accord

Package leaflet: Information for the user

Bendamustine 25 mg Powder for concentrate for Solution for Infusion Bendamustine 100 mg Powder for concentrate for Solution for Infusion

Bendamustine hydrochloride

The name of your medicine is **Bendamustine 25 mg Powder for concentrate for Solution for Infusion, Bendamustine 100 mg Powder for concentrate for Solution for Infusion** but in the rest of the leaflet it will be called "Bendamustine for Infusion".

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 for Infusion is and what it is used for

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

Bendamustine for Infusion 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 high-dose chemotherapy with autologous stem cell transplantation, thalidomide or bortezomib containing therapy is not appropriate for you.

2. What you need to know before you use Bendamustine for Infusion

Do not use Bendamustine for Infusion:
- if you are hypersensitive (allergic) to the active substance bendamustine hydrochloride or any of the other ingredients of this medicine (listed in section 6);
- while 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

Talk to your doctor before using Bendamustine for Infusion
- 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 for Infusion, 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 for Infusion. The 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 for Infusion. 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.

Men receiving treatment with Bendamustine for Infusion are advised not to conceive 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.

Other medicines and Bendamustine for Infusion

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

If Bendamustine for Infusion 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 for Infusion 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 for Infusion can cause genetic damage and has caused malformations in animal studies. You should not use Bendamustine for Infusion 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.

Fertility

If you are a woman of childbearing potential you must use an effective method of contraception both before and during treatment with Bendamustine for Infusion. If pregnancy occurs during your treatment with Bendamustine for Infusion you must immediately inform your doctor and should use genetic consultation.
If you are a man, you should avoid fathering a child during treatment with Bendamustine for Infusion and for up to 6 months after treatment has stopped. There is a risk that treatment with Bendamustine for Infusion will lead to infertility and you may wish to seek advice on conservation of sperm before treatment starts.

Breast-feeding

Bendamustine for Infusion must not be administered during breast-feeding. If treatment with Bendamustine for Infusion is necessary during lactation you must discontinue breast-feeding.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

No studies on the effects on the ability to drive and to use machines have been performed. Do not drive or operate machines if you experience side effects, such as dizziness or lack of coordination.

3. How to use Bendamustine for Infusion

Bendamustine for Infusion 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) have fallen to counts below 3,000 cells/ microliter and/or your blood platelets have fallen to counts below 75,000 cells/ microliter.
Your doctor will determine these values at regular intervals.

Chronic lymphocytic leukaemia

Bendamustine for Infusion 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 for Infusion 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 for Infusion 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 < 3,000/ microliter or < 75,000/ microliter, respectively. Treatment can be continued after white blood cell values have increased to > 4,000/ microliter and platelet values to > 100,000/ microliter.

Impaired liver or kidney function

Dependent on the degree of impairment of your liver function it may be necessary to adjust your dose. 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 for Infusion should be undertaken only by doctors experienced in tumour therapy. Your doctor will give you the exact dose of Bendamustine for Infusion 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 for Infusion. Duration of treatment depends on disease and response to treatment.
If you are at all worried or have any questions regarding treatment with Bendamustine for Infusion, please speak to your doctor or pharmacist.

If you forget to use Bendamustine for Infusion

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

If you stop using of Bendamustine for Infusion

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 for Infusion can cause side-effects, although not everybody gets them.

Tissue changes (due to cell injury which results in the premature death of cells) have been observed very rarely following unintentional injection into the

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The following information is intended for medical or healthcare professionals only:

As with all similar cytotoxic substances, strict 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 for Infusion (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 absorbent 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. 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

tissue outside blood vessels (extravascular). A burning sensation where the infusion needle is inserted may be a sign for administration outside the blood vessels. The consequence of administration in this way can be pain and poorly healing skin defects. The dose-limiting side-effect of Bendamustine for Infusion is impaired bone-marrow function, which usually returns to normal after treatment. Suppressed bone marrow function increases the risk of infection.

Very common (may affect more than 1 in 10 people):
- Low counts of white blood cells (leukocytopenia)
- Decrease in the red pigment of the blood (haemoglobin)
- Low counts of platelets (thrombocytopenia)
- Infections
- Feeling sick (nausea)
- Vomiting
- Mucosal inflammation
- Increased blood level of creatinine
- Increased blood level of urea
- 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)
- 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 (Aspartate transaminase) /ALT(Alanine transaminase) affecting liver function
- A rise in the enzyme alkaline phosphatase
- A rise in bile pigment (bilirubin & biliverdin)
- Low potassium blood levels
- 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

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 (myelodysplastic syndrome)
- Acute leukemia

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 (circulatory system fails to maintain the exchange of oxygen/carbon dioxide and supply of nutrients)
- 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 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)
- Anticholinergic syndrome (inhibiting the physiological action of acetylcholine, especially as a neurotransmitter)
- Neurological disorders (diseases of the brain, spine and the nerves that connect them)
- Lack of coordination (ataxia)
- Inflammation of the brain (encephalitis)
- Increased heart rate (tachycardia)
- Heart attack, chest pain (myocardial infarct)
- Heart failure
- 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 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.

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

A small number of cases of severe skin reactions (Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis) have been reported. The relationship with Bendamustine for Infusion is unclear.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Bendamustine for Infusion

Keep this medicine out of the sight and reach of children.
Do not use Bendamustine for Infusion after the expiry date which is stated on the label and the carton. The expiry date refers to the last day of that month.
This medicinal product does not require any special temperature storage conditions. Keep the container in the outer carton to protect the content from light.

Note on shelf-life after opening or preparing the solution
Solutions for infusions prepared according to the directions listed at the end of this leaflet are stable in polyethylene bags at 25ºC for 3.5 hours, and at 2ºC to 8ºC they are stable for 2 days. Bendamustine for Infusion contains no preservatives. 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.
It is the responsibility of the user to maintain aseptic conditions.
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 for Infusion contains
The active substance is bendamustine hydrochloride.
one vial contains 25 mg of bendamustine hydrochloride (as bendamustine hydrochloride monohydrate).
one vial contains 100 mg of bendamustine hydrochloride (as bendamustine hydrochloride monohydrate).
After reconstitution 1 ml of the concentrate contains 2.5 mg bendamustine hydrochloride (as bendamustine hydrochloride monohydrate).
The other ingredient is mannitol.

What Bendamustine for Infusion looks like and contents of the pack
Amber glass vials with bromobutyl rubber stopper and an aluminium flip-off cap.
Bendamustine for Infusion is available in packs containing 5, 10 and 20 vials with 25 mg of bendamustine hydrochloride and 1 and 5 vials with 100 mg of bendamustine hydrochloride.
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

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

This medicinal product is authorised in the Member States of the EEA under the following names:

Name of the Member State	Name of the medicinal product
Austria	Bendamustine Accord 2.5 mg/ml Pulver für ein Konzentrat zur Herstellung einer Infusionslösung
Denmark	Bendamustinhydrochlorid Accord
Finland	Bendamustine Accord 2.5 mg/ml kuiva-aine välikonsentraatiksi infuusionestettä varten, liuos
Ireland	Bendamustine 25 mg/100 mg Powder for concentrate for Solution for Infusion
Iceland	Bendamustine Accord 2,5 mg/ml stofn fyrir innrennslisþykkni, lausn
Norway	Bendamustine Accord
Poland	Bendamustine Accord
Spain	Bendamustina Accord 2.5 mg/ml polvo para concentrado para solución para perfusión
Slovak Republic	Bendamustine Accord 2,5 mg/ml prášok na infúzny koncentrát
Belgium	Bendamustine Accord 2,5 mg/ml Pulver für ein Konzentrat zur Herstellung einer Infusionslösung
Bulgaria	Bendamustine Accord 2,5 mg/ml Прах за концентрат за инфузионен разтвор
Cyprus	Bendamustine Accord 2.5 mg/ml
Czech Republic	Bendamustine Accord 2,5 mg/ml prášek pro koncentrát pro infuzní roztok
Germany	Bendamustine Accord 2,5 mg/ml Pulver zur Herstellung eines Infusionslösungskonzentrats
Estonia	Bendamustine Accord
Greece	Bendamustine Accord 2.5 mg/ml powder for concentrated solution for infusion
Hungary	Bendamustine Accord 2,5mg/ml por oldatos infúzióhoz való koncentrátumhoz
Italy	Bendamustina Accord
Latvia	Bendamustine Accord 2.5 mg/ml pulveris infūziju šķīduma koncentrāta pagatavošanai
Lithuania	Bendamustine Accord 2.5 mg/ml milteliai koncentratui infuziniam tirpalui
Malta	Bendamustine hydrochloride 2.5 mg/ml Powder for concentrate for solution for infusion
The Netherlands	Bendamustine Accord 2,5 mg/ml poeder voor concentraat voor oplossing voor infusie
Portugal	Bendamustine Accord 2,5 mg/ml pó para concentrado para solução para perfusão
Romania	Bendamustina Accord 2,5 mg/ml pulbere pentru concentrat pentru soluţie perfuzabilă
Slovenia	Bendamustine Accord 2,5 mg/ml prašek za koncentrat za raztopino za infundiranje
Sweden	Bendamustine Accord 2,5 mg/ml pulver till koncentrat till infusionsvätska, lösning
United Kingdom	Bendamustine hydrochloride 2.5 mg/ml Powder for concentrate for solution for infusion
France	BENDAMUSTINE ACCORD 2,5 mg/ml, poudre pour solution à diluer pour perfusion

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should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit (see section 4).
The concentrate and solution for infusion must be prepared as follows:
1. Preparation of the concentrate
- One vial of Bendamustine for Infusion containing 25 mg of bendamustine hydrochloride is first dissolved in 10 ml water for injections by shaking.
- One vial of Bendamustine for Infusion containing 100 mg of bendamustine hydrochloride is first dissolved in 40 ml water for injections by shaking.

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 for Infusion is immediately diluted with 0.9% (isotonic) saline solution to obtain a final volume of approximately 500 ml.
Bendamustine for Infusion must not be diluted with other solutions for infusion or injection.
Bendamustine for Infusion must not be mixed in an infusion with other substances.