Bortezomib NEAPOLIS®

BORTEZOMIB 3.5 mg

Lyophilised 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 NEAPOLIS is and what it is used for?

BORTEZOMIB NEAPOLIS 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 NEAPOLIS, as monotherapy, is indicated for the treatment of patients with progressive multiple myeloma who have received at least one previous treatment and who have already received or are ineligible for a bone marrow transplant.

BORTEZOMIB NEAPOLIS, in combination with melphalan and prednisone, is indicated for the treatment of patients with untreated multiple myeloma who are not eligible for intensive chemotherapy with bone marrow transplantation.

2. What you need to know before you use BORTEZOMIB NEAPOLIS?

Do not use BORTEZOMIB NEAPOLIS
- 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 hand or feet (neuropathy) in the past
- Heart or blood pressure problems
- Shortness of breath or cough
- Seizures
- Shingles (localised including around the eye 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 NEAPOLIS, to check your blood cell counts regularly.

You must read the package leaflets of all medicinal products to be taken in combination with BORTEZOMIB NEAPOLIS for information related to these medicines before starting treatment with BORTEZOMIB NEAPOLIS. 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 NEAPOLIS should not be used in children and adolescents because it is not known how the medicine will affect them.

Other medicines and BORTEZOMIB NEAPOLIS
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 NEAPOLIS if you are pregnant, unless clearly necessary.

Both men and women receiving BORTEZOMIB NEAPOLIS 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 NEAPOLIS. 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 NEAPOLIS 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 NEAPOLIS 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 NEAPOLIS

Your doctor will work out your dose of BORTEZOMIB NEAPOLIS according to your height and weight (body surface area). The usual starting dose of BORTEZOMIB NEAPOLIS 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 or the occurrence of certain side effects and on your underlying conditions (e.g. liver problems).

Progressive multiple myeloma
When BORTEZOMIB NEAPOLIS is given alone, you will receive 4 doses of BORTEZOMIB NEAPOLIS 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).

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

How BORTEZOMIB NEAPOLIS is given
This medicine is for intravenous or subcutaneous use. BORTEZOMIB NEAPOLIS will be administered by a health care professional experienced in the use of cytotoxic medicines.
BORTEZOMIB NEAPOLIS 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 thigh or the abdomen.

If you are given too much BORTEZOMIB NEAPOLIS
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 NEAPOLIS for multiple myeloma or mantle cell lymphoma, tell your doctor straightaway 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 NEAPOLIS 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 NEAPOLIS, 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 infection or flu-like symptoms.

If you are given BORTEZOMIB NEAPOLIS 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 hand 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, 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 -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 -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

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

5. How to store BORTEZOMIB NEAPOLIS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date stated on the vial and the carton after EXP. Do not store above 30°C.
Keep the vial in the outer carton in order to protect from light.
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 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.

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

6. Contents of the pack and other Information

What BORTEZOMIB NEAPOLIS lyophilised powder contains
- The active substance is bortezomib. Each vial contains 3.5 mg of bortezomib (as a mannitol boronicester).
- The other ingredients are mannitol.

Intravenous reconstitution:
After reconstitution, 1 ml of solution for intravenous injection contains 1 mg bortezomib.

Subcutaneous reconstitution:
After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

What BORTEZOMIB NEAPOLIS looks like and contents of the pack
BORTEZOMIB NEAPOLIS powder for solution for injection contains a type I glass 10 ml vial

Delivery conditions : list I
Marketing Authorisation Holder and Manufacturer: 939 305 1H

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Marketing authorization number : 939305 1H

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Bortezomib NEAPOLIS® BORTEZOMIB 3.5 mg

RECONSTITUTION INFORMATION

SUBCUTANEOUS USE	INTRAVENOUS USE
ADD **1.4 mL** 0.9% Sodium chloride	ADD **3.5 mL** 0.9% Sodium chloride
0.9% NaCl	
TO MAKE **2.5 mg / mL** Final concentration	TO MAKE **1 mg / mL** Final concentration

THIS IS A MEDICINE
- A medicine is a product but not like any other product.
- A medicine is a product that affects your health. If it's not used properly ; it can be health threatening.
- Strictly adhere to the prescription of your Doctor and the use instructions prescribed, follow your pharmacist advice.
- Your doctor and your pharmacist know the medicine, its use and side effect.
- Don't stop the use of the treatment on your own during the prescribed time.
- Don't retake, don't increase the doses without doctor's advice.

KEEP THE MEDICINES OUT OF REACH OF CHILDREN

Bortezomib NEAPOLIS®

BORTEZOMIB 3.5 mg

Lyophilised powder for solution for injection - Bortezomib

THE FOLLOWING INFORMATION IS INTENDED EXCLUSIVELY FOR HEALTH PROFESSIONALS

1. RECONSTITUTION FOR INTRAVENOUS INJECTION
Note: BORTEZOMIB NEAPOLIS is a cytotoxic agent. Therefore, handling and preparation should be done with care. The use of gloves and other protective clothing to prevent skin contact is recommended

ASEPTIC TECHNIQUE MUST BE STRICTLY OBSERVED THROUGHOUT HANDLING OF BORTEZOMIB NEAPOLIS SINCE NO PRESERVATIVE IS PRESENT.

1.1 **Preparation of the 3.5 mg vial: carefully add 3.5 ml** of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the BORTEZOMIB NEAPOLIS powder by using a syringe of the appropriate size without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 3 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. Be sure 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 NEAPOLIS 3.5 mg powder for solution for injection IS FOR SUBCUTANEOUS OR INTRAVENOUS USE. 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

ONLY THE 3.5 MG VIAL CAN BE ADMINISTERED SUBCUTANEOUSLY, AS DESCRIBED BELOW

1. RECONSTITUTION FOR SUBCUTANEOUS INJECTION
Note: BORTEZOMIB NEAPOLIS 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 NEAPOLIS SINCE NO PRESERVATIVE IS PRESENT
1.1 **Preparation of the 3.5 mg vial: carefully add 1.4 ml** of sterile, 9 mg/ml (0.9%) sodium chloride solution for injection to the vial containing the BORTEZOMIB NEAPOLIS powder by using a syringe of the appropriate size without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 3 minutes.
The concentration of the resulting solution will be 2.5 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. Be sure that the correct dose is being given for the **subcutaneous** route of administration (2.5 mg/ml).

1.3 The reconstituted product 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 subcutaneous administration).
- Inject the solution subcutaneously, under a 45-90° angle.
- The reconstituted solution is administered subcutaneously through the thighs (right or left) or abdomen (right or left).
- Injection sites should be rotated for successive injections.
- If local injection site reactions occur following BORTEZOMIB NEAPOLIS injection subcutaneously, either a less concentrated BORTEZOMIB NEAPOLIS solution (1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously or a switch to intravenous injection is recommended.

BORTEZOMIB NEAPOLIS 3.5 mg powder for solution for injection IS FOR SUBCUTANEOUS OR INTRAVENOUS USE. 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

NEAPOLIS PHARMA

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