1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PROFESSIONAL INFORMATION HUMAN MEDICINE

SCHEDULING STATUS:

S4 **MELPISPAL 50**

S3 **MELPISPAL SD**

1. NAME OF MEDICINE

MELPISPAL 50 (powder for injection)

MELPISPAL SD (solution for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Contains alcohol: Ethanol 5,2 % v/v

Sugar Free

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

MELPISPAL 50 (powder for injection / infusion) is a white to off white coloured lyophilized powder or cake

MELPISPAL SD (solution for injection) is a clear colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

MELPISPAL 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 MELPISPAL 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.

4.2 Posology and method of administration

Posology

General

MELPISPAL 50 is 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 MELPISPAL 50 is myelosuppressive, frequent blood counts are essential during therapy and the dosage should be adjusted if necessary (see section 4.4).

Multiple myeloma

MELPISPAL 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 mg/m^2 and 200 mg/m^2 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/m^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 MELPISPAL 50, treatment should be confined to specialist centers, 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 mg/kg and 0,4 mg/kg body mass (12 mg/m^2 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 MELPISPAL 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/m^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

Elderly population

Although MELPISPAL 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 MELPISPAL 50 in elderly patients is limited.

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

Renal impairment

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

When MELPISPAL 50 is used at conventional intravenous dosage (8 mg/m^2 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 hematological suppression.

For high intravenous doses of MELPISPAL 50 (100 mg/m^2 to 240 mg/m^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 (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 MELPISPAL 50 is not recommended in patients with more severe renal impairment (EDTA clearance less than 30 ml/min).

Paediatric population

High-dose MELPISPAL 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.

Method of administration

Parenteral administration

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

It is recommended that MELPISPAL 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, MELPISPAL 50 may be administered diluted in an infusion bag.

4.3 Contraindications

- MELPISPAL 50 should not be given to patients who have hypersensitivity to melphalan or to any of the excipients listed in section 6.1.
- Pregnancy and Lactation.
- Immunisation with live attenuated organism vaccines.

4.4 Special warnings and precautions for use

MELPISPAL 50 IS AN ACTIVE CYTOTOXIC MEDICINE FOR USE ONLY UNDER THE DIRECTION OF A MEDICAL PRACTITIONER EXPERIENCED IN THE ADMINISTRATION OF SUCH MEDICINES.

Safe handling of MELPISPAL 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.

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 MELPISPAL 50 (see section 4.2 and section 4.8).

Administration

MELPISPAL 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 MELPISPAL 50 is administered by injecting slowly into a fast-running intravenous infusion via a swabbed injection port, or via a central venous line.

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

Cyclophosphamide pretreatment has been shown to reduce the severity of the gastrointestinal damage induced by high-dose MELPISPAL 50; the literature should be consulted for details.

Parenteral administration

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

In patients receiving high-dose MELPISPAL 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 MELPISPAL 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 MELPISPAL 50 in elderly patients.

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

Monitoring

Since MELPISPAL 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 myelosupprression 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 ciclosporin to prevent graft-versus-host disease.

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

Mutagenicity

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

Carcinogenicity

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

MELPISPAL 50, may be leukemogenic in man especially in elderly patients after long combination therapy and radiotherapy. There have been reports of acute leukaemia occurring after prolonged melphalan 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 MELPISPAL 50, significantly increased the incidence of acute leukaemia.

The leukemogenic risk must be balanced against the potential therapeutic benefit when considering the use of MELPISPAL 50.

Teratogenicity

The teratogenic potential of MELPISPAL 50 has not been studied. In view of its mutagenic properties and structural similarity to known teratogenic compounds, MELPISPAL 50 could cause congenital defects in the offspring of patients treated with the medicine.

Solid tumours

Use of alkylating medicines, such as MELPISPAL 50, has been linked with the development of second primary malignancy (SPM). In particular, MELPISPAL 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 MELPISPAL 50 administration.

Contraception

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

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

Effects on fertility

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

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

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 MELPISPAL 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 MELPISPAL 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 MELPISPAL 50 is contraindicated during pregnancy, as mutagenicity has been documented in animals (see section 4.3).

Breastfeeding

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

Teratogenicity

In view of its mutagenic properties and structural similarity to known teratogenic compounds, MELPISPAL 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 MELPISPAL 50 and for at least a year after cessation of treatment (see section 4.3).

Fertility

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

Male infertility

Men who are receiving treatment with MELPISPAL 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 MELPISPAL 50 treatment (see section 4.4).

4.7 Effects on ability to drive and use machines

MELPISPAL 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 MELPISPAL 50 does not adversely affect their ability to do so safely.

4.8 Undesirable effects

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

Undesirable effects may vary in their incidence depending on the indication and dose received and also when given in combination with other therapeutic medicines.

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 MELPISPAL 50 therapy in myeloma patients with renal damage		

Description of selected adverse reactions

Allergic reactions

Allergic reactions of MELPISPAL 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 MELPISPAL 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 MELPISPAL 50; the literature should be consulted for details.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product 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 Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

Category and class: A.26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents, antineoplastic agents, alkylating agents, nitrogen mustard analogues ATC Code: L01AA03

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% the binding, and 20% is bound to α1-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.

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

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.

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

MELPISPAL 50

Hydrochloric Acid

Povidone K12

Water for Injections

MELPISPAL SD

Sodium citrate

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from light.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

MELPISPAL 50:

50 mg freeze-dried powder is packed in a 15 ml clear 20 mm collar vials (flat bottom) with 20 mm lyostoppers bromobutyl (single slotted) and sealed with 20 mm easy to open C/L ALU seals with matte finish plastic grey.

MELPISPAL SD:

Solvent is packed in 15 mL clear 20 mm collar vials (flat bottom) with 20 mm serum laminated chlorobutyl rubber stoppers and sealed with 20 mm easy to open C/L ALU seals with matte finish plastic white.

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

6.6 Special precautions for disposal of a used medicine and other handling

Preparation of Melphalan Injection Solution:

Melphalan Injection should be prepared at room temperature (approximately 25°C), by reconstituting the freeze-dried powder with the solvent-diluent provided.

It is important that both the freeze-dried powder and the solvent provided are at room temperature before starting reconstitution. Warming the diluent in the hand may aid reconstitution. 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 approximately 1 minute) until a clear solution, without visible particles, is obtained. Each vial must be reconstituted individually in this manner. The resulting solution contains the equivalent of 5 mg per ml anhydrous melphalan and has a pH of approximately 6.5.

MELPISPAL 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, MELPISPAL 50 had reduced stability and the rate of degradation increases rapidly with increasing temperature. If MELPISPAL 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 MELPISPAL 50 and in cases of poor peripheral venous access, consideration should be given to use of a central venous line.

If high-dose MELPISPAL 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.

MELPISPAL 50 Injection solution has limited stability and should be prepared immediately before use. Any solution unused after one hour should be discarded according to standard guidelines for handling and disposal of cytotoxic drugs.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

Unit 1, 96 Hartley Road

Durban. 4091

8 REGISTRATION NUMBER(S)

55/26/0558

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT