PROPOSED PROFESSIONAL INFORMATION FOR

VEXFAN 6 mg/ml

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

VEXFAN 6 mg/ml (Concentrate for solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **VEXFAN 6 mg/ml** injection contains 60 mg busulfan.

The inactive ingredients include dimethylacetamide (DMA) and polyethylene glycol 400.

VEXFAN is sugar free.

3 PHARMACEUTICAL FORM

VEXFAN 6 mg/ml: Clear solution, essentially free of visible particles, packed in a 10 ml clear vial with a grey rubber stopper and purple matte flip-off aluminium seal.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Conditioning treatment prior to haematopoeietic progenitor cell transplantation in adults, when the combination of **VEXFAN** and cyclophosphamide (Bu/Cy2) is considered the best available option.

4.2 Posology and method of administration

VEXFAN should not be given by rapid IV injection or bolus.

VEXFAN should be administered under the supervision of a qualified medical practitioner who is experienced in conditioning treatment prior to haematopoeietic progenitor cell transplantation, in the use of cancer chemotherapeutic medicines and in the management of patients with severe pancytopenia. It is recommended to use actual body weight for dosing. All patients should be premedicated with anticonvulsant medicines to prevent seizures reported with the use of high dose busulfan. Antiemetics should be administered prior to the first dose and continued on a fixed schedule through its administration.

The recommended dosage and regimen is 0,8 mg/kg body weight of **VEXFAN** as a two hour infusion every 6 hours over 4 consecutive days, for a total of 16 doses prior to haematopoietic progenitor cell transplantation.
Obese patients: For obese or severely obese patients, dosing based on adjusted ideal body weight could be considered. Ideal body weight (IBW) should be calculated as follows (height in cm and weight in kg):
IBW (kg; men) = 50 + 0,91 X (height - 152); IBW (kg; women) = 45 + 0,91 X (height-152).
Adjusted ideal body weight (AIBW) should be calculated as follows:
AIBW = IBW + 0,25 X (actual body weight - IBW).

Administration:

VEXFAN must be diluted before administration. A final concentration of approximately 0,5mg/ml busulfan should be achieved (see section 6.6 for the detailed preparation of dilution).
VEXFAN should be administered by IV infusion via central venous catheter.

4.3 Contraindications

- Hypersensitivity to busulfan or to any of the excipients of **VEXFAN**.
- Pregnancy and lactation.

- The safety and efficacy in children have not been established.
- Hepatic insufficiency.

4.4 Special warnings and precautions for use

VEXFAN should not be given by rapid IV injection or bolus.

The consequence of treatment with **VEXFAN** is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anaemia, or any combination thereof may develop.

Frequent complete blood counts, including differential white blood cell counts, and quantitative platelet counts should be monitored during the treatment and until recovery is achieved.

Prophylactic or empiric use of anti-infective medicines (bacterial, fungal, viral) should be considered for the prevention and management of infections during the neutropenic period.

Platelet and red blood cell support, as well as use of growth factors such as granulocyte colony stimulating medicine (G-CSF), should be employed as medically indicated.

Absolute neutrophil counts < $0,5x10^9$/l at a median of 4 days post-transplant may present in patients and recover at median day 10 and 13 days following autologous and allogeneic transplant respectively (median neutropenic period of 6 and 9 days respectively).

Prophylactic use of anti-infective medicines should be considered for the prevention and management of infections during the neutropenic period.

Thrombocytopenia (< $25x10^9$/l or requiring platelet transfusion) can occur in patients.

Anaemia (haemoglobin < 8,0 g/dl) may also develop.

VEXFAN has not been studied in patients with hepatic impairment. Since busulfan is mainly metabolised through the liver exposure to **[PRODUCTNAME**] is expected to increase if liver function is impaired and the use of **VEXFAN** in hepatic impaired population is contraindicated.

Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or a prior progenitor cell transplant may be at an increased risk of developing hepatic veno-occlusive disease with the recommended dose and regimen.

Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with **VEXFAN** due to a possible decrease in the metabolism of busulfan (See section 4.5).

Cardiac function should be monitored regularly in patients receiving **VEXFAN** (see section 4.8).

Acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis has been reported. In addition, busulfan might induce pulmonary toxicity that may be additive to the effects produced by other cytotoxic medicines. Therefore, attention should be paid to this pulmonary issue in patients with prior history of mediastinal or pulmonary radiation (see section 4.8).

Dose modification is not recommended for patients with renal impairment; however, caution is advised. Periodic monitoring of renal function should be considered during therapy with **VEXFAN** (see section 4.8).

Seizures have been reported with high dose busulfan treatment. Special caution should be exercised when administering the recommended dose of **VEXFAN** to patients with a history of seizures, head trauma, or receiving other potentially epileptogenic medicines. Patients should receive adequate anticonvulsant prophylaxis.

The increased risk of a second malignancy should be explained to the patient. Busulfan has been classified by the International Agency for Research on Cancer (IARC) as a human

carcinogen. The World Health Organisation has concluded that there is a causal relationship between busulfan exposure and cancer. Leukaemia patients treated with busulfan developed many different cytological abnormalities, and some developed carcinomas. Busulfan is thought to be leukemogenic.

Busulfan can impair fertility. Therefore, men treated with **VEXFAN** are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with **VEXFAN**. Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in pre-menopausal patients. Impotence, sterility, azoospermia, and testicular atrophy have been reported in male patients. The solvent dimethylacetamide (DMA) may also impair fertility.
Cases of thrombotic microangiopathy after hematopoietic cell transplantation (HCT), including fatal cases, have been reported in high-dose conditioning regimens in which busulfan was administered in combination with another conditioning treatment.

4.5 Interactions with other medicines and other forms of interaction

Administration of itraconazole to patients receiving high-dose **VEXFAN** may result in reduced busulfan clearance. Plasma levels of busulfan may increase after administration of metronidazole. Patients should be monitored for signs of busulfan toxicity when itraconazole or metronidazole is used as an antifungal prophylaxis with **VEXFAN**.
No interaction is observed when busulfan is combined with fluconazole (antifungal medicine).
Ketobemidone may be associated with high levels of busulfan. Special care is recommended when combining these two medicines.

For the BuCy2 regimen it has been reported that the time interval between the last oral busulfan administration and the first cyclophosphamide administration may influence the

development of toxicities. A reduced incidence of HVOD and other regimen-related toxicity have been observed in patients when the lag time between the last dose of oral busulfan and the first dose of cyclophosphamide is > 24 hours.

Paracetamol is described to decrease glutathione levels in blood and tissues and may therefore decrease busulfan clearance when used in combination (see section 4.4).

The concomitant systemic administration of phenytoin to patients receiving high-dose busulfan has been reported to increase busulfan clearance, due to induction of glutathion-S-transferase. However, no evidence of this effect has been seen in the IV data. No interaction has been reported when benzodiazepines such as diazepam, clonazepam or lorazepam have been used to prevent seizures with high-dose busulfan.
No interaction was observed when busulfan was combined with 5-HT3 antiemetics such as ondansetron or granisetron.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

Women of childbearing potential must use effective contraception during and up to 6 months after treatment.

Pregnancy

VEXFAN is contra-indicated in pregnancy.

Breastfeeding

It is not known whether **VEXFAN** is excreted in breast milk. Because of the tumorigenicity shown for busulfan in human and animal studies, breastfeeding should be discontinued at the start of therapy.

Fertility

Busulfan and DMA can impair fertility in man or woman. Therefore, it is advised not to father a child during the treatment and up to 6 months after treatment and to seek advice on cryo-

conservation of sperm prior to treatment because of the possibility of irreversible infertility (see section 4.4).

4.7 Effects on ability to drive and use machines

Confusion and dizziness have been reported with the use of **VEXFAN**. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

a) Summary of the safety profile

Serious toxicities involving the haematologic, hepatic and respiratory systems are considered as expected consequences of the conditioning regimen and transplant process. These include infection and Graft-versus host disease (GVHD) which although not directly related, are the major causes of morbidity and mortality, especially in allogeneic HPCT.

Blood and lymphatic system disorders:

Myelo-suppression and immuno-suppression are the desired therapeutic effects of the conditioning regimen. Therefore, all patients can experience profound cytopenia.

Immune system disorders:

Patients may experience a graft versus host disease (a-GVHD). Chronic GVHD (c-GVHD) may cause death.

Infections and infestations:

Patients may experience episodes of mild or moderate infection. Pneumonia can be fatal or life-threatening, including mild/ moderate fever and chills.

Hepato-biliary disorders:

Hepatic Veno Occlusive Disease (HVOD) is a recognized potential complication of conditioning therapy post-transplant.

Mild to moderate jaundice may develop in patients, associated with GVHD or HVOD.

Severe AST elevations can occur, that are mild to moderate.

Respiratory, thoracic and mediastinal disorders:

Acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis may occur.

b) Tabulated summary of adverse reactions

The following side effects to be considered in patients treated with **VEXFAN**:

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Rhinitis Pharyngitis		
Blood and lymphatic disorders	Neutropenia Thrombocytopenia Febrile neutropenia Anaemia Pancytopenia		
Immune system disorders	Allergic reaction		
Endocrine disorders			Hypogonadism
Metabolism and nutrition disorders	Anorexia Hyperglycaemia Hypocalcaemia Hypokalaemia Hypomagnesaemia Hypophosphatemia Hyponatremia		
Psychiatric disorders	Anxiety Depression Insomnia Confusion	Delirium Nervousness Hallucination Agitation	
Nervous system disorders	Headache Dizziness	Seizure Encephalopathy Cerebral haemorrhage	
Eye disorders			Cataract Corneal thinning
Cardiac disorders	Tachycardia Dysrhythmia Atrial fibrillation Cardiomegaly Pericardial effusion Pericarditis	Ventricular extrasystoles Bradycardia	
Vascular disorders	Hypertension, Hypotension Thrombosis	Femoral artery thrombosis Capillary leak syndrome	

	Vasodilatation		
Respiratory system, thoracic and mediastinal disorders	Dyspnoea, Epistaxis Cough Hiccup Hyperventilation Respiratory failure Alveolar haemorrhages Asthma Atelectasis Pleural effusion	Hypoxia	Interstitial lung disease
Gastrointestinal disorders	Stomatitis Diarrhoea Abdominal pain Nausea Vomiting Dyspepsia Ascites Constipation Anus discomfort Haematemesis Ileus Oesophagitis	Gastrointestinal haemorrhage	Tooth hypoplasia
Hepatobiliary disorders	Hepatomegaly Jaundice Veno-occlusive liver disease Increased hepatic enzymes		
Skin and subcutaneous tissue disorders	Rash Pruritis Alopecia Skin desquamation Erythema Pigmentation disorder		
Musculoskeletal and connective tissue disorders	Myalgia Back pain Arthralgia		
Renal and urinary disorders	Dysuria Oligurea Haematuria Moderate renal insufficiency		
Reproductive system and breast disorders			Premature menopause Ovarian failure
General disorders and administration site	Asthenia		

conditions	Chills Fever Chest pain Oedema Oedema general Pain Pain or inflammation at injection site Mucositis		
Investigations	Transaminases increased Bilirubin increased GGT increased Alkaline phosphatases increased Weight increased Abnormal breath sounds Creatinine elevated Blood urea nitrogen increase Decrease ejection fraction		

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 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

The main toxic effect is profound myeloablation and pancytopenia, but the central nervous system, liver, lungs and gastrointestinal tract may be affected.

There is no known antidote to **VEXFAN** other than haematopoietic progenitor cell transplantation. In the absence of haematopoietic progenitor cell transplantation, the recommended dose of **VEXFAN** would constitute an overdose of busulfan. The

haematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated.

Dialysis should be considered in the case of an overdose. Since, busulfan is metabolized through conjugation with glutathione, administration of glutathione might be considered.

It must be considered that overdose of **VEXFAN** will also increase exposure to DMA. The principal toxic effects are hepatotoxicity and central nervous system (CNS) effects. CNS changes precede any of the more severe side effects. No specific antidote for DMA overdose is known. In case of overdose, management would include general supportive care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatics

Pharmacotherapeutic group: Alkyl sulfonates, ATC code: L01AB01.

Mechanism of action

Busulfan is a cytotoxic medicine that results in myelosuppression. Busulfan is a bifunctional alkylating medicine in which two labile methane sulphonate groups are attached to opposite ends of a four-carbon alkyl chain. In aqueous media, release of the methane sulphonate groups produces carbonium ions which can alkylate DNA, thought to be an important biological mechanism for its cytotoxic effect.

5.2 Pharmacokinetic properties

The pharmacokinetics of busulfan has been investigated. The information presented on biotransformation and elimination is based on oral busulfan.

Similar blood exposure is observed when comparing plasma concentrations in adult patients receiving oral and intravenous busulfan at 1 mg/kg and 0,8 mg/kg respectively.

Distribution

Terminal volume of distribution V_z ranges between 0,62 and 0,85 l/kg.

Busulfan concentrations in the cerebrospinal fluid are comparable to those in plasma although these concentrations are probably insufficient for anti-neoplastic activity.

Reversible binding to plasma proteins is around 7 % while irreversible binding, primarily to albumin, is about 32 %.

Biotransformation

Busulfan is metabolised mainly through conjugation with glutathione (spontaneous and glutathione-S-transferase mediated). The glutathione conjugate is then further metabolised in the liver by oxidation. None of the metabolites is thought to contribute significantly to either efficacy or toxicity.

Elimination

Total clearance in plasma ranges from 2,25 - 2,74 ml/minute/kg. The terminal half-life ranges from 2,8 to 3,9 hours.

Approximately 30 % of the administered dose is excreted into the urine over 48 hours with 1 % as unchanged busulfan. Elimination in faeces is negligible. Irreversible protein binding may explain the incomplete recovery. Contribution of long-lasting metabolites is not excluded.

Linearity

The dose proportional increase of busulfan exposure is demonstrated following intravenous busulfan up to 1 mg/kg.

Compared to the four times a day regimen, the once-daily regimen is characterized by a higher peak concentration, no medicine accumulation, and a wash out period (without circulating busulfan concentration) between consecutive administrations. It seems that the recommended intravenous busulfan dose administered either as an individual infusion (3,2 mg/kg) or into 4 divided infusions (0,8 mg/kg) provides equivalent daily plasma exposure with similar both inter-and intra-patient variability. As a result, the control of intravenous busulfan

AUC within the therapeutic windows is not modified and a similar targeting performance between the two schedules is illustrated.

Pharmacokinetic/pharmacodynamic relationships

Literature on busulfan suggests a therapeutic AUC window between 900 and 1500 µmol/L.minute per administration (equivalent to a daily exposure between 3600 and 6000 µmol/L.minute).

Special populations

Hepatic or renal impairment

The effects of renal dysfunction on intravenous busulfan disposition have not been assessed.

The effects of hepatic dysfunction on intravenous busulfan disposition have not been assessed. Nevertheless, the risk of liver toxicity may be increased in this population.

No age effect on busulfan clearance is evidenced in patients over 60 years.

Pharmacokinetic/pharmacodynamic relationships:

Successful engraftment suggests the appropriateness of the targeted AUCs. Occurrence of VOD is not related to overexposure. PK/PD relationship is observed between stomatitis and AUCs in autologous patients and between bilirubin increase and AUCs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients include dimethylacetamide and polyethylene glycol 400.

6.2 Incompatibilities

This medicine must not be mixed with other products, except those mentioned in section 6.6.

Do not use polycarbonate syringes with **VEXFAN**.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at 2 - 8 °C under refrigerated conditions. Keep in the outer carton until required for use. **KEEP OUT OF REACH OF CHILDREN.**

Storage after Dilution:

VEXFAN, when diluted under aseptic conditions in 0,9 % Sodium Chloride Injection, USP or 5 % Dextrose Injection, USP is stable at room temperature (25 °C) for up to 8 hours, but the infusion must be completed within that timeframe.

VEXFAN, when diluted under aseptic conditions in 0,9 % Sodium Chloride Injection, USP is stable at refrigerated conditions (2 °C - 8 °C) for up to 12 hours, but the infusion must be completed within that timeframe.

Although chemical and physical stability of the reconstituted solution has been demonstrated, from a microbiological point of view, **VEXFAN** should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.5 Nature and contents of container

VEXFAN is packed in clear glass type I vials, with a grey chlorobutyl stopper, with a purple matte flip-off seal, packed in an outer carton containing an 8-hole divider.

Pack size: 8 vials per carton.

6.6 Special precautions for disposal and other handling

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

All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.

As with other cytotoxic medicines, caution should be exercised in handling and preparing the **VEXFAN** solution:

- The use of gloves and protective clothing is recommended.
- If **VEXFAN** or diluted **VEXFAN** solution comes in contact with the skin or mucosa, wash thoroughly with water immediately.

Preparation of dilution:

Procedures for proper handling and disposal of anticancer medicines should be followed. Caution should be exercised in handling and preparing the solution. The use of gloves is recommended as skin reactions may occur with accidental exposure. If this occurs, wash the skin or mucosa immediately and thoroughly with water.

VEXFAN must be diluted with 0,9 % sodium chloride or 5 % dextrose for injection. The quantity of the diluent must be 10 times the volume of **VEXFAN** to ensure the final concentration of busulfan remains at approximately 0,5 mg/ml.

For example, for a 70 kg (actual body weight) patient, the amount of medicine to be administered will be calculated as follows:

(70 kg patient) X (0,8 mg/kg)/ 6 mg/ml) = 9,3 ml **VEXFAN** (56 mg total dose).

To prepare the final solution for infusion, add 9,3 ml of **VEXFAN** to 93 ml of diluent 0,9 % sodium chloride or 5 % dextrose solution for injection) as calculated below:

(9,3 ml **VEXFAN** X (10) = 93 ml of either diluent plus the 9,3 ml **VEXFAN** to yield a final concentration of busulfan of 0,5 mg/ml (9,3 ml X 6 mg/ml/ 102,3 ml = 0,54 mg/ml).

All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood while wearing gloves and protective clothing.

Using a syringe fitted with a needle remove the calculated volume of **VEXFAN** from the vial and dispense the content of the syringe into an intravenous bag (or syringe) which already contains the calculated amount of diluent, making sure that the medicine flows into and through the solution. Do not put **VEXFAN** into an IV bag that does not contain

diluent. Always add **VEXFAN** to the diluent, not the diluent to **VEXFAN**. Mix thoroughly by inverting several times.

Do not use polycarbonate syringes with **VEXFAN**.

The entire prescribed dose should be administered over two hours. Prior to and following each infusion, flush the catheter line with approximately 5 ml of the diluent. Do not flush residual medicine in the administration tubing, as rapid infusion of **VEXFAN** is not recommended.

Do not infuse concomitantly with another IV solution.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

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2144

8 REGISTRATION NUMBERS

A 55/26/0347

9 DATE OF FIRST AUTHORISATION

06 April 2022

10 DATE OF REVISION OF TEXT

Not applicable

11 DOSIMETRY

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable