Package leaflet: Information for the user

Bortezomib Krka 1 mg

powder for solution for injection

bortezomib

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 or nurse.
- If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Bortezomib Krka is and what it is used for

Bortezomib Krka contains the active substance bortezomib, a so-called 'proteasome inhibitor'. Proteasomes play an important role in controlling cell function and growth. By interfering with their function, bortezomib can kill cancer cells.

Bortezomib Krka is used for the treatment of multiple myeloma (a cancer of the bone marrow) in patients older than 18 years:
- alone or together with the medicines pegylated liposomal doxorubicin or dexamethasone, for patients whose disease is worsening (progressive) after receiving at least one prior treatment and for whom blood stem cell transplantation was not successful or is unsuitable.
- in combination with the medicines melphalan and prednisone, for patients whose disease has not been previously treated and are unsuitable for high-dose chemotherapy with blood stem cell transplantation.
- in combination with the medicines dexamethasone or dexamethasone together with thalidomide, for patients whose disease has not been previously treated and before receiving high-dose chemotherapy with blood stem cell transplantation (induction treatment).

Bortezomib Krka is used for the treatment of mantle cell lymphoma (a type of cancer affecting the lymph nodes) in patients 18 years or older in combination with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone, for patients whose disease has not been previously treated and for whom blood stem cell transplantation is unsuitable.

2. What you need to know before you use Bortezomib Krka

Do not use Bortezomib Krka:
- if you are allergic to bortezomib, to boron or any of the other ingredients of this medicine (listed in section 6).
- if you have certain severe lung or heart problems.

Warnings and precautions

You should tell your doctor if you have any of the following:
- low numbers of red or white blood cells
- bleeding problems and/or low number of platelets in your blood
- diarrhoea, constipation, nausea or vomiting
- fainting, dizziness or light-headedness in the past
- kidney problems
- moderate to severe liver problems
- numbness, tingling, or pain in the hands or feet (neuropathy) in the past
- heart or blood pressure problems
- shortness of breath or cough
- seizures
- shingles (localised including around the eyes or spread across the body)
- symptoms of tumor lysis syndrome such as muscle cramping, muscle weakness, confusion, visual loss or disturbances and shortness of breath
- memory loss, trouble thinking, difficulty with walking or loss of vision. These may be signs of a serious brain infection and your doctor may suggest further testing and follow-up.

You will have to take regular blood tests before and during your treatment with Bortezomib Krka, to check your blood cell counts regularly.

If you have mantle cell lymphoma and are given the medicine rituximab with Bortezomib Krka you should tell your doctor:
- if you think you have hepatitis infection now or have had it in the past. In a few cases, patients who have had hepatitis B might have a repeated attack of hepatitis, which can be fatal. If you have a history of hepatitis B infection you will be carefully checked by your doctor for signs of active hepatitis B.

You must read the package leaflets of all medicinal products to be taken in combination with Bortezomib Krka for information related to these medicines before starting treatment with Bortezomib Krka. When thalidomide is used, particular attention to pregnancy testing and prevention requirements is needed (see Pregnancy and breast-feeding in this section).

Children and adolescents

Bortezomib Krka should not be used in children and adolescents because it is not known how the medicine will affect them.

Other medicines and Bortezomib Krka

Please tell your doctor, or pharmacist if you are taking, have recently taken or might take any other medicines.
In particular, tell your doctor if you are using medicines containing any of the following active substances:
- ketoconazole, used to treat fungal infections
- ritonavir, used to treat HIV infection
- rifampicin, an antibiotic used to treat bacterial infections
- carbamazepine, phenytoin or phenobarbital used to treat epilepsy
- St. John's Wort (*Hypericum perforatum*), used for depression or other conditions
- oral antidiabetics

Pregnancy and breast-feeding

You should not use Bortezomib Krka if you are pregnant, unless clearly necessary.

Both men and women receiving Bortezomib Krka must use effective contraception during and for up to 3 months after treatment. If, despite these measures, pregnancy occurs, tell your doctor immediately.

You should not breast-feed while using Bortezomib Krka. Discuss with your doctor when it is safe to restart breast-feeding after finishing your treatment.

Thalidomide causes birth defects and foetal death. When Bortezomib Krka is given in combination with thalidomide you must follow the pregnancy prevention programme for thalidomide (see package leaflet for thalidomide).

Driving and using machines

Bortezomib Krka might cause tiredness, dizziness, fainting, or blurred vision. Do not drive or operate tools or machines if you experience such side effects; even if you do not, you should still be cautious.

3. How to use Bortezomib Krka

Your doctor will work out your dose of Bortezomib Krka according to your height and weight (body surface area). The usual starting dose of Bortezomib Krka is 1.3 mg/m^2 body surface area twice a week.
Your doctor may change the dose and total number of treatment cycles, depending on your response to the treatment on the occurrence of certain side effects and on your underlying conditions (e.g. liver problems).

Progressive multiple myeloma

When Bortezomib Krka is given alone, you will receive 4 doses of Bortezomib Krka intravenously on days 1, 4, 8 and 11, followed by a 10-day 'rest period' without treatment. This 21-day period (3 weeks) corresponds to one treatment cycle. You might receive up to 8 cycles (24 weeks).

You may also be given Bortezomib Krka together with the medicines pegylated liposomal doxorubicin or dexamethasone.

When Bortezomib Krka is given together with pegylated liposomal doxorubicin, you will receive Bortezomib Krka intravenously as a 21-day treatment cycle and pegylated liposomal doxorubicin 30 mg/m^2 is given on day 4 of the Bortezomib Krka 21-day treatment cycle as an intravenous infusion after the Bortezomib Krka injection.
You might receive up to 8 cycles (24 weeks).

When Bortezomib Krka is given together with dexamethasone, you will receive Bortezomib Krka intravenously as a 21-day treatment cycle and dexamethasone 20 mg is given orally on days 1, 2, 4, 5, 8, 9, 11, and 12, of the Bortezomib Krka, 21-day treatment cycle.
You might receive up to 8 cycles (24 weeks).

Previously untreated multiple myeloma

If you have not been treated before for multiple myeloma, and **you are not** suitable for blood stem cell transplantation you will receive Bortezomib Krka intravenously together with two other medicines; melphalan and prednisone.
In this case, the duration of a treatment cycle is 42 days (6 weeks). You will receive 9 cycles (54 weeks).
- In cycles 1 to 4, Bortezomib Krka is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.
- In cycles 5 to 9, Bortezomib Krka is administered once weekly on days 1, 8, 22 and 29.

Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) are both given orally on days 1, 2, 3 and 4 of the first week of each cycle.

If you have not been treated before for multiple myeloma, and **you are** suitable for blood stem cell transplantation you will receive Bortezomib Krka intravenously together with the medicines dexamethasone, or dexamethasone and thalidomide, as induction treatment.

When Bortezomib Krka is given together with dexamethasone, you will receive Bortezomib Krka intravenously as a 21-day treatment cycle and dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the Bortezomib Krka 21-day treatment cycle. You will receive 4 cycles (12 weeks).

When Bortezomib Krka is given together with thalidomide and dexamethasone, the duration of a treatment cycle is 28 days (4 weeks). Dexamethasone 40 mg is given orally on days 1, 2, 3, 4, 8, 9, 10 and 11 of the Bortezomib Krka 28-day treatment cycle and thalidomide is given orally daily at 50 mg up to day 14 of the first cycle, and if tolerated the thalidomide dose is increased to 100 mg on days 15-28 and may be further increased to 200 mg daily from the second cycle onwards. You might receive up to 6 cycles (24 weeks).

Previously untreated mantle cell lymphoma

If you have not been treated before for mantle cell lymphoma you will receive Bortezomib Krka intravenously together with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone. Bortezomib Krka is given intravenously on days 1, 4, 8 and 11, followed by a 'rest period' without treatment. The duration of a treatment cycle is 21 days (3 weeks). You might receive up to 8 cycles (24 weeks).
The following medicinal products are given on day 1 of each Bortezomib Krka 21-day treatment cycle as intravenous infusions:
Rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2 and doxorubicin at 50 mg/m^2.
Prednisone is given orally at 100 mg/m^2 on days 1, 2, 3, 4 and 5 of the Bortezomib Krka treatment cycle.

How Bortezomib Krka is given

This medicine is for intravenous use only. Bortezomib Krka will be administered by a health care professional experienced in the use of cytotoxic medicines.

Bortezomib Krka powder has to be dissolved before administration. This will be done by a healthcare professional. The resulting solution is then injected into a vein rapidly, over 3 to 5 seconds.

If you are given too much Bortezomib Krka

As this medicine is being given by your doctor or nurse, it is unlikely that you will be given too much. In the unlikely event of an overdose, your doctor will monitor you for side effects.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Some of these effects may be serious.

If you are given Bortezomib Krka for multiple myeloma or mantle cell lymphoma, tell your doctor straight away if you notice any of the following symptoms:
- muscle cramping, muscle weakness
- confusion, visual loss or disturbances, blindness, seizures, headaches
- shortness of breath, swelling of your feet or changes in your heart beat, high blood pressure, tiredness, fainting
- coughing and breathing difficulties or tightness in the chest.

Treatment with Bortezomib Krka can very commonly cause a decrease in the numbers of red and white blood cells and platelets in your blood. Therefore, you will have to take regular blood tests before and during your treatment with Bortezomib Krka, to check your blood cell counts regularly.
You may experience a reduction in the number of:
- platelets, which may make you be more prone to bruising, or to bleeding without obvious injury (e.g., bleeding from your bowels, stomach, mouth and gum or bleeding in the brain or bleeding from the liver)
- red blood cells, which can cause anaemia, with symptoms such as tiredness and paleness
- white blood cells may make you more prone to infections or flu-like symptoms.

If you are given Bortezomib Krka for the treatment of multiple myeloma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Reduction in the number of red blood cells and or white blood cells (see above)
- Fever
- Feeling sick (nausea) or vomiting, loss of appetite
- Constipation with or without bloating (can be severe)
- Diarrhoea: if this happens, it is important that you drink more water than usual. Your doctor may give you another medicine to control diarrhoea
- Tiredness (fatigue), feeling weak
- Muscle pain, bone pain

Common side effects (may affect up to 1 in 10 people)
- Low blood pressure, sudden fall of blood pressure on standing which may lead to fainting
- High blood pressure
- Reduced functioning of your kidneys
- Headache
- General ill feeling, pain, vertigo, light-headedness, a feeling of weakness or loss of consciousness
- Shivering
- Infections, including pneumonia, respiratory infections, bronchitis, fungal infections, coughing with phlegm, flu like illness
- Shingles (localised including around the eyes or spread across the body)
- Chest pains or shortness of breath with exercise
- Different types of rash
- Itching of the skin, lumps on the skin or dry skin
- Facial blushing or tiny broken capillaries
- Redness of the skin
- Dehydration
- Heartburn, bloating, belching, wind, stomach pain, bleeding from your bowels or stomach
- Alteration of liver functioning
- A sore mouth or lip, dry mouth, mouth ulcers or throat pain
- Weight loss, loss of taste
- Muscle cramps, muscle spasms, muscle weakness, pain in your limbs
- Blurred vision
- Infection of the outermost layer of the eye and the inner surface of the eyelids (conjunctivitis)
- Nose bleeds
- Difficulty or problems in sleeping, sweating, anxiety, mood swings, depressed mood, restlessness or agitation, changes in your mental status, disorientation
- Swelling of body, to include around eyes and other parts of the body

Uncommon side effects (may affect up to 1 in 100 people)
- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- Failing of your kidneys
- Inflammation of a vein, blood clots in your veins and lungs
- Problems with blood clotting
- Insufficient circulation
- Inflammation of the lining around your heart or fluid around your heart
- Infections including urinary tract infections, the flu, herpes virus infections, ear infection and cellulitis
- Bloody stools, or bleeding from mucosal membranes, e.g., mouth, vagina
- Cerebrovascular disorders
- Paralysis, seizures, falling, movement disorders, abnormal or change in, or reduced sensation
- (feeling, hearing, tasting, smelling), attention disturbance, trembling, twitching
- Arthritis, including inflammation of the joints in the fingers, toes, and the jaw
- Disorders that affect your lungs, preventing your body from getting enough oxygen. Some of these include difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing
- Hiccups, speech disorders
- Increased or decreased urine production (due to kidney damage), painful passing of urine or blood/proteins in the urine, fluid retention
- Altered levels of consciousness, confusion, memory impairment or loss
- Hypersensitivity
- Hearing loss, deafness or ringing in the ears, ear discomfort
- Hormone abnormality which may affect salt and water absorption
- Overactive thyroid gland
- Inability to produce enough insulin or resistance to normal levels of insulin
- Irritated or inflamed eyes, excessively wet eyes, painful eyes, dry eyes, eye infections, lump in the eyelid (chalazion) and red and swollen eyelids, discharge from the eyes, abnormal vision, bleeding of the eye
- Swelling of your lymph glands
- Joint or muscle stiffness, sense of heaviness, pain in your groin
- Hair loss and abnormal hair texture
- Allergic reactions
- Redness or pain at the injection site
- Mouth pain
- Infections or inflammation of the mouth, mouth ulcers, oesophagus, stomach and intestines, sometimes associated with pain or bleeding, poor movement of the intestines (including blockage), abdominal or oesophageal discomfort, difficulty swallowing, vomiting of blood
- Skin infections
- Bacterial and viral infections
- Tooth infection
- Inflammation of the pancreas, obstruction of the bile duct
- Genital pain, problem having an erection
- Weight increase
- Thirst
- Hepatitis
- Injection site or injection device related disorders
- Skin reactions and disorders (which may be severe and life threatening), skin ulcers
- Bruises, falls and injuries
- Inflammation or haemorrhage of the blood vessels that can appear as small red or purple dots (usually on the legs) to large bruise-like patches under the skin or tissue
- Benign cysts
- A severe reversible brain condition which includes seizures, high blood pressure, headaches, tiredness, confusion, blindness or other vision problems.

Rare side effects (may affect up to 1 in 1,000 people)
- Heart problems to include heart attack, angina
- Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome)
- Flushing
- Discoloration of the veins
- Inflammation of the spinal nerve
- Problems with your ear, bleeding from your ear
- Underactivity of your thyroid gland
- Budd–Chiari syndrome (the clinical symptoms caused by blockage of the hepatic veins)
- Changes in or abnormal bowel function
- Bleeding in the brain
- Yellow discolouration of eyes and skin (jaundice)
- Serious allergic reaction (anaphylactic shock) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Breast disorders
- Vaginal tears
- Genital swelling
- Inability to tolerate alcohol consumption
- Wasting, or loss of body mass
- Increased appetite
- Fistula
- Joint effusion
- Cysts in the lining of joints (synovial cysts)
- Fracture
- Breakdown of muscle fibers leading to other complications
- Swelling of the liver, bleeding from the liver
- Cancer of the kidney
- Psoriasis like skin condition
- Cancer of the skin
- Paleness of the skin
- Increase of platelets or plasma cells (a type of white cell) in the blood
- Blood clot in small blood vessels (thrombotic microangiopathy)
- Abnormal reaction to blood transfusions
- Partial or total loss of vision
- Decreased sex drive
- Drooling
- Bulging eyes
- Sensitivity to light
- Rapid breathing
- Rectal pain
- Gallstones
- Hernia
- Injuries
- Brittle or weak nails
- Abnormal protein deposits in your vital organs
- Coma
- Intestinal ulcers
- Multi-organ failure
- Death

If you are given Bortezomib Krka together with other medicines for the treatment of mantle cell lymphoma the side effects you may get are listed below:

Very common side effects (may affect more than 1 in 10 people)
- Pneumonia
- Loss of appetite
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage
- Nausea and vomiting
- Diarrhoea
- Mouth ulcers
- Constipation
- Muscle pain, bone pain
- Hair loss and abnormal hair texture
- Tiredness, feeling weak
- Fever

Common side effects (may affect up to 1 in 10 people)
- Shingles (localized including around the eyes or spread across the body)
- Herpes virus infections
- Bacterial and viral infections
- Respiratory infections, bronchitis, coughing with phlegm, flu like illness
- Fungal infections
- Hypersensitivity (allergic reaction)
- Inability to produce enough insulin or resistance to normal levels of insulin
- Fluid retention
- Difficulty or problems in sleeping
- Loss of consciousness
- Altered level of consciousness, confusion
- Feeling dizzy
- Increased heartbeat, high blood pressure, sweating,
- Abnormal vision, blurred vision
- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- High or low blood pressure
- Sudden fall of blood pressure upon standing which may lead to fainting
- Shortness of breath with exercise
- Cough
- Hiccups
- Ringing in the ears, ear discomfort
- Bleeding from your bowels or stomach
- Heartburn
- Stomach pain, bloating
- Difficulty swallowing
- Infection or inflammation of the stomach and intestines
- Stomach pain
- Sore mouth or lip, throat pain
- Alteration of liver function
- Itching of skin
- Redness of skin
- Rash
- Muscle spasms
- Infection of the urinary tract
- Pain in limbs
- Swelling of body, to include eyes and other parts of the body
- Shivering
- Redness and pain at injection site
- General ill feeling
- Weight loss
- Weight increase

Uncommon side effects (may affect up to 1 in 100 people)
- Hepatitis
- Severe allergic reaction (anaphylactic reaction) signs of which may include difficulty breathing, chest pain or chest tightness, and/or feeling dizzy/faint, severe itching of the skin or raised lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Movement disorders, paralysis, twitching
- Vertigo
- Hearing loss, deafness
- Disorders that affect your lungs, preventing your body from getting enough oxygen. Some of these include difficulty breathing, shortness of breath, shortness of breath without exercise, breathing that becomes shallow, difficult or stops, wheezing
- Blood clots in your lungs
- Yellow discoloration of the eyes and skin (jaundice)
- Lump in the eyelid (chalazion), red and swollen eyelids

Rare side effects (may affect up to 1 in 1,000 people)
- Blood clot in small blood vessels (thrombotic microangiopathy)
- Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome)

Reporting of side effects

If you get any side effects, talk to your doctor or 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.

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KRKA

Article name.: PL Bortezomib Krka powd 1 mg IE
Prepared by: D. Primc
Date: 25.02.2021

5. How to store Bortezomib Krka

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

Do not store above 30°C.
Keep the vial in the outer carton in order to protect from light.

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25°C stored in the original vial.
From a microbiological point of view, unless the method of opening/ reconstitution precludes the risk of microbial contamination, the product should be used immediately.
If not used immediately, in-use storage times and conditions are the responsibility of the user.
The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration.

Do not use this medicine if you notice that vial is damaged.

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 Bortezomib Krka contains
- The active substance is bortezomib. Each vial contains 1 mg bortezomib (as mannitol boronic ester).
- The other ingredients are mannitol (E421) and nitrogen.

What Bortezomib Krka looks like and contents of the pack
Bortezomib Krka powder for solution for injection (powder for injection) is a white to off white cake or powder.

Type I glass 5 ml vial with a grey bromobutyl rubber stopper and an aluminium plastic cap with green plastic flip off part, containing 1 mg bortezomib.

Bortezomib Krka is available in packs containing 1, 5 or 10 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

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

Austria	Bortezomib HCS
Bulgaria	Бортезомиб Крка
Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Lihtuania, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom	Bortezomib Krka

This leaflet was last revised in

The following information is intended for healthcare professionals only:

Bortezomib Krka 1 mg powder for solution for injection

1. RECONSTITUTION FOR INTRAVENOUS INJECTION

Note: Bortezomib Krka is a cytotoxic agent. Therefore, caution should be used during handling and preparation. Use of gloves and other protective clothing to prevent skin contact is recommended.

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF Bortezomib Krka SINCE NO PRESERVATIVE IS PRESENT.

1.1 **Preparation of the 1 mg vial: carefully add 1.0 ml** of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the Bortezomib Krka powder by using a 1 ml syringe without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

The concentration of the resulting solution will be 1 mg/ml. The solution will be clear and colourless, with a final pH of 4 to 7. You do not need to check the pH of the solution.

1.2 Before administration, visually inspect the solution for particulate matter and discolouration. If any discolouration or particulate matter is observed, the solution should be discarded. Confirm concentration on vial to ensure that the correct dose is being given for the intravenous route of administration (1 mg/ml).

1.3 The reconstituted solution is preservative free and should be used immediately after preparation. However, the chemical and physical in-use stability has been demonstrated for 8 hours at 25°C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

It is not necessary to protect the reconstituted medicinal product from light.

2. ADMINISTRATION
- Once dissolved, withdraw the appropriate amount of the reconstituted solution according to calculated dose based upon the patient´s Body Surface Area.
- Confirm the dose and concentration in the syringe prior to use (check that the syringe is marked as intravenous administration).
- Inject the solution as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter into a vein.
- Flush the peripheral or intravenous catheter with sterile, 9 mg/ml (0.9%) sodium chloride solution.

Bortezomib Krka 1 mg powder for solution for injection IS FOR INTRAVENOUS USE ONLY. Do not give by other routes. Intrathecal administration has resulted in death.

3. DISPOSAL
A vial is for single use only and the remaining solution must be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.