Package leaflet: Information for the <patient> <user>
[Nationally approved name] 2.5 mg/ml powder for concentrate for solution for infusion

bendamustine hydrochloride

The name of your medicine is '[Nationally approved name] 2.5 mg/ml powder for concentrate for solution for infusion' but in the rest of the leaflet it will be called "[Nationally approved name]".

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** [Nationally approved name] **is and what it is used for**

[Nationally approved name] is a medicine which is used for the treatment of certain types of cancer (cytotoxic medicine).

[Nationally approved name] 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** [Nationally approved name]

Do not use [Nationally approved name]
- 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 [Nationally approved name] 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, <or> pharmacist < or nurse > before using [Nationally approved name]
- 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 [Nationally approved name], 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 [Nationally approved name]. 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 [Nationally approved name]. 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 [Nationally approved name]
Tell your doctor or pharmacist if you are taking/using, have recently taken/used or might take/use any other medicines.

If [Nationally approved name] 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 [Nationally approved name] is used in combination with medicines which alter you 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
[Nationally approved name] can cause genetic damage and has caused malformations in animal studies. You should not use [Nationally approved name] 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 [Nationally approved name]. If pregnancy occurs during your treatment with [Nationally approved name] you must immediately inform your doctor and should use genetic consultation.

Breast-feeding
[Nationally approved name] must not be administered during breast-feeding. If treatment with [Nationally approved name] 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 [Nationally approved name] 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 [Nationally approved name] and for up to 6 months after treatment has stopped. There is a risk that treatment with [Nationally approved name] will lead to infertility and you may wish to seek advice on conservation of sperm before treatment starts.

Driving and using machines
[Nationally approved name] 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 [Nationally approved name]

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

[Nationally approved name] 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

[Nationally approved name] 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

[Nationally approved name] 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

[Nationally approved name] 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.

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 [Nationally approved name] should be undertaken only by doctors experienced in tumour therapy. Your doctor will give you the exact dose of [Nationally approved name] 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 [Nationally approved name]. Duration of treatment depends on disease and response to treatment.

If you are at all worried or have any questions regarding treatment with [Nationally approved name], please speak to your doctor or pharmacist.

If you forget to use [Nationally approved name]
If a dose of [Nationally approved name] has been forgotten, your doctor will usually retain the normal dosage schedule.

If you stop using of [Nationally approved name]
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 FFECTS

Like all medicines, [Nationally approved name] 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 [Nationally approved name] 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 [Nationally approved name] 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 [Nationally approved name]. No clear relationship with [Nationally approved name] 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 the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store [Nationally approved name]

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

Do not use [Nationally approved name] 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. [Nationally approved name] 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 [Nationally approved name] 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 [Nationally approved name] looks like and contents of the pack
Amber glass vials with bromobutyl rubber stopper and an aluminium flip-off cap.

[Nationally approved name] 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

[To be completed nationally]

Manufacturer

Accord Healthcare Limited
Sage House,
319 Pinner Road,
North Harrow,
Middlesex HA1 4HF,
United Kingdom

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

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

<u>This medicinal product is authorised in the Member States of the EEA under the following names:</u>

[To be completed nationally]

This leaflet was last revised in MM/YYYY.

The following information is intended for medical or 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 [Nationally approved name] (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 [Nationally approved name] exclusively in water for Injections, as follows:

1. Preparation of the concentrate
   - One vial of [Nationally approved name] containing 25 mg of bendamustine hydrochloride is first dissolved in 10 ml by shaking
   - One vial of [Nationally approved name] containing 100 mg of bendamustine hydrochloride is first dissolved in 40 ml 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 [Nationally approved name] is immediately diluted with 0.9% (isotonic) saline solution to obtain a final volume of approximately 500 ml. [Nationally approved name] must not be diluted with other solutions for infusion or injection. [Nationally approved name] 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. Any unused 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 (see section 4).