1.3.1.1 Professional Information for Medicines for Human Use (Approved)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZIGOZARD 25 mg/Vial (Powder for concentrate for solution for Infusion)

ZIGOZARD 100 mg/Vial (Powder for concentrate for solution for Infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZIGOZARD 25/100 mg/Vial:

Each vial contains Bendamustine Hydrochloride 25 mg /100 mg Powder for Concentrate for Solution for Infusion.

Contains Sugar – Mannitol 42.50 mg / 170.0 mg

For the full list of excipients, (see section 6.1).

3. PHARMACEUTICAL FORM

For Lyophillised powder:

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

For Reconstituted solution:

A clear colorless solution essentially free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
- First-line treatment of indolent CD 20 positive non-Hodgkin's lymphoma in combination with rituximab.
- Indolent non-Hodgkin's lymphomas as monotherapy in patients, who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.
- Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment.

4.2. Posology and method of administration

For intravenous infusion over 30 to 60 minutes.

Infusion must be administered under the supervision of a medical practitioner qualified and experienced in the use of chemotherapeutic medicines.

Poor bone marrow function is related to increased chemotherapy-induced haematological toxicity. Treatment should not be started if leukocyte and/or platelet values dropped to < 3 x 10^9/L or < 75 x 10^9/L, respectively (see section 4.3).

Monotherapy for chronic lymphocytic leukaemia

100 mg/m^2 body surface area ZIGOZARD on days 1 and 2; every 4 weeks.

Combination treatment for first-line indolent non-Hodgkin's lymphoma

90 mg/m^2 body surface area ZIGOZARD on days 1 and 2 in combination with 375 mg/m^2 body surface area rituximab as a slow i.v. infusion on day 1; every 4 weeks.

Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab

120 mg/m^2 body surface area ZIGOZARD on days 1 and 2; every 3 weeks.

Multiple Myeloma

120-150 mg/m^2 body surface area ZIGOZARD on days 1 and 2, 60 mg/m2 body surface area prednisone i.v. or orally on days 1 to 4; every 4 weeks.

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to ≤ 3 x 10^9/L or ≤ 75 x 10^9/L, respectively. Treatment can be continued after leukocyte values have increased to > 4 x 10^9/L and platelet values to > 100 x 10^9/L.

The leukocyte and platelet Nadir is reached, after 14 - 20 days with regeneration after 3 – 5 weeks. During therapy free intervals strict monitoring of the blood count is recommended (see section 4.4).

In case of non-haematological toxicity dose reductions have to be based on the worst CTC grades in the preceding cycle. A 50 % dose reduction is recommended in case of CTC grade 3 toxicity. An interruption of treatment is recommended in case of CTC grade 4 toxicity.

If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle. For preparation and administration instructions (see Method of administration).

Special populations

Hepatic impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment [serum bilirubin < 34,2 µmol/L (2,0 mg/dl)].

A 30 % dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin [34,2 µmol/L – 51,3 µmol/L (2 – 3,0 mg/dl)].

No data is available in patients with severe hepatic impairment [serum bilirubin values of > 51,3 µmol/L (3,0 mg/dl)].

Renal impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with a creatinine clearance of > 10 mL/min. Experience in patients with severe renal impairment is limited.

Elderly patients

There is no evidence that dose adjustments are necessary in elderly patients (see section 5.2)

Paediatric patients

There is no experience in children and adolescents with ZIGOZARD.

Method of administration

The solution is administered by intravenous infusion over 30 - 60 min.

The vials are for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

4.3. Contraindications

- Hypersensitivity to the bendamustine hydrochloride or to any of the excipients in ZIGOZARD (see section 6.1)
- Pregnancy and lactation (See section 4.6)
- Severe hepatic impairment [serum bilirubin > 34,2 µmol/L (2,0 mg/dl)]

Jaundice

- Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3 x 10^9/L or < 75 x 10^9/L , respectively)

- Major surgery less than 30 days before start of treatment
- Infections, especially involving leukocytopenia
- Yellow fever vaccination or any other live (attenuated) vaccination
- Congenital QT prolongation
- Concomitant medicines causing QT prolongation

4.4. Special warnings and precautions for use

Myelosuppression

Patients treated with ZIGOZARD may experience myelosuppression. In the event of treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least weekly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values > 4,000/µl or > 100,000/µl, respectively.

Infections

Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV). Treatment with ZIGOZARD may cause prolonged lymphocytopenia (< 600/µl) and low CD4-positive T-cell (T-helper cell) counts (< 200/µl) for at least 7–9 months after the completion of treatment. Lymphocytopenia and CD4-positive T-cell depletion are more pronounced when bendamustine hydrochloride as ZIGOZARD is combined with rituximab. Patients with lymphopenia and low CD4-positive T-cell count following treatment with ZIGOZARD are more susceptible to (opportunistic) infections, including tuberculosis. In case of low CD4-positive T-cell counts (< 200/µl) Pneumocystis jirovecii pneumonia (PJP) prophylaxis should

be considered. All patients should be monitored for respiratory signs and symptoms throughout treatment.

Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of ZIGOZARD should be considered if there are signs of (opportunistic) infections.

Hepatitis B reactivation

Reactivation of hepatitis B in patients who are chronic carriers of this virus may occur after these patients received bendamustine hydrochloride as in ZIGOZARD. Some cases resulted in acute hepatic failure or a fatal outcome. Patients should be tested for HBV infection before initiating treatment with bendamustine hydrochloride. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B tests (including those with active disease) and for patients who test positive for HBV infection during treatment. Carriers of HBV who require treatment with ZIGOZARD should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy (see section 4.8).

Skin reactions

A number of skin reactions have been reported. These events have included rash, severe cutaneous reactions and bullous exanthema. Cases of Stevens – Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) and Medicine Reaction with Eosinophilia and Systemic Symptoms (DRESS), some fatal, have been reported with the use of Bendamustine hydrochloride. Patients should be advised of the signs and symptoms of these reactions by their medical practitioner and should be told to seek medical attention immediately if they develop these symptoms. Some events occurred when ZIGOZARD was given in combination with other anticancer medicines, so the precise relationship is uncertain. When skin reactions

occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, ZIGOZARD should be withheld or discontinued. For severe skin reactions with suspected relationship to bendamustine hydrochloride as ZIGOZARD, treatment should be discontinued.

Cardiac disorders

During treatment with ZIGOZARD the concentration of potassium in the blood of patients with cardiac disorders must be closely monitored and potassium supplement must be given when K+ <3.5 mEq/l and ECG measurement must be performed.

Fatal cases of myocardial infarction and cardiac failure have been reported with ZIGOZARD treatment.

Patients with concurrent or history of cardiac disease should be observed closely.

Nausea, vomiting

An antiemetic may be given for the symptomatic treatment of nausea and vomiting.

Tumour lysis syndrome

Tumour lysis syndrome (TLS) associated with ZIGOZARD treatment. The onset tends to be within 48 hours of the first dose of ZIGOZARD and, without intervention, may lead to acute renal failure and death.

Preventive measures such as adequate hydration, close monitoring of blood chemistry, particularly potassium and uric acid levels and the use of hypouricemic medicines (allopurinol and rasburicase) should be considered prior to therapy. There have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol were administered concomitantly.

Anaphylaxis

Infusion reactions to ZIGOZARD have been reported. Symptoms include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have

occurred. Patients must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy.

Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions.

Patients who experienced Grade 3 or worse allergic-type reactions. ZIGOZARD should be discontinued

Contraception

ZIGOZARD is teratogenic and mutagenic.

Women should not become pregnant during treatment. Male patients should not father a child during and up to 6 months after treatment. They should seek advice about sperm conservation prior to treatment with ZIGOZARD because of possible irreversible infertility.

Extravasation

An extravasal injection should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit.

There have been reports of necrosis, tumour lysis syndrome and anaphylaxis.

There have been reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma.

ZIGOZARD contains mannitol, should not take ZIGOZARD people who are allergic to mannitol.

4.5. Interaction with other medicines and other forms of interaction

No *in-vivo* interaction studies have been performed.

When ZIGOZARD is combined with myelosuppressive medicines, the effect of ZIGOZARD and/or the co-administered medicinal products on the bone marrow may be potentiated. Any treatment reducing the patient's performance status or impairing bone marrow function can increase the toxicity of ZIGOZARD.

Combination of ZIGOZARD with ciclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.

Cytostatics can reduce antibody formation following live-virus vaccination and increase the risk of infection which may lead to fatal outcome. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

Bendamustine hydrochloride as in ZIGOZARD metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme (see section 5.2). Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine exist.

4.6. Fertility, pregnancy and lactation

Fertility

Women of childbearing potential must use effective methods of contraception both before and during ZIGOZARD therapy.

Men being treated with ZIGOZARD are advised not to father a child during and for up to 6 months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with ZIGOZARD.

Pregnancy

There are insufficient data from the use of ZIGOZARD in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic.

Therefore, ZIGOZARD is contraindicated during pregnancy. The mother should be informed about the risk to the foetus. If pregnancy occurs during treatment, the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered.

Breast-feeding

It is not known whether Bendamustine passes into the breast milk, therefore, ZIGOZARD is contraindicated during breast feeding (see section 4.3). Breast feeding must be discontinued during treatment with ZIGOZARD.

4.7. Effects on ability to drive and use machines

ZIGOZARD has major influence on the ability to drive and use machines. Ataxia, peripheral neuropathy and somnolence have been reported during treatment with ZIGOZARD (see section 4.8). Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.

4.8. Undesirable effects

a. Summary of the safety profile

The most common adverse reactions with ZIGOZARD are hematological adverse reactions (leukopenia, thrombopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

Tabulated list of adverse reactions

For patients who received only ZIGOZARD, the following adverse reactions were reported during therapy plus follow-up for 14 days after treatment was stopped:

b. Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	FREQUENCY

Infections and infestations	
Infection (not otherwise specified) NOS, Including Opportunistic infection (e.g. Herpes zoster, cytomegalovirus, hepatitis B)	Frequent
Pneumocystis Jirovecii, Pneumonia, Sepsis, tuberculosis	Less Frequent
Pneumonia primary atypical	Frequency Not Known
Neoplasma benign, malignant and unspecified (including cyst and polyp)	
Tumour lysis syndrome	Frequent
Myelodysplastic syndrome, acute myeloid leukemia	Less Frequent
Blood and lymphatic system disorders	
Leukopenia NOS, Thrombocytopenia Lymphopenia, Haemorrhage, Anaemia, Neutropenia	Frequent
Pancytopenia Bone marrow failure	Less Frequent
Haemolysis	Frequency Not Known
Immune system disorders	
Hypersensitivity NOS	Frequent

Anaphylactic reaction, Anaphylactoid reaction	Less Frequent
Anaphylactic shock	Frequency Not Known
Nervous system disorders	
Headache, Insomnia, Dizziness,	Frequent
Somnolence, Aphonia	Less Frequent
Dysgeusia, Paraesthesia, Peripheral sensory neuropathy, Anticholinergic syndrome, Neurological disorders, Ataxia, Encephalitis	Frequency Not Known
Cardiac disorders	
Cardiac dysfunction such as palpitations, angina pectoris, Dysrhythmia, QT prolongation	Frequent
Pericardial effusion, Myocardial infarction, Cardiac failure	Less Frequent
Tachycardia, Atrial fibrillation	Frequency Not Known
Vascular disorders	

Hypotension, Hypertension	Frequent
Acute circulatory failure	Less Frequent
Phlebitis	Frequency Not Known
Respiratory, thoracic and media-stinal disorders	
Pulmonary Dysfunction	Frequent
Pulmonary fibrosis, Pneumonitis Pulmonary alveolar haemorrhage	Frequency Not Known
Gastrointestinal disorders	
Nausea, Vomiting Diarrhoea, Constipation, Stomatitis	Frequent
Hemorrhagic oesophagitis, Gastrointestinal haemorrhage	Frequency Not Known
Skin and subcutaneous tissue disorders	
Alopecia, Skin disorders NOS, Urticaria	Frequent
Erythema, Dermatitis, Pruritus, Maculopapular Rash, Hyperhidrosis	Less Frequent
Stevens – Johnson syndrome, Toxic Epidermal Necrolysis (TEN) Drug	Frequency Not Known

reaction with eosinophilia and systemic symptoms (DRESS)* (combination therapy with rituximab).	
Reproductive system and breast disorders	
Amenorrhea	Frequent
Infertility	Frequency Not Known
Hepatobiliary disorder	
Hepatic failure	Frequency Not Known
General disorders and administration site conditions	
Mucosal inflammation, Fatigue, Pyrexia Pain, Chills, Dehydration, Anorexia	Frequent
Multi organ failure	Frequency Not Known
Investigations	
Haemoglobin decrease, Creatinine increase, Urea increase AST increase, ALT increase, Alkaline phosphatase increase, Bilirubin increase, Hypokalemia	Frequent

Renal and urinary disorders	
Renal failure	Frequency Not Known

f. 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form,' found online under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8

4.9. Overdose

After application of a 30 min infusion of ZIGOZARD once every 3 weeks the maximum tolerated dose (MTD) was 280 mg/m^2.

Cardiac events of CTC grade 2 which were compatible with ischaemic ECG changes occurred which were regarded as dose limiting.

In a subsequent study with a 30 min infusion of ZIGOZARD at day 1 and 2 every 3 weeks the MTD was found to be 180 mg/m^2. The dose limiting toxicity was grade 4 thrombocytopenia. Cardiac toxicity was not dose limiting with this schedule.

Treatment

There is no specific antidote. Bone marrow transplantation and transfusions (platelets, concentrated erythrocytes) may be made or haematological growth factors may be given as effective countermeasures to control haematological side effects.

ZIGOZARD and its metabolites are dialyzable to a small extent.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic medicines, alkylating medicines,

ATC code: L01AA09

Bendamustine hydrochloride is an alkylating antitumor medicine with unique activity. The antineoplastic and cytocidal effect of Bendamustine hydrochloride is based essentially on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. The antitumor effect of bendamustine hydrochloride has been demonstrated by several *in vitro* studies in different human tumour cell lines (breast cancer, non-small cell and small cell lung cancer, ovarian carcinoma and different leukaemias) and *in vivo* in different experimental tumour models with tumours of animal (mouse, rat) and human origin (melanoma, breast cancer, sarcoma, lymphoma, leukaemia and small cell lung cancer).

Bendamustine hydrochloride showed an activity profile in human tumour cell lines different to that of other alkylating medicines. The active substance revealed no or very low cross-resistance in human tumour cell lines with different resistance mechanisms at least in part due to a comparatively persistent DNA interaction. Additionally, it was shown in clinical studies that there is no complete cross-resistance of bendamustine with anthracyclines, alkylating agents, or rituximab.

However, the number of assessed patients is small.

5.2. Pharmacokinetic properties

Distribution

The elimination half-life $t_{1/2ß}$ after 30 min i.v. infusion of 120 mg/m^2 area to 12 subjects was 28.2 minutes.

Following 30 min i.v. infusion the central volume of distribution was 19.3 L. Under steady-

state conditions following i.v. bolus injection the volume of distribution was 15.8-20.5 L .

More than 95 % of the substance is bound to plasma proteins (primarily albumin).

Biotransformation

A major route of clearance of bendamustine is the hydrolysis to monohydroxy- and dihydroxy-bendamustine. Formation of N-desmethyl-bendamustine and gamma-hydroxy-bendamustine by hepatic metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Another major route of clearance of bendamustine metabolism involves conjugation with glutathione.

In-vitro bendamustine does not inhibit CYP 1A4, CYP 2C9/10, CYP 2D6, CYP 2E1 or CYP 3A4.

Elimination

The mean total clearance after 30 min i.v. infusion of 120 mg/m^2 body surface area to 12 subjects was 639.4 mL/minute.

About 20% of the administered dose was recovered in urine within 24 hours. Amounts excreted in urine were in the order monohydroxy-bendamustine > bendamustine > dihydroxy-bendamustine > oxidised metabolite > N-desmethyl bendamustine. In the bile, primarily polar metabolites are eliminated.

Special populations

Hepatic impairment

In patients with 30 - 70% tumour infestation of the liver and mild hepatic or moderate hepatic impairment (serum bilirubin < 34,2 µmol/L (2,0 mg/dL_the pharmacokinetic behaviour was not changed. There was no significant difference to patients with normal liver and kidney function with respect to Cmax, tmax, AUC, $t_{1/2ß}$, volume of distribution and clearance. AUC and total body clearance of bendamustine correlate inversely with serum bilirubin.

Renal impairment

In patients with creatinine clearance > 10 mL/min including dialysis dependent patients, no significant difference to patients with normal liver and kidney function was observed with respect to Cmax, tmax, AUC, $t_{1/2ß}$, volume of distribution and clearance.

Elderly

Subjects up to 84 years of age were included in pharmacokinetic studies. Higher age does not influence the pharmacokinetics of bendamustine.

5.3 Preclinical safety data

Not applicable

Environmental Risk Assessment

ZIGOZARD is a well-established active ingredient used in pharmaceutical preparations for human use. Given the anticipated pattern of use and disposal of the product, the environmental exposure of the active substance and metabolites are expected to be very limited. The use of ZIGOZARD 25/100 mg Vial is not considered warranting any environmental concerns or requiring any special product labelling.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol Ph.Eur

Tert-Butanol[$] IHS

Nitrogen USNF/Ph.Eur/IHS

Water for injection USP/Ph.Eur/IHS[$]

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months shelf life has been proposed

6.4. Special precautions for storage

Store at or below 25 °C. Keep in a dry place.

STORE OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

25 mg/Vial:

Lyophillised Powder is filled in Glass vial tubular Type-I, 26 mL Amber with 20 mm neck (20R ISO Vial) stoppered with 20 mm grey bromobutyl rubber stopper (LYO-IGLOO) and sealed with 20 mm aluminum seal having sky blue colour PP disc.

These Vials shall be packed in pre-printed carton with a packaging leaflet. The proposed labeling text for the primary and secondary pack is given in Module 1.3.3.

100 mg/Vial:

Lyophillised Powder is filled in Glass vial moulded Type-I, 60 mL (50 H) Amber with 20 mm neck stoppered with 20 mm grey bromobutyl rubber stopper (LYO-IGLOO) and sealed with 20 mm aluminum seal having sky blue colour PP disc.

These Vials shall be packed in pre-printed carton with a packaging leaflet. The proposed labeling text for the primary and secondary pack is given in Module 1.3.3.

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

When handling ZIGOZARD, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes). Contaminated body parts should be carefully rinsed with water and soap, the eyes should be rinsed with physiological saline solution, if possible it is recommended to work on special workbenches (laminar flow) with

liquid-impermeable, absorbent disposable foil. Pregnant personnel should be excluded from handling cytostatics.

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, diluted with sodium chloride 9 mg/mL (0,9 %) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used

Instructions for use

When handling ZIGOZARD, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes). Contaminated body parts should be carefully rinsed with water and soap, the eyes should be rinsed with physiological saline solution. If possible it is recommended to work on special safety workbenches (laminar flow) with liquid impermeable, absorbent disposable foil. Pregnant personnel should be excluded from handling cytostatics.

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, diluted with sodium chloride 9 mg/mL (0,9 %) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

1. Reconstitution

- Reconstitute each vial of ZIGOZARD containing 25 mg ZIGOZARD in 10 mL water for injection by shaking.
- Reconstitute each vial of ZIGOZARD containing 100 mg ZIGOZARD in 40 mL water for injection by shaking.

The reconstituted concentrate contains 2,5 mg ZIGOZARD per mL and appears as a clear colourless solution.

2. Dilution

As soon as a clear solution is obtained (usually after 5-10 minutes) dilute the total recommended dose of ZIGOZARD immediately with 0,9 % NaCl solution to produce a final volume of about 500 mL.

ZIGOZARD must be diluted with 0,9% NaCl solution only and not with any other injectable solution.

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

ZIGOZARD 25 MG 55/26/0657.655

ZIGOZARD 100 MG 55/26/0658.656

9. DATE OF FIRST AUTHORISATION

21.02.2023

10. DATE OF REVISION OF TEXT

To be advised.