

Package leaflet: Information for the user

Bendamustine 25 mg and 100 mg Powder for Concentrate for Solution for Infusion

bendamustine hydrochloride

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bendamustine is and what it is used for
2. What you need to know before you use Bendamustine
3. How to use Bendamustine
4. Possible side effects
5. How to store Bendamustine
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1. What Bendamustine is and what it is used for

Bendamustine is a medicine which is used for the treatment of certain types of cancer (cytotoxic medicine).

Bendamustine 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's 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 use Bendamustine

Do not use Bendamustine

- if you are allergic to bendamustine hydrochloride or any of the other ingredients of this medicine (listed in section 6)
- while breast-feeding; if treatment with Bendamustine is necessary during lactation you must discontinue breast-feeding
- 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 (leucocytopenia)
- in combination with yellow fever vaccines.

Warnings and precautions

At any time during or after your treatment, tell your doctor immediately 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).

Contact your doctor 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.

Talk to your doctor, pharmacist or nurse before or during treatment with Bendamustine:

- 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, 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.
- in case of reactions on your skin during treatment with Bendamustine. 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 Bendamustine. Your doctor may ensure you are adequately hydrated and give you other medicines to help prevent it.
- in case of severe allergic or hypersensitivity reactions. You should pay attention to infusion reactions after your first cycle of therapy.

Other medicines and Bendamustine

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

If Bendamustine 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 is used in combination with medicines which alter your immune response, e.g. ciclosporin and tacrolimus, this effect may be intensified.

Medicines such as bendamustine (cytostatic medicines) 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).

If Bendamustine is used in combination with medicines which inhibit a special liver enzyme (CYP1A2), such as fluvoxamine (antidepressant), ciprofloxacin (used to treat bacterial infections), acyclovir (used to treat virus infections) and cimetidine (used to treat heartburn and stomach ulcers), these medicines can interfere with each other.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Pregnancy

Bendamustine can cause genetic damage and has caused malformations in animal studies. You should not use Bendamustine during pregnancy unless certainly indicated by your doctor. In case of treatment you should seek medical consultation about the risk of potential adverse effects of your therapy for the unborn child and genetic consultation is recommended.

Fertility

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

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

Breast-feeding

Bendamustine must not be administered during breast-feeding. If treatment with Bendamustine is necessary during lactation you must discontinue breast-feeding.

Driving and using machines

Bendamustine 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.

3. How to use Bendamustine

Bendamustine 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

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

Non-Hodgkin's lymphomas

Bendamustine 120 mg per square meter of your body surface area (based on your height and weight)	on Days 1 + 2
Repeat the cycle after 3 weeks at least 6 times	

Multiple myeloma

Bendamustine 120 – 150 mg per square meter of your body surface area (based on your height and weight)	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 – 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 severe 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 Bendamustine should be undertaken only by doctors experienced in tumour therapy. Your doctor will give you the exact dose of Bendamustine 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 Bendamustine. Duration of treatment depends on disease and response to treatment.

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

If you forget to use Bendamustine

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

If you stop using Bendamustine

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 medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of the findings listed below may be found after tests are performed by your doctor.

Tissue decay (necrosis) has been observed very rarely following leakage of Bendamustine 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 Bendamustine 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, anemia or a heightened risk of bleeding.

Very common (*may affect more than 1 in 10 people*)

- 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))
- Low counts of platelets (colorless blood cells that help blood clot)
- Infections
- Feeling sick (nausea)
- Vomiting
- Mucosal inflammation
- Headache
- Increased blood level of creatinine (a chemical waste product that is produced by your muscle)
- Increased blood level of urea (a chemical waste product)
- Fever
- Fatigue

Common (*may affect up to 1 in 10 people*)

- Bleeding (haemorrhage)
- Disturbed metabolism caused by dying cancer cells releasing their contents into the blood stream

- 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 cells important to fighting off infections)
- Hypersensitivity reactions such as allergic inflammation of the skin (dermatitis), nettle rash (urticaria)
- 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)
- Disturbed function (dysfunction) of the heart
- Disturbed heart rhythms (arrhythmia)
- Low or high blood pressure (hypotension or hypertension)
- Disturbed lung function
- Diarrhoea
- Constipation
- Sore mouth (stomatitis)
- Loss of appetite
- Hair loss
- Skin changes
- Missed periods (amenorrhoea)
- Pain
- Insomnia
- Chills
- Dehydration
- Dizziness
- Itchy rash (urticaria)

Uncommon (*may affect up to 1 in 100 people*)

- Inflammation of the lungs (pneumocystis jirovecii pneumonia)
- Accumulation of fluid in the heart sac (escape of fluid into the pericardial space)
- Ineffective production of all blood cells in the bone marrow (the spongy material inside your bones where blood cells are made)
- Acute leukemia
- Heart attack, chest pain (myocardial infarction)
- Heart failure

Rare (*may affect up to 1 in 1,000 people*)

- Infection of the blood (sepsis)
- Reduction in your bone marrow function, which may make you feel unwell or show up in your blood tests
- Severe allergic hypersensitivity reactions (anaphylactic reactions)
- Signs similar to anaphylactic reactions (anaphylactoid reactions)
- Drowsiness
- Loss of voice (aphonia)
- 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)
- Reddening of the skin (erythema)
- Inflammation of the skin (dermatitis)
- Itching (pruritus)
- Skin rash (macular exanthema)
- Excessive sweating (hyperhidrosis)

Very rare (*may affect up to 1 in 10,000 people*)

- Primary atypical inflammation of the lungs (pneumonia)

- Break-down of red blood cells
- 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
- Lack of coordination (ataxia)
- Inflammation of the brain (encephalitis)
- Increased heart rate (tachycardia)
- Inflammation of the veins (phlebitis)
- Formation of tissue in the lungs (fibrosis of the lungs)
- Bleeding and inflammation of the gullet (haemorrhagic oesophagitis)
- Bleeding of stomach or gut
- Infertility
- Multiple organ failure

Not known (*frequency cannot be estimated from the available data*)

- Liver failure
- Renal failure
- 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
- Excessive urination, including at night, and excessive thirst even after drinking fluids (nephrogenic diabetes insipidus)

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

Contact your doctor or seek medical attention immediately if you notice any of the following side effects (frequency not known):

- 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).

Reporting of side effects

If you get any 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 directly via HPRA Pharmacovigilance, Website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bendamustine

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after 'EXP'. The expiry date refers to the last day of that month..

Unopened

This medicinal product does not require any special storage conditions.

Reconstituted concentrate

The powder should be reconstituted immediately after opening of the vial.

The reconstituted concentrate should be diluted immediately with 0.9% sodium chloride solution (see instructions at the end of this leaflet).

Solution for infusion

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 °C/ 60% RH, in normal light conditions and 2 days at 2 °C to 8 °C, protected from light, in polyethylene bags.

From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6. Contents of the pack and other information

What Bendamustine contains

- The active substance is bendamustine hydrochloride. After reconstitution, 1 ml of concentrate contains 2.5 mg bendamustine hydrochloride. One 26 ml vial contains 25 mg bendamustine hydrochloride. One 60 ml vial contains 100 mg bendamustine hydrochloride.
- The other ingredient is mannitol.

What Bendamustine looks like and contents of the pack.

White to off-white lyophilisate powder.

Type I amber glass vials of 26 ml or 60 ml with type I rubber (bromobutyl) lyo-stopper and an aluminium cap with polypropylene disk. Vials are sheathed in protective sleeve.

26 ml-vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 1, 5, 10 and 20 vials.

60 ml-vials contain 100 mg bendamustine hydrochloride and are supplied in packs of 1 and 5 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Teva B.V., Swensweg 5, 2031GA Haarlem, The Netherlands

Manufacturer

S.C. SINDAN-PHARMA S.R.L., 11th Ion Mihalache Boulevard, 011171, Bucharest 1, Romania.

This medicine is authorised in the Member States of the European Economic Area under the following names:

Austria	Bendamustin 2,5 mg/ml Pulver für ein Konzentrat zur Herstellung einer Infusionslösung
Bulgaria	Bendamustine Actavis
Croatia	Bendamustin Teva 2,5 mg/ml prašak za koncentrat za otopinu za infuziju
Denmark	Bendamustin Actavis
Greece	Bendamustine/ Actavis
Hungary	Bendamustin Teva 2,5 mg/ml por oldatos infúzióhoz való koncentrátumhoz
Ireland	Bendamustine 25 mg & 100 mg Powder for Concentrate for Solution for

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The following information is intended for healthcare professionals only:

As with all similar cytotoxic substances, stricter safety precautions apply as far as nursing staff and doctors are concerned, due to the potentially genome-damaging and cancer-causing effect of the preparation. Avoid inhalation (breathing in) and contact with the skin and mucous membranes when handling Bendamustine (wear gloves, protective clothing, and possibly a face mask!). If any parts of the body become contaminated, clean them carefully with soap and water, and flush the eyes with 0.9 % (isotonic) saline solution. If possible, it is advisable to work on a special safety work bench (laminar flow) with a disposable absorbing sheet that is impermeable to liquids. Contaminated articles are cytostatic waste. Please comply with national guidelines on the disposal of cytostatic material! Pregnant staff must be excluded from working with cytostatics.

The solution ready for use must be prepared by dissolving the contents of a vial of Bendamustine exclusively in water for injections as follows:

1. Preparation of the concentrate

- One 26 ml vial of Bendamustine containing 25 mg of bendamustine hydrochloride is first dissolved in 10 ml of water for injections by shaking.
- One 60 ml vial of Bendamustine containing 100 mg of bendamustine hydrochloride is first dissolved in 40 ml of water for injections by shaking.

The reconstituted concentrate contains 2.5 mg bendamustine hydrochloride per ml and appears as a clear colourless solution.

2. Preparation of the solution for infusion

As soon as a clear solution is obtained (generally after 5-10 minutes), the total recommended dose of Bendamustine is immediately diluted with 0.9 % (isotonic) saline solution to obtain a final volume of approximately 500 ml. Bendamustine must not be diluted with other solutions for infusion or injection. Bendamustine must not be mixed in an infusion with other substances.

3. Administration

The solution is administered by intravenous infusion over 30-60 min.
The vials are for single use only.

Do not use this medicine if you notice any visible signs of deterioration or damage to the vials. Following reconstitution and dilution, the product should be inspected visually for particulate matter or discoloration. The solution should only be used if the solution is clear and free from particles.

Unintentional injection into the tissue outside blood vessels (extravasal injection) should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit (see section 4).

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