PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

EQUIBEN 25, 25 mg/vial powder for concentrate for solution for infusion

EQUIBEN 100, 100 mg/vial powder for concentrate for solution for infusion

Bendamustine hydrochloride

Contains sugar (mannitol 42,5 mg per 25 mg vial and 170 mg per 100 mg vial)

Read all of this leaflet carefully before you are given EQUIBEN

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

What is in this leaflet

1. What EQUIBEN is and what it is used for
2. What you need to know before you are given EQUIBEN
3. How EQUIBEN is given
4. Possible side effects
5. How to store EQUIBEN
6. Contents of the pack and other information

1. What EQUIBEN is and what it is used for

EQUIBEN is a medicinal product which is used for the treatment of certain types of cancer (cytostatic medicine).

EQUIBEN 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 chemotherapy is not appropriate for you,
- non-Hodgkin lymphomas, which had not, or only shortly, responded to prior rituximab treatment,

- multiple myeloma in cases where thalidomide or bortezomib containing therapy is not appropriate for you.

2. What you need to know before you are given EQUIBEN

EQUIBEN should not be administered to you

- if you are hypersensitive (allergic) to bendamustine hydrochloride or any of the other ingredients of EQUIBEN (listed in section 6).
- during pregnancy, or if you are breastfeeding your baby
- 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 (white blood cells and/or thrombocyte values drop to < 3 x 10^9/L or < 75 x 10^9/L, respectively);
- 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 (leucocytopenia).
- in combination with yellow fever vaccines or other live attenuated vaccines.
- if you have a condition called congenital QT prolongation where your heart has an abnormal rhythm
- if you are taking medicines that can cause abnormal heart rhythms such as medicines for mental disorders (e.g., citalopram, chlorpromazine, lithium, haloperidol, venlafaxine), antibiotics (e.g., clarithromycin, efavirenz, moxifloxacin), antifungals (e.g., fluconazole, voriconazole), medicines for heart conditions (e.g., amiodarone, flecainide, sotalol), medicines for malaria (e.g., quinine), cancer medicines (e.g., dasatinib, lapatinib, pazopanib)

Warnings and precautions

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

- if you have a 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 EQUIBEN, before each subsequent course of treatment and in the intervals between courses of treatment.
- if you have any infections which may include TB (tuberculosis). You should contact your doctor if you have signs of infection, including fever or lung symptoms.

- if you notice or someone notices in you: memory loss, trouble thinking, difficulty walking or sight loss – these may be due to a very rare but serious brain infection which can be fatal (progressive multifocal leukoencephalopathy or PML).
- if you get reactions on your skin during treatment with EQUIBEN. The skin reactions may increase in severity.
- if you notice any suspicious skin changes because there may be an increased risk of certain types of skin cancer (non-melanoma skin cancer) with the use of this medicine.
- if you have 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 had before light sensitivity, infections of the respiratory system (e.g., bronchitis) and/or fever.
- if you have an existing heart disease (e.g., heart attack, chest pain, severely disturbed heart rhythms).
- if 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 EQUIBEN. Your doctor may ensure you are adequately hydrated and give you other medicines to help prevent it.
- if you get severe allergic or hypersensitivity reactions. You should pay attention to infusion reactions after your first cycle of therapy.
- If you are a man receiving treatment with EQUIBEN 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.

Unintentional injection into the tissue outside blood vessels (extravasal injection) may cause local tissue damage. Your doctor will treat this.

Other medicines and EQUIBEN

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

If EQUIBEN 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 EQUIBEN is used in combination with medicines which alter your immune response, this effect may be intensified. Cytostatic medicines (medicines used to destroy cancer cells) may diminish the effectiveness of live-virus vaccination. Additionally cytostatic medicines increase the risk of an infection after vaccination with live vaccines (e.g., viral vaccination).

Pregnancy, breastfeeding, and fertility

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 healthcare provider for advice before taking EQUIBEN.

Women of childbearing potential must use effective methods of contraception before and during EQUIBEN therapy, and for up to 6 months after stopping treatment.

Men being treated with EQUIBEN are advised to use effective contraceptive measures and 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 EQUIBEN.

Pregnancy

EQUIBEN can cause genetic damage and has caused malformations in animal studies. You should not use EQUIBEN if you are pregnancy.

Breastfeeding

EQUIBEN must not be administered if you are breastfeeding your baby. If treatment with EQUIBEN is necessary, you must stop breastfeeding your baby until your treatment with EQUIBEN has been completed.

Fertility

There is a risk that treatment with EQUIBEN will lead to infertility (in men), and you may wish to seek advice on conservation of your sperm cells before your treatment starts.

Driving and using machines

EQUIBEN has major influence on the ability to drive and to use machines. Do not drive or operate machines if you experience side effects, such as dizziness or lack of coordination.

It is not always possible to predict to what extent EQUIBEN may interfere with your daily activities. You should

ensure that you do not engage in driving or operating machinery until you are aware of the measure to which EQUIBEN affects you.

3. How EQUIBEN is given

How EQUIBEN is administered

You will not be expected to give yourself EQUIBEN. It will be given to you by a person who is qualified to do so.

Treatment with EQUIBEN should be undertaken only by doctors experienced in cancer therapy. Your doctor will give you the exact dose of EQUIBEN and use the necessary precautions.

Your attending doctor will administer the solution for infusion after preparation as prescribed. The solution is administered into a vein as a short-term infusion over 30 – 60 minutes.

Duration of use

There is no time limit laid down as a general rule for treatment with EQUIBEN.

Duration of treatment depends on your disease and your response to treatment.

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

If you receive more EQUIBEN than you should

Since a healthcare provider will administer EQUIBEN, he / she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If you forget to use EQUIBEN

Since a healthcare provider will administer EQUIBEN, it is unlikely that the dose will be missed.

4. Possible side effects

EQUIBEN can have side effects.

Not all side effects reported for EQUIBEN are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking EQUIBEN, please consult your healthcare provider for advice.

Tell your doctor immediately if experience any of the following side effects, you may need urgent medical attention or hospitalisation:

- severe allergic hypersensitivity reactions (anaphylactic reactions)
    - swelling of the hands, feet, ankles, face, lips and mouth or throat, which may cause difficulty in swallowing or breathing,
    - rash or itching,
    - fainting.
- rapid decrease in blood pressure sometimes with skin reactions or rash (anaphylactic shock)

These are all very serious side effects. If you have them, you may have had a serious reaction to EQUIBEN. 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:

Frequent side effects:

- infections including Herpes zoster (viral infection of the nerves causing painful rash occurring in a strip), cytomegalovirus (a kind of herpesvirus which usually produces very mild symptoms in an infected person but may cause severe neurological damage in people with weakened immune systems and in the new-born), hepatitis B (liver infection).
- disturbed metabolism caused by dying cancer cells releasing their contents into the blood stream (tumour lysis syndrome)
- low counts of white blood cells (disease-fighting cells in your blood)
- blood platelet count is low (thrombocytopenia)
- a condition in which there is a lower-than-normal number of lymphocytes (a type of white blood cell) in the blood (lymphopenia)
- reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)
- your body does not have enough neutrophils, an important white blood cell that fights infections (neutropenia)
- bleeding (haemorrhage)
- increased heart rate (tachycardia)

- rapid, strong, or irregular heartbeat (palpitations)
- a condition marked by severe pain in the chest, often also spreading to the shoulders, arms, and neck, owing to an inadequate blood supply to the heart (angina pectoris)
- disturbed function (dysfunction) of the heart
- disturbed heart rhythms (dysrhythmia, QT prolongation)
- impaired lung function
- decrease in the red pigment of the blood (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 or 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 your heart)

Less frequent side effects:

- serious fungal infection of the lungs that causes inflammation and fluid build-up in your lungs
- infection of the blood (septicaemia)
- a life-threatening immune system reaction to an infection (sepsis)
- primary atypical inflammation of the lungs (pneumonia)
- bacterial infection which is spread through the air and usually affects the lungs (tuberculosis)
- ineffective production of all blood cells in the bone marrow (the spongy material inside your bones where blood cells are made) (myelodysplastic syndrome)
- acute leukaemia
- a condition in which there is a lower-than-normal number of red and white blood cells and platelets in the blood (pancytopenia)
- reduction in your bone marrow function, which may make you feel unwell or show up in your blood tests

- break-down of red blood cell (haemolysis)
- inflammation of the brain (encephalitis)
- accumulation of fluid in the heart sac (escape of fluid into the pericardial space)
- heart attack, chest pain (myocardial infarct)
- heart failure
- acute circulatory collapse (failure of blood circulation mainly from a cardiac origin with failure to maintain the supply of oxygen and other nutrients to the tissues and removing toxins)

Frequency of side effects not known:

- irregular and often rapid heart rate (atrial fibrillation)
- inflammation of the walls of the alveoli (air sacs) in the lungs (pneumonitis)
- bleeding from the lungs
- liver failure
- renal failure
- serious skin rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. These 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.
- drug rash in combination therapy with rituximab 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 serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

Frequent side effects:

- headache
- sleeplessness (insomnia)
- dizziness
- low or high blood pressure (hypotension or hypertension)

- feeling sick (nausea)
- vomiting
- diarrhoea
- constipation
- sore mouth (stomatitis)
- hair loss (alopecia)
- skin disorders
- itchy rash (urticaria)
- missed periods (amenorrhoea)
- mucosal inflammation
- fatigue
- fever (pyrexia)
- pain
- chills
- dehydration
- anorexia

Less frequent side effects:

- drowsiness
- loss of voice (aphonia)
- disturbed sense of taste
- altered sensations (paraesthesia)
- malaise and pain in the limbs (peripheral neuropathy)
- disease of the nervous system (anticholinergic syndrome)
- disorders that affect the brain as well as the nerves found throughout the human body and the spinal cord (neurological disorders)
- lack of coordination (ataxia)
- inflammation of the veins (phlebitis)

- formation of scar tissue in the lungs (fibrosis of the lungs)
- inflammation and bleeding of the gullet (haemorrhagic oesophagitis)
- bleeding of stomach or gut
- reddening of the skin (erythema)
- inflammation of the skin (dermatitis)
- itching (pruritus)
- skin rash (macular exanthema)
- excessive sweating (hyperhidrosis)
- infertility
- multiple organ failure

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

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 Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. By reporting side effects, you can help provide more information on the safety of EQUIBEN.

5. How to store EQUIBEN

Store all medicines out of reach of children.

Store at or below 25 °C.

There are no special storage instructions for EQUIBEN.

Do not use after the expiry date stated on the label.

Note on shelf-life after opening or preparing the solution

Solutions for infusions prepared according to the directions are stable in polyethylene bags 25 °C for 3,5 hours, and in a refrigerator, they are stable for 2 days. EQUIBEN contains no preservatives. The solutions should not therefore be used after these lengths of time.

Do not dispose of unused medicine in drains or sewerage systems (e.g., toilets).

6. Contents of the pack and other information

What EQUIBEN contains

- The active substance is bendamustine hydrochloride. EQUIBEN 25 contains 25 mg of bendamustine hydrochloride per vial and EQUIBEN 100 contains 100 mg bendamustine hydrochloride per vial. After reconstitution 1 mL of the concentrate contains 2,5 mg bendamustine hydrochloride.
- The other ingredient is mannitol.

What EQUIBEN looks like and contents of the pack

White to off white lyophilized powder or plug filled in amber vial with rubber stopper and Aluminium seal.

EQUIBEN 25 is available in 20 mL/20 mm Amber Flat Bottom tubular type-1 glass vial with 20 mm Grey bromo butyl double slotted Lyo stopper and 20 mm Aluminium Flip off Red colour seal.

The 20 mL vial contains 25 mg bendamustine hydrochloride and are supplied in packs of 1, 5, 10 and 20 vials per outer carton.

EQUIBEN 100 is available in 50 mL/20 mm Amber Moulded type-1 glass vial with 20 mm Grey bromo butyl double slotted Lyo stopper and 20 mm Aluminium Flip off Red colour seal.

The 50 mL vial contains 100 mg bendamustine hydrochloride and are supplied in packs of 1 and 5 vials per outer carton.

Not all pack sizes may be marketed.

Holder of Certificate of Registration

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This leaflet was last revised in

04 September 2026

Registration numbers

EQUIBEN 25: 56/26/0822

EQUIBEN 100: 56/26/0823

Access to the corresponding Professional Information

An electronic copy of the Professional Information (PI) is available on the Equity website

http://www.equitypharmaceuticals.co.za or http://www.sahpra.org.za.