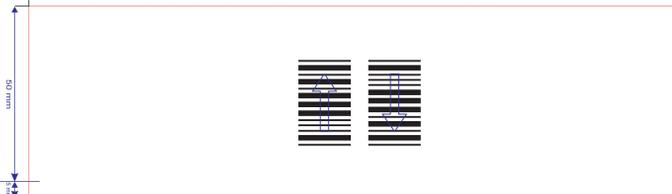


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Front Page

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Package leaflet: Information for the user Bortezomib 3.5 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.
- If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Bortezomib is and what it is used for
2. What you need to know before you use Bortezomib
3. How to use Bortezomib
4. Possible side effects
5. How to store Bortezomib
6. Contents of the pack and other information

1. What Bortezomib is and what it is used for

Bortezomib powder 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 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 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

Do not use Bortezomib

- if you are allergic to bortezomib, boron or to 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, to check your blood cell counts regularly.

If you have mantle cell lymphoma and are given the medicine rituximab with bortezomib 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 for information related to these medicines before starting treatment with bortezomib. 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 should not be used in children and adolescents because it is not known how the medicine will affect them.

Other medicines and Bortezomib

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 if you are pregnant, unless clearly necessary.

Both men and women receiving bortezomib 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. Discuss with your doctor when it is safe to restart breast-feeding after finishing your treatment.

Thalidomide causes birth defects and fetal death. When bortezomib 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 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

Your doctor will work out your dose of bortezomib according to your height and weight (body surface area). The usual starting dose of bortezomib is 1.3 mg/m² 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 is given alone, you will receive 4 doses of bortezomib intravenously or subcutaneously 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 together with the medicines pegylated liposomal doxorubicin or dexamethasone.

When bortezomib is given together with pegylated liposomal doxorubicin, you will receive bortezomib intravenously or subcutaneously as a 21-day treatment cycle and pegylated liposomal doxorubicin 30 mg/m² is given on day 4 of the bortezomib 21-day treatment cycle as an intravenous infusion after the bortezomib injection. You might receive up to 8 cycles (24 weeks).

When bortezomib is given together with dexamethasone, you will receive bortezomib intravenously or subcutaneously 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 21-day treatment cycle. You might receive up to 8 cycles (24 weeks).

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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 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 is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.
- In cycles 5 to 9, bortezomib is administered once weekly on days 1, 8, 22 and 29.

Melphalan (9 mg/m²) and prednisone (60 mg/m²) 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 intravenously or subcutaneously together with the medicines dexamethasone, or dexamethasone and thalidomide, as induction treatment.

When bortezomib is given together with dexamethasone, you will receive bortezomib intravenously or subcutaneously 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 21-day treatment cycle. You will receive 4 cycles (12 weeks).

When bortezomib 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 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 15-20 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 intravenously or subcutaneously together with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone.

Bortezomib is given intravenously or subcutaneously 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 21-day treatment cycle as intravenous infusions: Rituximab at 375 mg/m², cyclophosphamide at 750 mg/m² and doxorubicin at 50 mg/m².

Prednisone is given orally at 100 mg/m² on days 1, 2, 3, 4 and 5 of the bortezomib treatment cycle.

How Bortezomib is given

This medicine is for intravenous or subcutaneous use. Bortezomib will be administered by a healthcare professional experienced in the use of cytotoxic medicines.

Bortezomib powder has to be dissolved before administration. This will be done by a healthcare professional. The resulting solution is then either injected into a vein or under the skin. Injection into a vein is rapid, taking 3 to 5 seconds. Injection under the skin is in either the thighs or the abdomen.

If you are given too much Bortezomib

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 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 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, 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 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 kidney
- 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 flushing 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)
- falling of your kidneys
- 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
- inflammation of a vein, blood clots in your veins and lungs
- problems with blood clotting

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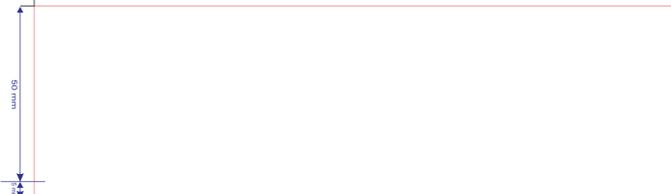
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insufficient circulation

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

hiccup, 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 bloating, abdominal or oesophageal discomfort, difficulty swallowing, vomiting of food)

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

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 discoloration 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

distal

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 liver

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

drooping

bulging eyes

sensitivity to light

rapid breathing

rectal pain

gallstones