Package leaflet: Information for the user

[Product name] 2.5 mg/ml 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 [Product name] is and what it is used for
2. What you need to know before you use [Product name]
3. How to use [Product name]
4. Possible side effects
5. How to store [Product name]
6. Contents of the pack and other information

1. What [Product name] 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 high-dose chemotherapy with autologous stem cell transplantation, thalidomide or bortezomib containing therapy is not appropriate for you.

Kommentiert [Mo1]: The MAH would like to keep this statement to be in line with the SmPC

2. What you need to know before you use [Product name]

DO NOT use [Product 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 [Product 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 nurse before using [Product 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 [Product 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 cases of existing **heart disease** (e.g. heart attack, chest pain, severely disturbed heart rhythms).

Talk to your doctor or nurse during use of [Product name]
- in cases of **nausea, vomiting**. Your doctor may give you a drug to reduce nausea (antiemetic).
- 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 [Product name]. Your doctor may ensure you are adequately hydrated and give you other medicines to help prevent it.
- in case of **reactions on your skin** during treatment with [Product 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 case of **severe allergic or hypersensitivity reactions**. You should pay attention to infusion reactions after your first cycle of therapy.

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).

Children and adolescents
There is no experience in children and adolescents with bendamustine hydrochloride.

Other medicines and [Product name]
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

If [Product 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 [Product name] 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 taking this medicine.

Pregnancy
[Product name] can cause genetic damage and has caused malformations in animal studies. You should not use [Product name] during pregnancy unless certainly indicated by your doctor.

Kommentiert [Mo2]: The heading is not in line with the originator but the MAH would like to keep the separated heading

Kommentiert [Mo3]: The MAH would like to keep this paragraph to be in line with the SmPC

Kommentiert [Mo4]: The MAH would like to keep this paragraph to be in line with the SmPC

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 [Product name]. If pregnancy occurs during your treatment with [Product name] you must immediately inform your doctor and should use genetic consultation.

Breast-feeding
[Product name] must not be administered during breast-feeding. If treatment with [Product name] is necessary during lactation you must discontinue breast-feeding.

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

Kommentiert [DL5]: MAH comment:
The MAH proposes to move this information to subsection "Fertility", as it is in line with the reference product "Levact 2.5 mg/ml powder for concentrate for solution for infusion" (DE/H/1250, last update 10.2017).

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.

Kommentiert [DL6]: MAH comment:
The MAH proposes to amend this information, as it is in line with the reference product "Levact 2.5 mg/ml powder for concentrate for solution for infusion" (DE/H/1250, last update 10.2017).

3. How to use [Product name]

[Product 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 platlets have fallen to counts below determined levels.

Kommentiert [DL7]: MAH comment:
The MAH proposes to add this information, as it is in line with the reference product "Levact 2.5 mg/ml powder for concentrate for solution for infusion" (DE/H/1250, last update 10.2017).

Your doctor will determine these values at regular intervals.

Chronic lymphocytic leukaemia

[Product 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	

Kommentiert [Mo8]: MAH comment:
In line with the originator but not with the SmPC section 4.2

Non-Hodgkin's lymphomas

[Product 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

[Product 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) i.v or per os.	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 [Product name] should be undertaken only by doctors experienced in tumour therapy. Your doctor will give you the exact dose of [Product 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 [Product name]. Duration of treatment depends on disease and response to treatment.
If you are at all worried or have any questions regarding treatment with [Product name], please speak to your doctor or nurse.

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

If you stop using [Product 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 medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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).

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

Kommentiert [DL9]: MAH comment:
The MAH proposes add this information, as it is in line with the reference product "Levact 2.5 mg/ml powder for concentrate for solution for infusion" (DE/H/1250, last update 10.2017).

Very common side effects (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 (thrombocytopenia)

- 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 side effects (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)
- 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
- itchy rash (urticaria)
- missed periods (amenorrhoea)
- pain
- insomnia
- chills
- dehydration
- dizziness

Uncommon side effects (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 blood cells in the bone marrow (the spongy material inside your bones where blood cells are made)
- acute leukaemia
- heart attack, chest pain (myocardial infarct)
- heart failure

Kommentiert [DL10]: MAH comment:
The MAH proposes to add this information, as it is in line with the reference product "Levact 2.5 mg/ml powder for concentrate for solution for infusion" (DE/H/1250, last update 10.2017).

Rare side effects (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 side effects (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 inflammation of the gullet (haemorrhagic oesophagitis)
- bleeding of stomach or gut
- infertility
- multiple organ failure

Not known side effects (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

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

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [to be completed nationally]. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store [Product name]

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 carton after 'EXP'. The first two digits indicate the month and the last four digits indicate the year. The expiry date refers to the last day of that month.

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 room temperature / 60 % relative humidity for 3.5 hours, and in a refrigerator they are stable for 2 days. [Product name] contains no preservatives. The solutions should not therefore be used after these lengths of time.
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 protect the environment.

6. Contents of the pack and other information

What [Product name] contains

- The active substance is bendamustine hydrochloride.
  1 vial contains 25 mg of bendamustine hydrochloride
  1 vial contains 100 mg of bendamustine hydrochloride
  After reconstitution 1 ml of the concentrate contains 2.5 mg bendamustine hydrochloride.
- The other ingredient is Mannitol.

What [Product name] looks like and contents of the pack
White to off-white freeze-dried powder in an amber glass vial with a stopper and alu-cap with flip-top.

Type I glass vials of 25 ml.
Type I glass vials of 50 ml.
[Product name] is available in packs containing 5 and 20 injection vials with 25 mg of bendamustine hydrochloride and 5 and 20 injection vials with 100 mg of bendamustine hydrochloride.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
[To be completed nationally]

Manufacturer(s):
[To be completed nationally]

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

Austria	Bendamustin STADA 2,5 mg/ml Pulver für ein Konzentrat zur Herstellung einer Infusionslösung
Denmark	Bendamustinhydrochlorid „Stada“
Poland	Bendamustine STADA, 2,5mg/ml, proszek do sporzadzania koncentratu roztworu do infuzji

This leaflet was last revised in February 2018.

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 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 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.

The solution ready for use must be prepared by dissolving the contents of an injection vial of bendamustine exclusively in water for injections, as follows:

1. Preparation of the concentrate
- One injection vial of bendamustine containing 25 mg of bendamustine hydrochloride is first dissolved in 10 ml by shaking
- One injection vial of bendamustine 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 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.