APPROVED PATIENT INFORMATION LEAFLET

Scheduling status: S4

BENDAMUSTINE 180 mg/4 ml DRL

Concentrate for Solution for Infusion

Read all of this leaflet carefully before you are given BENDAMUSTINE 180 mg/4 ml DRL

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

What is in this leaflet

1. What BENDAMUSTINE 180 mg/4 ml DRL is and what it is used for

The active ingredient, bendamustine hydrochloride (as monohydrate), is used for the treatment of certain types of cancer (cytostatic medicine).

BENDAMUSTINE 180 mg/4 ml DRL is used alone (monotherapy) or in combination with other medicines for the treatment of the following forms of cancer:

- Chronic lymphocytic leukaemia in cases where fludarabine combination therapy is not appropriate.
- Non-Hodgkin's lymphoma which was not treated before, in combination with rituximab

- Non-Hodgkin's lymphomas which was not treated before, as monotherapy in patients who have progressed during or within 6 months following treatments with rituximab or a rituximab-containing regimen.
- **Multiple myeloma**

Ask your doctor if you have any questions about why BENDAMUSTINE 180 mg/4 ml DRL has been prescribed for you.

2. What you need to know before you are given BENDAMUSTINE 180 mg/4 ml DRL

BENDAMUSTINE 180 mg/4 ml DRL should not be administered to you:

- if you are hypersensitive (allergic) to bendamustine hydrochloride or to butylhydroxytoluene or Macrogol 300
- if you are pregnant or breastfeeding. If treatment with bendamustine hydrochloride is necessary during lactation you must discontinue breastfeeding (see section Pregnancy and breastfeeding)
- if you have severe liver dysfunction (damage to the functional cells of the liver)
- if you have yellowing of the skin or whites of the eyes caused by liver or blood problems (jaundice)
- if you have severely disturbed bone marrow function (bone marrow depression) and serious changes in your number of white blood cells and platelets in the blood
- if you have had major surgical operations less than 30 days before starting treatment
- if you have an infection, especially one accompanied by a reduction in white blood cells (leukocytopenia)
- in combination with yellow fever vaccines or other live attenuated vaccine
- if you have a hereditary cardiac disease characterized by a disorder of the heart's electrical system (prolongation of the QT interval)
- If you receive other medicines that can cause the QT prolongation

Warnings and precautions

Tell your doctor or healthcare professional:

- If you get severe allergic or hypersensitivity reactions. You should pay attention to infusion reactions after your first cycle of therapy.
- In case of reduced capability of the bone marrow to replace blood cells. You should have your number of white blood cells and platelets in the blood checked before starting treatment with BENDAMUSTINE 180 mg/4 ml DRL, before each subsequent course of treatment and in the intervals between courses of treatment.
- In case of infections, which may include tuberculosis (TB). You should contact your doctor if you have signs of infection, including fever or lung symptoms.
- If you have had hepatitis B. Reactivation of hepatitis B may occur in patients who are chronic carriers of this virus when receiving BENDAMUSTINE 180 mg/4 ml DRL.
- In case of reactions on your skin during treatment with BENDAMUSTINE 180 mg/4ml DRL. These reactions may increase in severity with subsequent courses.
- In case of painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membrane (e.g. mouth and lips), in particular if you have had light sensitivity, infections of the respiratory system (e.g. bronchitis) and/or fever before.
- If you have an existing heart disease (e.g. heart attack, chest pain, severely disturbed heart rhythms).
- In case you notice any pain in your side, blood in your urine or reduced amount of urine. When your disease is very severe, your body may not be able to clear all the waste products from the dying cancer cells. This is called tumour lysis syndrome and can cause kidney failure and heart problems within 48 hours of the first dose of BENDAMUSTINE 180 mg/4 ml DRL. Your doctor may ensure you are adequately hydrated and give you other medicines to help prevent it.

If you are a man receiving treatment with BENDAMUSTINE 180 mg/4 ml DRL you should not father a child during your treatment and for up to 6 months afterwards. Before starting treatment,

you should seek advice on storing your sperm cells because of the possibility of permanent infertility (see Pregnancy, Breastfeeding, and Fertility).

Other medicines and BENDAMUSTINE 180 mg/4 ml DRL

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

If BENDAMUSTINE 180 mg/4 ml DRL is used in combination with medicines which inhibit the formation of blood in the bone marrow, the effect on the bone marrow may be intensified.

If BENDAMUSTINE 180 mg/4 ml DRL is used in combination with medicines such as ciclosporin or tacrolimus which alter your immune response, this effect may be intensified.

BENDAMUSTINE 180 mg/4 ml DRL may diminish the effectiveness of live-virus vaccination. Additionally BENDAMUSTINE 180 mg/4 ml DRL may increase the risk of an infection after vaccination with live vaccines (e.g. viral vaccination).

BENDAMUSTINE 180 mg/4 ml DRL may interact with medicines which block the enzymes involved in its metabolism (cytochrome P450 1A2 isoenzyme) such as fluvoxamine (an antidepressant), ciprofloxacin (an antibiotic), acyclovir (an antiviral medicine), and cimetidine (medicine for heartburn or ulcers).

Pregnancy, breastfeeding, and fertility

You should not receive BENDAMUSTINE 180 mg/4 ml DRL if you are pregnant or breastfeeding your baby.

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other health care provider for advice before receiving this medicine.

Pregnancy

Bendamustine hydrochloride can cause genetic damage and has caused malformations in animal studies.

If you are a woman of childbearing potential, you must use an effective method of contraception both before and during treatment with BENDAMUSTINE 180 mg/4 ml DRL. If pregnancy occurs during your treatment with BENDAMUSTINE 180 mg/4 ml DRL you must immediately inform your doctor and should have genetic consultation.

Breastfeeding

BENDAMUSTINE 180 mg/4 ml DRL must not be administered during breastfeeding. If treatment with BENDAMUSTINE 180 mg/4 ml DRL is necessary during lactation you must discontinue breastfeeding.

Fertitility

Men receiving treatment with BENDAMUSTINE 180 mg/4 ml DRL are advised not to father a child during treatment and for up to 6 months afterwards. Before starting treatment, you should seek advice on storing sperm because of the possibility of permanent infertility.

Driving and using machines

It is not always possible to predict to what extent BENDAMUSTINE 180 mg/4 ml DRL may interfere with the daily activities of a patient.

Do not drive or operate machines if you experience side effects such as drowsiness, dizziness or lack of coordination.

3. How to use BENDAMUSTINE 180 mg /4 ml DRL

You will not be expected to give yourself BENDAMUSTINE 180 mg/4 ml DRL. It will be given to you by a person who is qualified to do so.

How BENDAMUSTINE 180 mg /4 ml DRL will be administered

BENDAMUSTINE 180 mg/4 ml DRL will be administered into a vein over 30 – 60 minutes in various dosages, either alone (monotherapy) or in combination with other medicines.

Treatment should not be started if your white blood cells (leukocytes) and/or your blood platelets have fallen to counts below determined levels. Your doctor will determine these values at regular intervals.

Treatment with BENDAMUSTINE 180 mg/4 ml DRL should be undertaken only by doctors experienced in tumour therapy.

Your doctor will give you the exact dose of BENDAMUSTINE 180 mg/4 ml DRL and use the necessary precautions.

Your doctor will administer the solution for infusion after preparation as prescribed.

Duration of use

There is no time limit laid down as a general rule for treatment with BENDAMUSTINE 180 mg/4 ml DRL. Duration of treatment depends on disease and response to treatment.

If you are at all worried or have any questions regarding your treatment, please speak to your doctor or pharmacist.

Chronic lymphocytic leukaemia

The usual dose is 100 mg per m^2 of your body surface area BENDAMUSTINE 180 mg/4 ml DRL (based on your height and weight): On days 1 and 2.

Repeat the cycle after 4 weeks

Combination treatment for non-Hodgkin's lymphoma

The usual dose is 90 mg per m2 body surface area BENDAMUSTINE 180 mg/4 ml DRL (based on your height and weight) on days 1 and 2 in combination with 375 mg per m2 body surface area rituximab as a slow I.V. infusion on day 1; every 4 weeks.

Non-Hodgkin's lymphomas resistant to Rituximab

The usual dose is120 mg per m2 of your body surface area BENDAMUSTINE 180 mg/4 ml DRL (based on your height and weight: On days 1 and 2.

Repeat the cycle after 3 weeks.

Multiple myeloma

The usual dose is 120 mg – 150 mg per m2 of your body surface area BENDAMUSTINE 180 mg/4 ml DRL (based on your height and weight): On days 1 and 2.

Prednisone 60 mg per m2 of your body surface area (based on your height and weight) by injection or orally: on days 1 to 4.

Repeat the cycle after 4 weeks.

Treatment should be terminated if white blood cell (leukocyte) and/or platelet values drop to determined levels. Treatment can be continued after white blood cell and platelet values have increased.

Impaired liver or kidney function

Dependent on the degree of impairment of your liver function it may be necessary to adjust your dose (by 30 % in case of moderate liver dysfunction).

No dose adjustment is necessary in case of impairment of kidney function. Your doctor will decide whether a dosage adjustment is necessary.

The elderly

There is no evidence that dose adjustments are necessary in elderly patients.

If you receive more BENDAMUSTINE 180 mg /4 ml DRL than you should

Since a healthcare professional will administer BENDAMUSTINE 180 mg/4 ml DRL, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If you missed a dose of BENDAMUSTINE 180 mg /4 ml DRL

Since a healthcare provider will administer BENDAMUSTINE 180 mg/4 ml DRL, it is unlikely that the dose will be missed.

When treatment with BENDAMUSTINE 180 mg /4 ml DRL is stopped

The doctor treating you will decide whether to interrupt the treatment or to change over to a different preparation.

4. Possible side effects

BENDAMUSTINE 180 mg/4 ml DRL can have side effects.

Not all side-effects reported for BENDAMUSTINE 180 mg/4 ml DRL are included in this leaflet. Should your general health worsen or if you experience any untoward effects while receiving while receiving BENDAMUSTINE 180 mg/4 ml DRL, please consult your doctor, pharmacist or other healthcare professional for advice.

Some of the findings listed below may be found after tests performed by your doctor.

Tissue decay (necrosis) has been observed very rarely following leakage of BENDAMUSTINE 180 mg/4 ml DRL into the tissue outside the blood vessels (extravascular). A burning sensation where the infusion needle is inserted may be a sign of leakage outside the blood vessels. The consequence can be pain and poorly healing skin defects.

BENDAMUSTINE 180 mg/4 ml DRL can cause impaired bone-marrow function, which usually returns to normal after treatment.

Suppressed bone marrow function may lead to low counts of blood cells, which in turn may lead to an increased risk of infection, anaemia or a heightened risk of bleeding.

Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:

- Swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing;
- Serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. These conditions can appear as reddish target-like macules or circular patches often with central blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes, and can be preceded by fever and flu-like symptoms.

- Widespread rash, high body temperature, enlarged lymph nodes and other body organs involvement (drug reaction with eosinophilia and systemic symptoms which is also known as DRESS or drug hypersensitivity syndrome).

These are all very serious side effects. If you have them, you may have had a serious reaction to BENDAMUSTINE 180 mg/4 ml DRL. You may need urgent medical attention or hospitalisation.

Frequent side effects:

- Infections
- Low counts of white blood cells (leukocytopenia)
- Low counts of platelets (colourless blood cells that help blood clot –thrombocytopenia
- Bleeding (haemorrhage)
- Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)
- Low counts of neutrophils (a common type of white blood cell important to fighting off infections)
- A reduced level of lymphocytes (a certain type of white blood cell important in out body's immune defence against disease) (lymphopenia)
- Hypersensitivity reactions
- Disturbed metabolism caused by dying cancer cells releasing their contents into the blood stream (Tumour lysis syndrome)
- Sleeplessness (insomnia)
- Disturbed function of the heart (palpitations, angina pectoris)
- Disturbed heart rhythms (arrhythmia)
- Low or high blood pressure (hypotension or hypertension)
- Disturbed lung function
- Nausea

- Vomiting
- Diarrhoea
- Constipation
- Sore mouth (stomatitis)
- Hair loss
- Skin changes
- Itchy rash (urticaria)
- Missed periods (amenorrhoea)
- Mucosal inflammation
- Fever
- Fatigue
- Loss of appetite
- Pain
- Chills
- Dehydration
- Decreased haemoglobin, a protein in red blood cells that carries oxygen throughout the body
- Increased blood level of creatinine (a chemical waste product that is produced by your muscle)
- Increased blood level of urea (a chemical waste product)
- A rise in liver enzymes AST/ALT (which may indicate inflammation of damage to cells in the liver)
- A rise in the enzyme, alkaline phosphatase (an enzyme made mostly in the liver and bones)
- A rise in bile pigment (a substance made during the normal breakdown of red blood cells)
- Low potassium blood levels (a nutrient that is necessary for the function of nerve and muscle cells, including those in the heart)

Less frequent side effects

- Infection of the blood (septicaemia)
- Primary atypical inflammation of the lungs (pneumonia)
- Tuberculosis (a potentially serious infectious disease that mainly affects your lungs)

- Breakdown of red blood cells
- Severe allergic hypersensitivity reactions (anaphylactic reactions)
- Signs similar to anaphylactic reactions
- Rapid decrease in blood pressure sometimes with skin reactions or rash (anaphylactic shock)
- Drowsiness
- Loss of voice (aphonia)
- Disturbed sense of taste
- Altered sensations (paraesthesia)
- Malaise and pain in the limbs (peripheral neuropathy)
- Serious condition resulting in the blockade of specific receptor in the nervous system
- Disorders of the nervous system
- Lack of coordination (ataxia)
- Inflammation of the brain (encephalitis)
- Accumulation of fluid in the heart sac (escape of fluid into the pericardial space
- Increased heart rate (tachycardia)
- Heart attack, chest pain (myocardial infarction)
- Acute circulatory collapse (failure of blood circulation mainly from a cardiac origin with failure to maintain supply of oxygen and other nutrients to the tissues, and removing toxins)
- Inflammation of the veins (phlebitis)
- Formation of tissue in the lungs (fibrosis of the lungs)

- Bleeding inflammation of the gullet (haemorrhagic oesophagitis)
- Bleeding of stomach or gut
- Reddening of the skin (erythema)
- Inflammation of the skin (dermatitis)
- Itching (pruritus)
- Skin rash (maculo-papular rash)
- Excessive sweating (hyperhidrosis)
- Infertility
- Multiple organ failure
- Ineffective production of blood cells in the bone marrow (the spongy material inside your bones where blood cells are made)
- Acute leukemia
- Reduction in your bone marrow function, which may make you feel unwell or show up in your blood tests
- Accidental administration of BENDAMUSTINE 180 mg/4 ml DRL outside of the vein may cause the surrounding body tissue to die (necrosis)

Side effects with frequency unknown

- Inflammation of lung tissue (pneumonitis)
- Bleeding from the lungs
- Renal failure
- There have been reports of tumours (myelodysplastic syndrome, acute myeloid leukaemia, bronchial carcinoma) following treatment with bendamustine hydrochloride. The secondary cancer may develop several years after chemotherapy has been discontinued.

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

Laboratory tests may show:

Blood and kidney problems.

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. 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 BENDAMUSTINE 180 mg/4 ml DRL.

5. How to store BENDAMUSTINE 180 mg/4 ml DRL

Store all medicines out of reach of children.

Store and transport refrigerated (2 – 8 °C). Do not freeze.

Keep the vial in the outer carton to protect the content from light.

Your healthcare professional will check that the BENDAMUSTINE 180 mg/4 ml DRL is not past its expiry date stated on the label and carton before giving you the injection.

Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets). Return all unused medicine to your pharmacist.

6. Contents of the pack and other information

What BENDAMUSTINE 180 mg /4 ml DRL contains

- The active substance is bendamustine hydrochloride (as a monohydrate)

One vial contains 180 mg /4 ml of bendamustine hydrochloride.

1 ml of the concentrate contains 45 mg of bendamustine hydrochloride.

- The other ingredients are butylhydroxytoluene and Macrogol 300.

What BENDAMUSTINE 180 mg/4 ml DRL looks like and contents of the pack

5 ml amber glass vials with grey rubber stopper and aluminium flip-off seal with a red plastic disc.

Clear, pale yellow to yellow, viscous solution, free from visible extraneous matter.

Available in 1 vial pack size. Not all pack sizes may be marketed.

Holder of Certificate of Registration

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Access to the corresponding Professional Information

www.drreddys.co.za