Package leaflet: Information for the patient

Pfizer Bortezomib®
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, pharmacist or nurse.
- 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 nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

What Pfizer Bortezomib is
Pfizer Bortezomib contains the active substance bortezomib, also called 'proteasome inhibitor'.

How Pfizer Bortezomib works
Proteasomes play an important role in controlling cell function and growth. By interfering with their function, bortezomib can kill cancer cells.

What Pfizer Bortezomib is used for
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 Pfizer Bortezomib

Do not use Pfizer 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 severe lung or heart problems.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Pfizer Bortezomib, if you have any of the following:

- bleeding problems and/or low number of platelets in your blood
- the presence of abnormally few neutrophils in the blood, leading to increased susceptibility to infection
- deficiency of red cells or of haemoglobin in the blood
- diarrhoea, constipation, nausea or vomiting
- kidney problems
- moderate to severe liver problems
- numbness, tingling, or pain in the hands or feet (neuropathy) in the past
- existing heart disease
- 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
- normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycaemics
- 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 Pfizer 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 Pfizer Bortezomib for information related to these medicines before starting treatment with Pfizer 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 Pfizer Bortezomib
Tell your doctor or pharmacist if you are using/taking, have recently used/taken or might use/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
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

You should not use bortezomib if you are pregnant, no clinical data are available for bortezomib with regard to exposure during pregnancy. The effect of bortezomib on development of the embryo or fetus has not been fully investigated.

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.

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

It is not known whether bortezomib is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants, breast-feeding should be discontinued during treatment with Pfizer Bortezomib.

Driving and using machines
Bortezomib might cause tiredness, dizziness, temporary loss of consciousness caused by a fall in blood pressure, 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 Pfizer 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/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 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/m^2 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).

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 intravenously or subcutaneously 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/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 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 15-28 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 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/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 treatment cycle.

How Pfizer Bortezomib is given
This medicine is for intravenous or subcutaneous use only. Bortezomib will be administered by a health care 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 Pfizer 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.

Use in children and adolescents
The safety and efficacy of Bortezomib in children below 18 years of age have not been established.

If you use more Pfizer Bortezomib than you should
If you think you have used too much Pfizer Bortezomib, talk to your doctor or nurse straight away. Overdose more than twice the recommended dose has been associated with the decrease in blood pressure and deficiency of platelets in the blood with fatal outcomes In case if you think you have used too much Pfizer Bortezomib, the patient's vital signs should be monitored and appropriate supportive care (such as fluids, pressors, and/or inotropic agents) should be given to maintain blood pressure and body temperature.

If you forget to use Pfizer Bortezomib
Do not take a double dose to make up for a forgotten dose.

If you stop using Pfizer Bortezomib
If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

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 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

If you are given bortezomib 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
- Abnormally low levels platelets in the blood
- Fever, often with other signs of infection, in a patient with abnormally low number of neutrophils in the blood
- Reduced number of white cells in the blood
- Deficiency of red cells or of haemoglobin in the blood
- Abnormally low level of lymphocytes in the blood
- 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)
- Herpes virus infections
- Bacterial and viral infections
- Respiratory infections
- 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

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. Healthcare professionals are asked to report any suspected adverse reactions via ind.aereporting@pfizer.com or Tel.: +92 213 2200121-5, +91 22 6693-2208.

By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Pfizer Bortezomib

Store below 30°C. Protect from heat, light and moisture.

Do not use this medicine after the expiry date which is stated on the carton after EXP.

The reconstituted solution should be used immediately after preparation. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. However, the reconstituted solution is stable for 8 hours at 5°C and 25°C stored in the original vial and/or a syringe, with a total storage time for the reconstituted medicine not exceeding 8 hours prior to administration.

Pfizer Bortezomib is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

Do not throw away any medicines via wastewater. 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 Pfizer Bortezomib contains
The active substance is bortezomib.

Pfizer Bortezomib 3.5 mg powder for solution for injection
Each vial contains 3.5 mg of bortezomib (as a mannitol boronic ester).

After reconstitution, 1 mL of solution for intravenous injection contains 1 mg Bortezomib and 1 mL of solution for subcutaneous injection contains 2.5 mg Bortezomib.

The other ingredient is mannitol (E421), *Tertiary*-butanol, Water for Injection and Nitrogen.

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

Each carton of 3.5 mg Pfizer Bortezomib contains a Type I glass 10 ml vial with grey chlorobutyl elastomeric closures and aluminium seals with plastic flip-off top.

Pfizer Bortezomib/PIL/PK-01
According to Pfizer Bortezomib/LPD/PK-01

Marketed by:
Karachi, Pakistan.