

Applicant: Aurogen South Africa (Pty) Ltd
Product Name: IBOZARD 25/100 mg/vials
Dosage form and strength: Each vial contains Bendamustine Hydrochloride 25/100 mg Powder for Concentrate for Solution for Infusion.

MODULE 1

1.3.2

Date: 2023.02.21

1.3.2 Patient Information Leaflet (Approved)

SCHEDULING STATUS

S4

PATIENT INFORMATION LEAFLET

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

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

Read all of this leaflet carefully before you start taking IBOZARD

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- IBOZARD has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet:

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

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1. What IBOZARD is and what it is used for

IBOZARD is used for the treatment of certain types of cancer (cytostatic medicine).

IBOZARD is used alone (monotherapy) or in combination with other medicines for the treatment of the following forms of cancer:

- chronic lymphocytic leukaemia
- non-Hodgkin lymphoma which was not treated before, in combination treatment with rituximab or which had not, or only shortly, responded to prior rituximab treatment (monotherapy)
- multiple myeloma

2. What you need to know before you take IBOZARD

Do not take IBOZARD:

- If you are hypersensitive (allergic) to the active ingredient Bendamustine hydrochloride or any other ingredients of this medicine.
- If you are a pregnant woman or breastfeeding your baby;
- If you have severe liver damage (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 the number of white blood cells and platelets in your blood (white blood cells and/or thrombocyte values drop to $< 3 \times 10^9/L$ or $< 75 \times 10^9/L$, 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

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(leucopenia).

- In combination with yellow fever vaccines or other live attenuated vaccines.

Warnings and precautions IBOZARD

- 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 IBOZARD before each subsequent course of treatment and in the intervals between courses of treatment.
- In case of infections. You should contact your doctor if you have signs of infection, including fever or lung symptoms including respiratory signs and symptoms. (including respiratory signs and symptoms).
- In case of reactions on your skin during treatment with IBOZARD. The skin reactions may increase in severity.
- 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 had before light sensitivity, infections of the respiratory system (e.g. bronchitis) and/or fever.
- In cases of 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 IBOZARD. Your doctor may ensure you are adequately hydrated and give you other medicines to help prevent it.



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- In case of severe allergic or hypersensitivity reactions. You should pay attention to infusion reactions after your first cycle of therapy.
- Hepatitis B reactivation. Cases of patients with history diagnosis of hepatitis B.
- Contraception.

Taking other medicines with IBOZARD:

Always tell your healthcare professional if you are taking any other medicine (this includes complementary or traditional medicines). See Do not take IBOZARD.

Tell your doctor before taking IBOZARD if you are taking any of the medicines listed below:

- If IBOZARD 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 IBOZARD is used in combination with medicines which alter your immune response, this effect may be intensified.
 - Cytostatic medicines (medicine that slows or stops the growth of
 - cells, including cancer cells, without killing them) 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, breastfeeding your baby or planning to have a baby, please consult your doctor, pharmacist or other healthcare professional for advice before IBOZARD is administered to you.

Pregnancy

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

You should not use IBOZARD during pregnancy unless certainly indicated by your doctor.

In case of treatment you should use medical consultation about the risk of potential adverse effects of your therapy for the unborn child and genetic consultation is recommended.

If you are a woman of childbearing potential you must use an effective method of contraception both before and during treatment with IBOZARD. If pregnancy occurs during your treatment with IBOZARD you must immediately inform your doctor and should use genetic consultation.

Breast-feeding

IBOZARD must not be administered during breast feeding.

If treatment with IBOZARD is necessary during lactation you must discontinue breast-feeding.

Ask your doctor or pharmacist for advice before taking any medicine.

Fertility

Men receiving treatment with IBOZARD 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.

If you are a man, you should avoid fathering a child during treatment with IBOZARD and for up to 6 months after treatment has stopped. There is a risk that treatment with IBOZARD will lead to infertility and you may wish to seek advice on conservation of sperm before treatment starts.

Driving and using machines

IBOZARD has major influence on the ability to drive and to use machines. Do not drive



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or operate machines if you experience side effects, such as, somnolence (sleepiness or state of being drowsy) dizziness or lack of coordination.

IBOZARD contains mannitol:

DO NOT USE this IBOZARD. If you had an allergic reaction when you took the medicines contained in mannitol.

3. How to take IBOZARD

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

IBOZARD is 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.

Chronic lymphocytic leukaemia

IBOZARD 100 mg per square meter of your body surface area (based on your height and weight) on days 1 and 2; every 4 weeks.	on Days 1+2
Repeat the cycle after 4 weeks up to 6 times	

Non-Hodgkin lymphomas

IBOZARD 90 mg per square meter of your body surface area (based on your height and weight) on days 1 and 2 in combination with 375 mg/m ² body surface	on Days 1 + 2
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area rituximab as a slow i.v. infusion on day 1; every 4 weeks.	
Repeat the cycle after 3 weeks at least 6 times	

Multiple myeloma

IBOZARD 120 - 150 mg per square meter of your body surface area (based on your height and weight) on days 1 and 2.	on Days 1 + 2
Prednisone 60 mg per square meter of your body surface area (based on your height and weight) by injection or orally on days 1 to 4; every 4 weeks.	on Days 1 – 4
Repeat the cycle after 4 weeks at least 3 times	

Treatment should be terminated if white blood cell (leukocyte) and/or platelet values dropped 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 attending doctor will decide whether a dosage adjustment is necessary.

How it is administered Treatment with IBOZARD should be undertaken only by doctors experienced in tumour therapy. Your doctor will give you the exact dose of IBOZARD and use the necessary precautions.

Your attending doctor will administer the solution for infusion after preparation as

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

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

IBOZARD will be given to you, by injection, by your doctor or another health care professional. You should check with your doctor or pharmacist if you are unsure. If you have the impression that the effect of IBOZARD is too strong or too weak, talk to your doctor or pharmacist.

If you take more IBOZARD than you should

Since a healthcare professional will administer this medicine, he/she will control the dosage. However, in the event of over dosage your doctor will manage the over dosage.

If you are concerned that you may take more IBOZARD, contact your doctor or another healthcare professional immediately.

If you missed a dose of IBOZARD

If a dose of IBOZARD has been forgotten, your doctor will usually retain the normal dosage schedule.

If you stop using IBOZARD

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

If you have any further questions on the use of this product, ask your doctor or pharmacist.

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4. Possible side effects

IBOZARD can have side effects:

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

Tissue decay (necrosis) has been observed very rarely following leakage of IBOZARD 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.

The dose-limiting side-effect of IBOZARD is 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.

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

- Swelling of your hands, feet, ankles, face, mouth or throat, which may cause difficulty in swallowing or breathing.
- Rash or itching.
- Fainting.

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



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

Frequent Side effects:

- Chest pain (angina),
- Disturbed function (dysfunction) of the heart
- Disturbed heart rhythms (arrhythmia)
- Disturbed lung function

Less frequently effects:

- Primary atypical inflammation of the lungs (pneumonia).
- Severe allergic hypersensitivity reactions (anaphylactic reactions).
- Signs similar to anaphylactic reactions (anaphylactoid reactions)
- Accumulation of fluid in the heart sac (escape of fluid into the pericardial space).
- Heart attack, chest pain (myocardial infarction).
- Heart failure.
- Increased heart rate (tachycardia),
- Acute circulatory collapse (failure of blood circulation mainly from the heart with failure to maintain the supply of oxygen and other nutrients to the tissues and removing toxins)
- Pneumocystis jirovecii pneumonia (a fungal infection of the lungs, causing cough, often mild and dry and fever.



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Frequency not known side effects:

- 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.
- 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 serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

Frequently side effects:

- Low counts of white blood cells (disease-fighting cells in your blood)
- Decrease in the red pigment of the blood (haemoglobin: a protein in red blood cells that carries oxygen throughout the body) causing shortness of breath, irregular heartbeats, dizziness, unusual tiredness
- Low counts of platelets (colorless blood cells that help blood clot)
- Infections (including shingles, cytomegalovirus, hepatitis B virus infection)
- Feeling sick (nausea)
- Vomiting
- Mucosal inflammation
- Headache
- Increased blood level of creatinine (a chemical waste product that is produced by your muscle)

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- Increased blood level of urea (a chemical waste product)
- Fever
- Fatigue (unusual weakness or tiredness).
- Bleeding (haemorrhage)
- Disturbed metabolism caused by dying cancer cells releasing their contents into the blood stream (Tumour lysis syndrome),
- 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 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),
- Low or high blood pressure (hypotension or hypertension)
- Diarrhoea
- Constipation
- Sore mouth (Stomatitis)
- Loss of appetite
- Hair loss
- Skin changes



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- Missed periods (amenorrhoea)
- Pain
- Insomnia
- Chills
- Dehydration
- Dizziness
- Itchy rash (urticaria),

Less frequent side effects

- Tuberculosis (TB) (a persistent cough, constant tiredness, loss of body mass, loss of appetite, fever, coughing up blood, night sweats).
- Ineffective production of all blood cells in the bone marrow (the spongy material inside your bones where blood cells are made),
- Acute leukaemia, (a cancer of the myeloid line of blood cells, characterised by the rapid growth of abnormal cells that build up in the bone marrow and blood and interfere with normal blood cells).
- Infection of the blood (sepsis),
- Reduction in your bone marrow function, which may make you feel unwell or show up in your blood tests,
- Drowsiness,
- Loss of voice (Aphonia),
- Reddening of the skin (erythema)
- Inflammation of the skin (dermatitis)
- Itching (pruritus)
- Skin rash (macular exanthema)



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- Excessive sweating (hyperhidrosis)
- Break-down of red blood cell (haemolysis)
- Rapid decrease in blood pressure sometimes with skin reactions or rash (anaphylactic shock),
- 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 systems,
- Disorders of the nervous system,
- Anticholinergic syndrome (leading to dilated pupils, decreased sweating, elevated temperature or rapid heartbeat).
- Lack of coordination (ataxia),
- Inflammation of the brain (encephalitis),
- 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,
- Infertility,
- Multiple organ failure,

Frequency not known side effects:

- Liver failure,
- Renal failure,



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- Irregular and often rapid heart rate (atrial fibrillation),
- 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,
- Drug rash in combination therapy with rituximab,
- Pneumonitis,
- Bleeding from the lungs,

There have been reports of tumours (myelodysplastic syndrome, AML, bronchial carcinoma) following treatment with IBOZARD. No clear relationship with IBOZARD could be determined.

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



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Reporting of side effects

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 via the " 6.04 Adverse Drug reaction Reporting Form found online under SAHPRA's publications

https://www.sahpra.org.za/documents/86422f1b6.04_ARF1_Jul16_v4.pdf. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store IBOZARD

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

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

Do not use after expiry date stated on the label.

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

Return all unused medicine to your pharmacist.

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

6. Contents of the pack and other information

What IBOZARD contains

Bendamustine Hydrochloride

Mannitol

Tert-Butanol

Nitrogen

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Water for injection

What IBOZARD looks like and contents of the pack

IBOZARD 25/100 mg Vial:

25 mg/Vial:

Lyophilised Powder is filled in Glass vial sealed with 20 mm aluminum seal having sky blue colour PP disc. These Vials are packed in pre-printed carton with a packaging leaflet.

100 mg/Vial:

Lyophilised Powder is filled in Glass vial with 20 mm aluminum seal having sky blue colour PP disc. These Vials are packed in pre-printed carton with a packaging leaflet.

**NAME, BUSINESS ADDRESS AND TELEPHONE NUMBER OF THE HOLDER OF THE
CERTIFICATE OF REGISTRATION**

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor 53 Phillip Engelbrecht Avenue

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Johannesburg

South Africa

Registration number

IBOZARD 25 MG 55/26/0655

IBOZARD 100 MG 55/26/0656

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