PACKAGE LEAFLET

Package leaflet: Information for the user

Bendamustine 25 mg/ml 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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or healthcare professional. 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

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 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 (see section warnings and precautions on 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 (leucocytopenia);
- in combination with yellow fever vaccines.

Warnings and precautions
Talk to your doctor , pharmacist or nurse before using 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.

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.

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, this effect may be intensified.

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).

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 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 Bendamustine. If pregnancy occurs during your treatment with Bendamustine you must immediately inform your doctor and should use genetic consultation.

Breast-feeding
Bendamustine must not be administered during breast-feeding. If treatment with Bendamustine 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 Bendamustine 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 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.

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

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

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 metre 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 lymphomas

Bendamustine 120 mg per square metre 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 metre of your body surface area (based on your height and weight)	on Days 1 + 2
Prednisone 60 mg per square metre 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.

<u>Impaired liver or kidney function</u>
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 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 pharmacist.

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 product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, Bendamustine 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
- 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
- Headache

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 cell important to fighting off infections)
- Abnormally low concentration of neutrophils (a type of white blood cell) in the blood leading to increased susceptibility to infection (neutropenia)
- 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)**:**
- 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 infarct)
- Heart failure

Rare (may affect up to 1 in 1,000 people)**:**
- Infection of the blood (sepsis)
- 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)
- Reduction in your bone marrow function, which may make you feel unwell or show up in your blood tests

Very rare (may affect up to 1 in 10,000 people)**:**
- Primary atypical inflammation of the lungs (pneumonia)
- Break-down of red blood cell
- 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 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)**:**
- Renal failure
- Liver 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 membranes (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 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).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

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 the carton after EXP. The expiry date refers to the last day of that month.

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

Do not use this medicine if you notice visible particles or if the solution is not clear, colourless to yellow.

After opening of the vial
Chemical, physical and microbiological in use stability has been demonstrated for 28 days at 2 - 8°C. Once opened, the product may be stored for a maximum of 28 days at 2 - 8°C.

Solution for infusion
After dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 ºC and 2 days at 2 - 8ºC 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.

Minimisation of the risk of contamination of the multidose vial during withdrawal of each dose is the responsibility of the user. Record date and time of the first dose withdrawal on the vial label. Between uses do not balance product solution with water for injection or any diluent and return the multidose vial to the recommended storage condition of 2 - 8°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Bendamustine contains
The active substance is bendamustine hydrochloride.

Each ml of concentrate for solution for infusion contains 25 mg bendamustine hydrochloride (as monohydrate).
Each vial of 1 ml contains 25 mg bendamustine hydrochloride (as monohydrate).
Each vial of 4 ml contains 100 mg bendamustine hydrochloride (as monohydrate).

The other ingredients are butylhydroxytoluene (E 321) and macrogol.

What Bendamustine looks like and contents of the pack
Clear colourless to yellow solution in an amber glass vials with chlorobutyl rubber stopper containing 1ml and 4ml concentrate for solution for infusion. One ml vial supplied with aluminium seal with red coloured plastic flip off plain top cap and 4ml vial supplied with red coloured aluminium seal with white coloured plastic flip off plain top cap. Vials are sheathed in a protective sleeve.

Bendamustine is available in packs containing 1 or 5 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder

Accord Healthcare Ireland Limited
Euro House, Euro Business Park,
Little Island, Cork, T45 K857,
Ireland

Manufacturers

Accord Healthcare Polska Sp.z o.o.
ul. Lutomierska 50,
95-200 Pabianice
Poland

Accord Healthcare B.V.
Winthontlaan 200, 3526KV Utrecht
The Netherlands

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Name of the Member State	**Name of the medicinal product**
The Netherlands	Bendamustine Accord 25 mg/ml concentraat voor oplossing voor infusie
Austria	Bendamustine Accord 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Belgium	Bendamustine Accord 25 mg/ml, solution à diluer pour perfusion/ concentraat voor oplossing voor infusie / Konzentrat zur Herstellung einer Infusionslösung
Denmark	Bendamustinhydrochlorid Accord
Estonia	Bendamustine Accord
Finland	Bendamustine Accord 25 mg/ml infuusiokonsentraatti, liuosta varten
Germany	Bendamustine Accord 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Iceland	Bendamustine Accord 25 mg/ml innrennslisþykkni, lausn.
Latvia	Bendamustine Accord 25 mg/ml koncentrāts infūziju šķīduma pagatavošanai
Lithuania	Bendamustine Accord 25 mg/ml koncentratas infuziniam tirpalui
Norway	Bendamustine Accord
Sweden	Bendamustine Accord 25 mg/ml koncentrat till infusionsvätska, lösning.
Spain	Bendamustina Accord 25 mg/ml concentrado para solución para perfusión
Cyprus	Bendamustine Accord 25 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Greece	Bendamustine Accord 25 mg / ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Italy	Bendamustina Accord
Portugal	Bendamustine Accord 25 mg/ml concentrado para solução para perfusão
Poland	Bendamustine Accord
Bulgaria	Bendamustine Accord 25 mg/ml концентрат за инфузионен разтвор
Czech Republic	Bendamustine Accord
Hungary	Bendamustine Accord 25 mg/ml koncentrátum oldatos infúzióhoz
Romania	Bendamustină Accord 25 mg/ml concentrat pentru soluţie perfuzabilă

Slovakia	Bendamustine Accord 25 mg/ml infúzny koncentrát
Slovenia	Bendamustin Accord 25 mg/ml koncentrat za raztopino za infundiranje
Ireland	Bendamustine 25 mg/ml concentrate for solution for infusion
France	Bendamustine Accord 25 mg/ml solution à diluer pour perfusion
United Kingdom (Northern Ireland)	Bendamustine hydrochloride 25 mg/ml concentrate for solution for infusion

This leaflet was last revised in 11/2023.

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 cytotoxic waste. Please comply with national guidelines on the disposal of cytotoxic material. Pregnant staff must be excluded from working with cytotoxics.

The concentrate for solution for infusion has to be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

1. Dilution
Aseptically withdraw the volume needed for the required dose from the Bendamustine 25 mg/ml vial. Dilute the total recommended dose of Bendamustine 25 mg/ml with 0.9% sodium chloride solution to produce a final volume of about 500 ml.

While diluting the product it should be noted that the concentration (25 mg/ml) of bendamustine in Bendamustine 25 mg/ml concentrate for solution for infusion is higher than in usual bendamustine concentrates resulting from reconstitution of bendamustine powder containing medicinal products.

Bendamustine 25 mg/ml must be diluted with 0.9% NaCl solution and not with any other injectable solutions.

Dilution, as recommended, results in a clear colourless to yellowish solution, practically free from visible particles.

2. Administration
The solution is administered by intravenous infusion over 30 - 60 min.

The vials are for multiple dose use.

Product should be inspected before use. When inspected, visible particles in the solution or discolouration of solution is a sign of deterioration. Deteriorated medicinal product must not be used.

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

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.