PROPOSED PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

VEXFAN 6 mg/ml

Busulfan

Read all of this leaflet carefully before you are given VEXFAN

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other health care professional.

What is in this leaflet

1 What VEXFAN is and what it is used for

What VEXFAN is

VEXFAN contains the active substance ‘busulfan’, which belongs to a group of medicines called alkylating agents. **VEXFAN** destroys the original bone marrow before the transplant.

What VEXFAN is used for

VEXFAN is used in adults as a treatment prior to transplantation in combination with cyclophosphamide (used in adults to suppress the immune system). You will receive this preparative medicine before receiving a transplant of either bone marrow or haematopoietic progenitor cell.

2 What you need to know before you use VEXFAN

VEXFAN should not be administered to you

- if you are hypersensitive (allergic) to busulfan or any of the other ingredients of **VEXFAN** (listed in section 6).
- if you are pregnant or think you may be pregnant.
- there is no experience of use of **VEXFAN** in children.
- Liver failure.

Warnings and Precautions

VEXFAN is a potent cytotoxic medicine that results in profound decrease of blood cells. At the recommended dose, this is the desired effect. Therefore, careful monitoring will be performed, including frequent blood tests. It is possible that use of **VEXFAN** may increase the risk of suffering another malignancy or type of cancer in the future.

Tell your doctor or healthcare professional before being given the injection:

- if you have a liver, kidney, heart or lung problem.
- if you have a history of seizures, head injury or receiving any potentially epileptic medicine.
- if you have a prior history of chest or lung radiation.
- If you plan to father children, as **VEXFAN** can cause infertility.

  It is advised not to father a child during and up to 6 months after treatment and to seek advice on preserving sperm prior to treatment because of the possibility of irreversible infertility due to therapy with **VEXFAN**.

Cases of formation of blood clots in the small blood vessels may appear after hematopoietic cell transplantation (HCT) with high-dose of your treatment in combination with other medicines.

Paracetamol should be used with caution during the 72 hours prior to or with **VEXFAN** administration.

Other medicines and VEXFAN

Always tell your health care professional if you are taking any other medicine. (This includes all complementary or traditional medicines).

In particular, tell your health care professional if you are taking any of the following medicines:

- Itraconazole or metronidazole (used to treat certain types of fungal infections)
- ketobemidone (to treat pain)
- The use of paracetamol during the 72 hours prior to or with **VEXFAN** administration should be used with caution.

Pregnancy, breastfeeding and fertility

If you are pregnant or breastfeeding your baby, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare professional for advice before being given **VEXFAN**.

Pregnancy

Women must not be pregnant during treatment with **VEXFAN** and up to 6 months after treatment.

Breast-feeding

Women must stop breast-feeding before starting their treatment with **VEXFAN**.

Contraception

Adequate contraceptive precautions should be used when either partner is receiving **VEXFAN**.

Fertility

It may no longer be possible for you to achieve a pregnancy (infertility) after treatment with busulfan. If you are concerned about having children, you should discuss this with your doctor before treatment. **VEXFAN** can also produce symptoms of menopause and in pre-adolescent girls it can prevent the onset of puberty.

Men treated with **VEXFAN** are advised not to father child during and up to 6 months after treatment.

Driving and using machines

Do not drive or operate machines if you feel confused or dizzy after taking **VEXFAN**.

It is not always possible to predict to what extent **VEXFAN** may interfere with your daily activities. You should ensure that you do not engage in any activities that require mental alertness (e.g. driving, riding, flying, sailing, operating machines/ equipment), until you are aware of the measure to which **VEXFAN** affects you.

VEXFAN contains:

Dimethylacetamide (DMA) and polyethylene glycol 400, which can affect your ability to have children.

VEXFAN is sugar free.

3 How to use VEXFAN

Do not share medicines prescribed for you with any other person.

Always use **VEXFAN** exactly as your doctor has told you. Check with your doctor if you are not sure.

The dose of **VEXFAN** will be calculated according to your body weight.

VEXFAN in combination with cyclophosphamide:

- The recommended dose of **VEXFAN** is 0,8 mg/kg
- Each infusion will last 2 hours
- **VEXFAN** will be administered every 6 hours during 4 consecutive days, for a total of 16 doses prior to transplant.

You will not be expected to give yourself **VEXFAN**. It will be given to you by a person who is qualified to do so. **VEXFAN** is administered by a qualified health care professional as a central intravenous infusion, after dilution of the individual vial.

Medicines to be taken before you receive VEXFAN:

Before receiving **VEXFAN**, you will be medicated with

- anticonvulsive medicines to prevent seizures (phenytoin or benzodiazepines) and
- anti-nausea medicines to prevent vomiting.

If you use more VEXFAN than you should

In the event of overdosage, consult your doctor or pharmacist. If neither is available, contact the nearest hospital or poison centre.

You will be closely monitored, and vigorous supportive measures taken as medically indicated.

Symptoms of an overdose of busulfan includes tiredness, weakness, headache, shortness of breath, rapid heart rate, cold hands or feet, pale skin, bleeding problems.

Overdose, due to exposure to the excipient Dimethylacetamide (DMA), may include symptoms of a rash, stomach pain, nausea and vomiting, tiredness, dark-coloured urine, light-coloured bowel movements, yellow skin and eyes, loss of appetite. Any central nervous system effects, that include confusion, abnormal thinking, anxiety, agitation, sleep disturbances, drowsiness.

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4 Possible side effects

VEXFAN can have side effects.

Not all side effects reported for **VEXFAN** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **VEXFAN**, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, stop taking **VEXFAN** and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Graft-versus host disease (GVHD) - symptoms include mouth ulcers, abdominal pain and rash, as it is a major cause of death.
- Pneumonia that can be fatal - symptoms include coughing, phlegm, fever, chills and difficulty breathing.

- Hepatic Veno Occlusive Disease (HVOD), a potentially life-threatening condition where small veins in the liver are obstructed. Signs and symptoms include weight gain, yellowing of the skin and eyes, dark coloured urine and an increase in liver size.
- Life-threatening acute respiratory distress syndrome. Symptoms include shortness of breath, rapid breathing, blue skin, coughing, muscle weakness.
- Encephalopathy - symptoms include declining ability to reason and concentrate, memory loss, personality change, seizures and twitching
- Cerebral haemorrhage (a brain bleed). Symptoms may include numbness or weakness in part of the face, difficulty speaking or walking, decreased level of consciousness
- Respiratory failure (condition in which your blood doesn't pass enough oxygen into your blood)
- Alveolar haemorrhage, a life-threatening disorder that causes bleeding in the respiratory tract

These are all very serious side effects. If you have them, you may have had a serious reaction to **VEXFAN**. You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Yellowed skin and eyes, stomach pain and swelling, nausea, vomiting, tiredness, dark-coloured urine. All can be signs of liver complications.
- A fall in the number of white blood cells (the cells that fight infection), platelets (the cells that help the blood to clot, which may lead to bleeding disorders) and red blood cells (anaemia leading to tiredness and weakness).
- Hives, rash, fever, itching, wheezing or breathing problems, as you may experience an allergic reaction.
- Dysrythmia (irregular heartbeat)

- Thrombosis (forming of blood clots) - symptoms may include leg pain or swelling
- Capillary leak syndrome, that causes repeated flares of massive leakinage of plasma from blood vessels, that causes a sharp drop in blood pressure. If not treated, can cause organ failure or death.
- Collapsing of the lung (atelectasis), that causes trouble breathing, coughing and a low-grade fever
- Hypoxia (absence of enough oxygen)
- Vomiting of blood, due to gastrointestinal obstruction
- Gastrointestinal bleeding
- Heart failure (decreased ejection fraction). Symptoms include shortness of breath, swelling of feet and lower legs, tiredness and weakness, abdominal discomfort, pain or nausea, mental confusion

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

<u>Frequent side effects:</u>

- Infection of the sinuses that surround the nose
- Pain or irritation in the throat that can occur with or without swelling
- Anorexia/ decreased appetite
- High blood sugar levels. Symptoms include increased thirst, headaches, blurred vision, tiredness, frequent urinating, and weight loss
- Low levels of potassium, calcium, phosphate, magnesium, sodium or phosphates in the blood
- Anxiety, depression, sleeplessness or confusion
- Headache, dizziness
- Fast heart rate, atrial fibrillation (irregular, rapid heartbeat)

- Cardiomegaly (enlarged heart) - symptoms include shortness of breath and swelling
- Pericardial effusion (build-up of fluid around the heart) or pericarditis - symptoms include shortness of breath, discomfort lying down, chest pain, tiredness, fever
- High or low blood pressure
- Vasodilatation (widening of blood vessels), causing nausea, blurred vision, dizziness, confusion and weakness
- Difficult or laboured breathing, nose bleeds, cough, hiccup, hyperventilation, asthma (reoccurring inflamed airways, that produce mucus, making it difficult to breathe)
- Build-up of fluid in lungs (Pleural effusion), that may include coughing, chest pain or shortness of breath
- Painful swelling and sores inside the mouth (stomatitis)
- Diarrhoea, abdominal pain, nausea, vomiting, indigestion, abdominal swelling, constipation, anus discomfort, inflammation of the oesophagus
- Enlargement of the liver and other liver complications
- Rash, itching, hair-loss, skin peeling, skin redness, pigmentation disorder
- Muscle pain, back pain, joint pain
- Painful or difficult urination, a decrease in urination, blood in urine, moderate kidney failure that can also lead to an increase in urea (type of protein present indicative of how well your kidneys are working)
- Weakness or lack of energy, chills, fever, chest pain, water retention or swelling in extremities, pain, pain or inflammation at injection site, painful inflammation and ulceration of mucous membranes
- Weight increased, abnormal breath sounds
- Feeling dehydrated, tiredness, swelling, shortness of breath and confusion, due to increase in creatine in the body

<u>Less frequent side effects:</u>

- Delirium (confused thinking, reduced awareness), nervousness, hallucination, agitation
- Seizure
- Ventricular extrasystoles (a type of irregular heart rhythm), slow heart rate
- Femoral artery thrombosis (forming of blood clots) - symptoms may include leg pain or swelling and tenderness

Frequency is not known:

- Hypogonadism, a condition causing a decrease in hormones (testosterone and oestrogen). Symptoms include reduced sex drive, sexual dysfunction, tiredness, hot flashes, muscle weakness, absence of menstruation, infertility, irritability, mood swings.
- Cataract, corneal thinning
- Group of disorders causing progressive scarring of lung tissue
- Defect or damage in tooth enamel
- Premature menopause, ovarian failure

If you notice any side-effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effect

If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects 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 By reporting side effects, you can help provide more information on the safety of **VEXFAN**.

5 How to store VEXFAN

- Store all medicines out of reach of children.

- Store at 2 - 8 °C under refrigerated conditions. Keep in the outer carton until required for use.

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.

- Do not use after the expiry date stated on the label / carton/ bottle.
- Do not use **VEXFAN** if you notice any visible signs of deterioration.
- Return all unused medicine to your pharmacist.
- Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

Shelf-life

24 months

6 Contents of the pack and other information

What VEXFAN contains

The active substance is busulfan.

The other ingredients are: dimethylacetamide and polyethylene glycol 400.

What VEXFAN looks like and contents of the pack

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.

Holder of Certificate of Registration

Eurolab (Pty) Ltd.

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3 Stirrup Lane, Van Reenens Avenue,

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This leaflet was last revised in

Not applicable

Registration number

To be allocated