PACKAGE LEAFLET: INFORMATION FOR THE USER

BEASTİN 100 mg İ.V. powder for concentrate for solution for infusion

Aadministered intravenously

• ***Drug substance:*** 1 vial contains 100 mg of bendamustine hydrochloride. (Milliliter after reconstitution 5 mg bendamustine hydrochloride is found).

• ***Excipients:*** Mannitol.

Read all of this leaflet carefully before you start using this medicine, 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. Do not pass it on to others.*

• *When using this medicine, tell the doctor or your doctor if you go to the hospital that you are using this medicine.*

• *We sleep exactly as written in this instruction. Do not use **high or low doses** other than the recommended dose for the medication.*

What is in this leaflet:

1. What Beastin is and what it is used for?

BEASTİN is a vial which contains 100 mg of an active ingredient called bendamustine hydrochloride.

It was presented to the market in 1 vial of 20R volume packs containing white lyophilized powder.

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

BEASTİN is used alone (monotherapy) or in combination with other medicines for the treatment of the following forms of cancer:

• Chronic lymphocytic leukemia disease

• Monotherapy during combination therapy with rituximab or rituximab, or indolent lymphomas with progression in the first 6 months,
• In second line treatment of multiple myeloma cases unfit for first-line treatment or unresponsive for recurrent autologous stem cell transplantation

2. Things to pay attention before using Beastin

Do not use Beastin in the following situations

- If you are allergic to bendamustine hydrochloride or any of the other ingredients of this medicine,

- While breast-feeding,

- If you have severe liver dysfunction,

- 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 (cells in blood coagulation) in the blood (white blood cell and / or platelet counts fall below <3000 / microL or <75000 / microL, respectively)

- 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.

Use Beastin caution in the following situations

- 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 Beastin, 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 Beastin. The skin reactions may increase in severity.

- 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 Beastin. 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.

- Your doctor may give you antiemetic (nausea) to treat nausea and vomiting.

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

Women of childbearing potential you must use an effective method of contraception both before and during treatment with Beastin.

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.

Use of BEASTIN with food and beverage

Due to the way of application, there is no problem in taking food.

Pregnancy

Consult your doctor or pharmacist before using this medicine.

Beastin can cause genetic damage and has caused malformations in animal studies. You should not use Beastin 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 Beastin. If pregnancy occurs during your treatment with Beastin 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 Beastin and for up to 6 months after treatment has stopped. There is a risk that treatment with Beastin will lead to infertility and you may wish to seek advice on conservation of sperm before treatment starts.

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

Breast-feeding

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

Consult your doctor or pharmacist before using this 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.

Important information about some *excipient* contained in BEASTIN

BEASTIN contains 170 mg of mannitol per vial. However, no warning is required with the reason for the implementation path.

Use with other medicines

- If Beastin 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 Beastin 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).

Please inform your doctor or pharmacist if you are using or have recently used any medicine with or without a prescription.

3. How to use BEASTIN
Instructions for proper use and dose / application frequency:

BEASTIN is administered alone (monotherapy) or in combination with other medicines at doses calculated according to body surface area (determined according to throat and kiln).

Treatment should not be started if your white blood cells (leukocytes <3000 cell/mikroL) and platelets (<75000 cell/mikroL) have fallen to counts below determined levels.

Your doctor will determine these values at regular intervals.

Chronic lymphocytic leukemia (a kind of blood cancer)

BEASTIN is repeated up to 6 treatments at a dose of 70 mg per square meter of body surface area per square meter of body surface area per square meter of body weight, if followed in subsequent courses.

Chronic lymphocytic leukemia with recurrent or non-responsive treatment

BEASTİN first cure is applied at a dose of 70 mg per square meter body surface area, followed by 90 mg per square meter body surface area in subsequent courses.

In combination with rituximab in the initial treatment of advanced follicular lymphoma

BEASTIN is applied on a 1st and 2nd day every 28 days in a dose of 90 mg per square meter of body surface area.

In the second line treatment of multiple myeloma

BEASTIN is used alone or in combination on days 1 and 2 every 4 weeks with a maximum dose of 100 mg per square meter body surface area.

If the number of white blood cells and thrombocytes falls in the order of <3000 / microL and <75000 / microL, treatment is stopped. If the number of white blood cells is> 4000 / microL and the platelet count is> 100000 / microL, treatment can be continued.

Administration route and method:

BEASTIN is administered at various doses in a vein for 30-60 minutes.

Treatment with BEASTIN should be done under the supervision of a doctor who specializes in tumor treatment.

Your doctor will give you the required dose of BEASTIN and take the necessary precautions.

The prescription dose of infusion solution will be administered by a qualified healthcare professional.

Application time:

There is no definite overall time limit for BACSTIN treatment. The duration of treatment depends on the disease and the treatment received.

If you have any concerns or questions about your BEAST treatment, contact your physician.

Different age groups:

Use in children: There is no information about the use of BEASTIN in children.

Elderly use: There is no data on elderly patients requiring dosage adjustment

Special use cases

Impaired liver or kidney function

Dependent on the degree of impairment of your liver function it may be necessary to decrease your Beastin dose (by 30% in case of moderate liver dysfunction).

Your attending doctor will decide whether a dosage adjustment is necessary.

Unless your doctor recommends otherwise follow these instructions.

Do not forget to take your medicine on time.

If you have an impression that the BEASTIN effect is too strong or too weak, talk to your doctor or pharmacist.

If you use more BEAST than you need:

If you have used too much BEASTIN , talk to a doctor or pharmacist.

If you forget to use BEASTIN:

Do not take double doses to compensate for forgotten doses.

If the BEASTIN application is skipped, your doctor will usually resume the normal practice schedule.

The effects that may occur when treatment with BEASTIN is terminated:

Your treating doctor will decide whether treatment should be discontinued or if another treatment should be undertaken.

Consult your doctor or pharmacist for further questions.

4. Possible Side Effects?

As with all medicines, there may be side effects in people sensitive to substances in the BEASTIN content.

The following definitions of frequency are used when assessing side-effects:

Very common: affects more than 1 user in 10

Common: affects 1 to 10 users in 100

Uncommon: affects 1 to 10 users in 1,000

Rare: affects 1 to 10 users in 10,000

Very rare: affects less than 1 user in 10,000

Not known: frequency cannot be estimated from the available data

Tissue decay (necrosis) has been observed very rarely following leakage of Beastin 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 Beastin is impaired bone-marrow function, which usually returns to normal after treatment. Suppressed bone marrow function may lead to low blood cells, which in turn may lead to an increased risk of infection, anemia or a heightened risk of bleeding.

<u>Very common:</u>

• Low counts of white blood cells (diseasefighting 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

Common:

• 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

• Missed periods (amenorrhoea)

• Pain

• Insomnia

• Chills

• Dehydration

Uncommon:

• Accumulation of fluid in the heart sac (escape of fluid into the pericardial space)

Rare:

• 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 (sudden collapse in circulation)

• Reddening of the skin (erythema)

• Inflammation of the skin (dermatitis)

• Itching (pruritus)

• Skin rash (macular exanthema)

• Excessive sweating (hyperhidrosis)

Very rare:

• 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)

• Nervous system disease (anticholinergic syndrome)

• Disorders of the nervous system

• Coordination loss (ataxia)

• Inflammation of the brain (encephalitis)

• Increased heart rate (tachycardia)

• Heart attack, chest pain (myocardial infarction)

• 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

There have been reports of secondary tumors (myelodysplastic syndrome, acute myeloid leukemia, bronchial carcinoma) following treatment with bendamustine hydrochloride. There was no definite relationship with bendamustine hydrochloride.

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

if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Reporting side effects

If you have any side effects, talk to your doctor, pharmacist or nurse. In addition, you can notified side effects to "Drug Side Impact Statement" located in the by clicking on www.titck.gov.tr the icon directly to Türkiye Farmakovijilans Merkezi (TÜFAM), and you can use the number 2 side impact statement line. By reporting side effects, you will contribute to learning more about the safety of the medicine you are using.

5. How To Store Beastin:

Keep the BEASTIN in its place and on its packaging where children can not, can not reach. Store at room temperature below 25 ° C to protect from light.

Use in accordance with expiration dates.

Do not use BEASTIN after the expiration date on the package / card / bottle.

Do not use BEASTIN if you notice any defects in the product and / or package

Note on shelf-life after opening or preparing the solution

This should be used within the specified periods of time as diluted as described at the end of the instructions for use and stored in specified storage conditions after dilution. The solution obtained in 5 minutes with water for injection should be immediately diluted with 0.9% NaCl. The diluted infusion solution is stable for 3.5 hours at room temperature not exceeding 25 ° C and for 2 days at 2-8 ° C (refrigerator). it must be implemented immediately before this time expires. BEASTIN does not contain preservatives. For this reason, the solution should not be used after the specified time.

BEASTIN should be stored under aseptic conditions after dilution.

This product is for single use only.

The product used should not be disposed of in wastewater or household waste.

Marketing Authorisation Holder:

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THE FOLLOWING INFORMATION THAT THE LEGACY WILL BE IMPLEMENTED IN HEALTH PERSONNEL

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 Beastin (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.

BEASTIN should be dissolved in water for injection and prepared as follows:

1. Concentrate is prepared:

- Add 20 mL of sterile water for injections into 100 mg of BEASTIN and dissolve with stirring. This results in a clear, colorless-pale yellow solution of 5 mg / ml bendamustine in HCl. The lyophilized powder is completely dissolved in 5 minutes. Diluted solution should not be used if particulate matter is observed.

2. Preparation of infusion solution

- A sufficient volume of the solution (relative to the concentration of 5 mg / ml) is taken aseptically for the required dose and 500 ml of 0.9% sodium chloride is transferred to the infusion solution immediately. The reconstituted solution should be immediately transferred to the infusion bag after reconstitution. After transfer, the contents in the infusion bag are thoroughly mixed. The mixture should be clear and colorless-pale yellow solution. BEASTIN should not be diluted with other infusion or injection solutions and should not be mixed with other medicines.