or in combination with other cytotoxic medicines.

Ovarian cancer: ZALCAREN Injection, either alone or in combination with other cytotoxic medicines.

ZALCAREN Injection, 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 ZALCAREN Injection 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.

4.2. Posology and method of administration

General:

ZALCAREN is a cytotoxic medicine, which falls into the general class of alkylating medicines. It should be prescribed only by medical practitioners experienced in the management of malignant disease with such medicines.

Since ZALCAREN is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be adjusted if necessary (see sections 4.4 and 4.8)

Posology

Thromboembolic events

ZALCAREN, 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, ZALCAREN 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 ZALCAREN treatment.

Multiple myeloma:

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

When used as a single agent 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), but autologous bone marrow rescue becomes essential following doses in excess of 140 mg/m2^2 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 ZALCAREN, treatment should be confined to specialist centres, with the appropriate facilities, and only be administered by experienced medical practitioners (see sections 4.4 and 4.8).

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~~^{2} body surface area) have been used at intervals of 4 to 6 weeks.

Advanced malignant melanoma:

Hyperthermic regional perfusion with ZALCAREN 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:

Dosages between 100 and 240 mg/m~~2~~^{2} 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.

SPECIAL POPULATIONS

Use in children:

High-dose ZALCAREN, 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 ZALCAREN 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 ZALCAREN in elderly patients is limited.

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

Dosage in renal impairment:

ZALCAREN clearance, though variable, is decreased in renal impairment. When ZALCAREN Injection is used at conventional intravenous dosage (8 - 40 mg/m~~2~~^{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 ZALCAREN Injection (100 - 240 mg/m~~2~~^{2}), 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 [Ethylenediaminetetraacetic acid (EDTA) clearance 30 - 50 mL/min], a dose reduction of 50 % is usual. Adequate hydration and forced diuresis are also necessary.

High-dose ZALCAREN is not recommended in patients with more severe renal impairment (EDTA clearance less than 30 mL/min).

Method of Administration

Parenteral administration:

Except in cases where regional arterial perfusion is indicated, ZALCAREN Injection is for intravenous use only.

It is recommended that ZALCAREN 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, ZALCAREN Injection solution may be administered diluted in an infusion bag.

4.3. Contraindications

- ZALCAREN should not be given to patients who have suffered a previous allergic reaction to melphalan or to any of the excipients of ZALCAREN listed in section 6.1.
- ***Lactation:*** Mothers receiving ZALCAREN should not breastfeed.
- ***Pregnancy:*** The use of melphalan is contra-indicated during pregnancy, as mutagenicity has been documented in animals.
- Immunisation with live attenuated organism vaccines.

4.4. Special warnings and precautions for use

ZALCAREN IS AN ACTIVE CYTOTOXIC MEDICINE FOR USE ONLY UNDER THE DIRECTION OF MEDICAL PRACTITIONERS EXPERIENCED IN THE ADMINISTRATION OF SUCH MEDICINES.

Warnings

- Safe handling of ZALCAREN formulations should follow guidelines for the handling of cytotoxic medicines according to prevailing local recommendations and/or regulations. Immunisation with live organism vaccines
- Immunization using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunizations with live organism vaccines are contraindicated.

Renal Impairment

- Patients with renal impairment should be closely observed, as they may have uraemic marrow suppression. Dosage reduction may be necessary.
- A fifty percent dosage reduction is essential in patients with impaired renal function, who are given high-dose ZALCAREN Injection.

Monitoring:

Since ZALCAREN 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.

Thromboembolic events:

Patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone, have an increased risk of thromboembolic events (see section 4.8). Especially in patients with additional thrombotic risk factors antithrombotic prophylactic measures should be considered (see sections 4.2 and 4.8).

Neutropenia and thrombocytopenia

Increased rate of haematological toxicities, particularly, neutropenia and thrombocytopenia, was observed in newly diagnosed elderly multiple myeloma in patients treated with melphalan in combination with lenalidomide and prednisone or thalidomide and prednisone or dexamethasone. Patients and medical practitioners are advised to be observant for signs and symptoms of bleeding,

including petechiae and epistaxis, especially in patients receiving combination drug regimens described.

Mutagenicity:

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

Carcinogenicity:

Melphalan~~,~~ 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 medicines with those who did not, showed that the use of alkylating medicines, 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.

Ethanol

ZALCAREN contains small amounts of ethanol (alcohol), 0,52 mL per 10 mL.

4.5 Interaction with other medicinal products and other forms of interaction

- 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.
- Ciclosporin: those who subsequently received ciclosporin to prevent graft-versus-host disease.
- Vaccinations with live organism vaccines are not recommended in immunocompromised individuals.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

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

Pregnancy

ZALCAREN should not be used during pregnancy. There are no data from the use of melphalan in pregnant women. Studies in animals have shown reproductive toxicity. In view of its mutagenic properties and structural similarity to known teratogenic compounds, it is possible that ZALCAREN could cause congenital defects in the offspring of patients treated with the medicine.

Breast-feeding

Mothers receiving ZALCAREN should not breast-feed.

Effects on fertility:

ZALCAREN causes suppression of ovarian function in premenopausal women, resulting in amenorrhoea in a significant number of patients.

Sterility in males

It is possible that ZALCAREN may cause temporary or permanent sterility in male patients. It is recommended that men who are receiving treatment with melphalan not father a child during treatment and up to 6 months afterwards and that they have a consultation on sperm reservation
before treatment due to the possibility of irreversible infertility as a result of melphalan treatment.

4.7 Effects on ability to drive and use machines

Effects on the ability to drive and operate machinery in patients taking this medicine have not been studied.

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 ZALCAREN therapy in myeloma patients with renal damage		

b. Description of selected adverse reactions

Allergic reactions

Allergic reactions of ZALCAREN 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 IV doses of ZALCAREN 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 ZALCAREN; the literature should be consulted for details.

c. Other special population

Chemotherapy

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

Renal Impairment

Such patients should be closely observed for uraemic marrow suppression. Temporary significant elevation of blood urea has been seen in the early stages of treatment in myeloma patients with renal damage.

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

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 melphalan in combination with thalidomide or lenalidomide and prednisone is considered, as it has been shown that these combinations may increase the leukaemogenic risk.

d. 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 medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via The '**6.04 Adverse Drug Reactions Reporting Form'**. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms and signs:

The immediate effects of acute intravenous over dosage 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 haemotological growth factors.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, alkylating agents, nitrogen mustard analogues

ATC Code: L01AA03

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

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.

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 α1-acid lycoprotein. 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 medicine. Low concentrations (~10 % of that in plasma) were observed in a single high-dose study in the paediatric population.

Biotransformation:

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

Elimination:

In 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 medicine being recovered in the urine over 24 h.

In 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 drug'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 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 children and adults given high- dose IV 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 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 patients with advanced malignant melanoma. A mean clearance of 55.0 ± 9.4 mL/min was recorded.

Special Populations

Renal impairment

Melphalan clearance may be decreased in renal impairment.

Elderly

No correlation has been shown between age and melphalan clearance or with melphalan terminal elimination half-life.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Melphalan 50 mg, powder for injection/infusion

Melphalan Ph.Eur

Tert – butanol HP

Hydrochloric acid, concentrated Ph.Eur

Povidone Ph.Eur (Kollidone® 12 PF)

Water for injection USP/Ph.Eur/IH

Nitrogen USNF/Ph.Eur/IH

Solvent for solution for Melphalan powder for injection/infusion

Sodium citrate (Tri Sodium Citrate Anhydrous)

Propylene Glycol Ph.Eur

Ethanol Ph.Eur (96 %)

Water for injection USP/Ph.Eur/IH

Nitrogen USNF/Ph.Eur/IH

5.3 Incompatibilities

ZALCAREN 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, ZALCAREN had reduced stability, and the rate of degradation increases rapidly with increasing temperature. If ZALCAREN 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 ZALCAREN and in cases of poor peripheral venous access, consideration should be given to use of a central venous line.

If high-dose ZALCAREN Injection 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.

5.4 Shelf life

2 years

5.5 Special precautions for storage

Store at or below 25°C.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

5.6 Nature and contents of container

Melphalan powder for injection/infusion

1 Vial

19 mL Tubular Type I Clear Glass vial

White to off – white lyophilized cake or powder filled in Type – I, clear tubular glass vial with 20 mm neck stoppered with 20 mm grey igloo lyophilized bromobutyl rubber stopper and sealed with cleared lacquered Aluminium seal having sky blue colour PP disc.

These vials shall be placed in pre thermoformed tray along with one vial of solvent diluent*. This combo pack of pre thermoformed tray is further packed in one printed carton along with package insert.

Solvent for solution for Melphalan powder for injection/infusion

1 Vial

10R Tubular Type I Clear BB Glass vial

Clear colourless solution is filled in 10R tubular Type – I, clear BB glass vial with 20 mm neck stoppered with 20 mm dark grey colour rubber stopper with bromobutyl based rubber formulation and sealed with cleared lacquered Aluminium seal having sky blue colour PP disc.

These vials shall be placed in pre thermoformed tray along with one vial of Melphalan 50 mg Powder for Injection*. This combo pack of pre thermoformed tray is further packed in one printed carton along with package insert.

5.7 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Safe Handling of ZALCAREN

ZALCAREN should be prepared for use in the aseptic unit equipped with a suitable vertical laminar flow cabinet. Where such a facility is not available, a specially designated side room of a ward or clinic may be used.

Staff who are pregnant or trying to conceive should not handle ZALCAREN.

Personnel preparing or handling ZALCAREN should wear the following protective clothing:

- Disposable gloves of surgical latex or polyvinylchloride of a suitable quality (rubber gloves are not adequate);
- Surgical facemask of suitable quality;
- Protective goggles or glasses which should be washed thoroughly with water after use;
- Disposable apron.
- In an aseptic facility, other suitable clothing will be required.

Preparation of ZALCAREN Solution

ZALCAREN should be prepared, AT ROOM TEMPERATURE, by reconstituting the freeze-dried powder with the solvent provided.

If the solvent is used at cold temperature, the freeze-dried powder may not reconstitute properly and undissolved particles may be observed.

10 ml of this 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 colourless solution without visible particles, is obtained.

Each vial must be reconstituted individually in this manner. Slow solvent addition and delaying the shaking may lead to the formation of insoluble particles. It should also be noted that the shaking process creates a considerable amount of very small air bubbles. These bubbles may persist and may take a further 2 to 3 minutes to clear, as the resulting solution is quite viscous. The resulting solution contains the equivalent of 5 mg/ml anhydrous melphalan and has a pH of approximately 6.5.

The reconstituted solution should be colourless, clear and practically free from visible particles.

ZALCAREN Injection solution has limited stability and should be prepared immediately before use.

Any unused solution remaining after one hour should be discarded (see Disposal below).

The reconstituted solution should not be refrigerated, as this will cause precipitation. When further diluted in an infusion solution, ZALCAREN Injection has reduced stability and the rate of degradation increases
rapidly with rise in temperature. If administration occurs 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 hour.

ZALCAREN is not compatible with infusion solutions containing dextrose and it is recommended that ONLY Sodium Chloride Intravenous Infusion 0.9 % *w/v* is used.
Should any visible turbidity or crystallisation appear in the reconstituted or diluted solutions the preparation must be discarded.

Spillage

Any spillage should be dealt with immediately (by personnel wearing suitable protective clothing), by mopping with damp, disposable paper towels which are placed in a high-risk waste disposal bag after use and disposed of in compliance with relevant local legislation. Contaminated surfaces should be washed with copious quantities of water.

Should ZALCAREN solution come into contact with the skin, wash immediately and thoroughly with soap and plenty of cold water. In such instances it may be prudent to seek medical advice.

In case of contact with eyes, IMMEDIATE irrigation with sodium chloride eye wash should be carried out and medical attention sought without delay. If sodium chloride solution is not available, large volumes of water may be used.

Disposal

ZALCAREN solution should be disposed of in compliance with relevant local legislation. In the absence of such guidelines, the solution should be disposed of in a manner appropriate for toxic chemicals, for example, high-temperature incineration or deep burial.

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

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF TEXT