Package leaflet: Information for the user

BİEMİB 3,5 mg powder for solution for injection

It is applied intravenously or subcutaneously.

Sterile

Active substance: 3,5 mg bortezomib (After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib. after reconstitution, 1 ml of solution for intravenous injection contains 1 mg bortezomib).

Excipients: Mannitol (E421)

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
- This medicine has been prescribed for you personally, do not give it to others.
- When using this medicine, tell your doctor if you go to the hospital or doctor.
- 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 BİEMİB is and what it is used for**
- BİEMİB (bortezomib) is given as a white or whitish powder, in the form of a 10 ml single dose vial containing 3.5 mg bortezomib.
- BİEMİB is presented on a gray colored bromobutyl rubber stopper with a white colored Alu-PP flip-off lid and a cardboard box containing one colorless 10 ml type I glass vial.
- BİEMİB is included in a group of drugs known as antineoplastics.
- BİEMİB is a drug called cytotoxic. They are used to kill cancer cells.

• BİEMİB is used in the treatment of bone marrow cancers of adults (multiple myeloma and mantle cell lymphoma).

• In the case of multiple myeloma patients over 65 years of age with no chance of autologous transplantation or in multiple myeloma patients with a 13th deletion, a multidrug chemotherapy scheme may be added along with thalidomide in the first step or BİEMİB with appropriate combination chemotherapy scheme.

• Thalidomide or BİEMİB treatments can be started when disease progression develops after at least 2 cycles of VcAD and / or melphalan / prednisolone therapy in all other multiple myeloma patients.

• BİEMİB, for patients who have received at least one pretreatment and whose disease has worsened in the last treatment; should be used in patients who have previously undergone bone marrow transplantation (transplantation).

2. What you need to know before you use BİEMİB

The safety and efficacy of BİEMİB in children has not been determined.

Your doctor will examine you and get your medical history. You will need to give blood samples before or during treatment with BİEMİB.

Do not use BİEMİB

Eğer:

- if you are allergic to bortezomib, boron or to any of the other ingredients of this medicine
- If you have a certain serious lung or heart disease
- Rarely seen; If you have Posterior Reversible Encephalopathy Syndrome, which is often reversible and a neurological disorder caused by seizures, hypertension, headache, lethargy, confusion, blindness, other visual and neurological disorders

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)

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

Please consult your doctor if these reminders apply to you at any time in the past.

Use of BİEMİB with food and drink

There is no interaction with food and beverages in terms of method of application.

Pregnancy

Consult your doctor or pharmacist before using this medication.

Do not use BİEMİB if you are pregnant and you are not told that you should definitely use it by your doctor. Be careful not to get pregnant while using BİEMİB.

Both men and women should be confident that they have taken all the precautions related to contraception when using BİEMİB or after 3 months of treatment. If you are pregnant despite these precautions, tell your doctor immediately.

If you notice that you are pregnant during your treatment, consult your doctor immediately.

Breast-feeding

Consult your doctor or pharmacist before using this medication.

Do not breast-feed your baby while using BİEMİB. If you want to breastfeed after BİEMİB treatment, you should consult your doctor beforehand; he will tell you when it will be safe to start breastfeeding.

Vehicle and machine use

BİEMİB can lead to fatigue, dizziness, fainting or blurred vision. If you experience such side effects, do not drive and do not use any vehicle regulator or machine. Even if you have not experienced these side effects, be careful.

Important information about some of the auxiliary substances contained in BİEMİB

Mannitol (E421): This medicinal product contains mannitol.

No warning is required due to the way of use and the desire.

Diğer ilaçlar ile birlikte kullanımı

Eğer;

- ketoconazole (a drug used in the treatment of fungal infections),
- 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.

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 BİEMİB

Your doctor will work out your dose of BİEMİB according to your height and weight (body surface area). The usual starting dose of BİEMİB 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).

Application frequency:

Monotherapy (BİEMİB used alone):

A treatment period with BİEMİB consists of 4 doses in total. Doses are given on days 1, 4, 8 and 11, followed by a 10-day no-treatment interval. Therefore, a treatment period consists of 21 days (3 weeks).

Combined treatment (situations when BİEMİB is used with melphalan and prednisone):

If you have multiple myeloma and you have not previously been treated for this disease, BİEMİB will be given to you with two drugs called melphalan and prednison. BİEMİB, when used in combination with melphalan and prednisone, consists of 9 cycles (54 weeks).

In this case, a treatment period (cycle) consists of 6 weeks.

- Bimist is administered twice a week in cycles 1-4 (days 1, 4, 8, 11, 22, 25, 29 and 32).
- Cycle 5-9 is performed once a week for BİEMİB (days 1, 8, 22 and 29).
- Melphalan and prednisone, both of which are given either by oral route, are given on days 1, 2, 3 and 4 of the first week of each treatment period (cycle). Nine cycles, each 6 weeks old.

Your doctor can change your dosage during treatment and decide on the total number of periods required for you. All of this depends on your answer to your treatment.

Application path and method:

Once the drug is reconstituted, it is given either intravenously or subcutaneously. Your treatment with BİEMİB will be made in a special department under the supervision of a health professional experienced in the use of cancer drugs.

The powder inside the BİEMİB vials will be diluted before application. The dilution process will be done by a health officer. After reconstitution, the resulting solution will be given to you either via the vein or under the skin. The application made from the vine is fast enough to last 3-5 seconds. Applying under the skin will be done under your leg or abdomen skin.

If you have an impression that BİEMİB's effect is too strong or weak, talk to your doctor or pharmacist.

Different age groups

Pediatric population:

The safety and efficacy of BİEMİB in children under 18 years of age have not been determined (see Sections 5.1 and 5.2).

Geriatric population:

There is no evidence to suggest dose adjustment in patients aged 65 years or older.Özel kullanım durumları

Patients with hepatic insufficiency:

Patients with mild severe hepatic insufficiency do not need dose adjustment and should be treated according to the recommended dose. In the case of patients with moderate or severe hepatic insufficiency, your doctor will make the necessary dose adjustments.

Patients with renal insufficiency:

The pharmacokinetic properties of bortezomib are not affected by mild and moderate renal insufficiency; for this reason, dose adjustment is not necessary in such patients. It is not known whether the pharmacokinetic properties of bortezomib are affected in patients with severe renal failure without dialysis treatment. The medication should be administered after the dialysis procedure as the dialysis may reduce BİEMİB concentrations

If you use more BEAUTY than you need:

If you have used more than BİEMİB, talk to a doctor or pharmacist.

A dose higher than twice the recommended dose may be associated with decreased blood pressure and decreased platelet counts giving acute symptoms.

4. Olası yan etkiler nelerdir?

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

Treatment with BİEMİB 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 BİEMİB, 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.

Very common side effects (may affect more than 1 in 10 people)

- Headache
- Different types of rinses
- 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)

- Heart failure, acceleration in heartbeat
- High blood pressure
- Reduced functioning of your kidneys
- Headache
- General ill feeling, pain, vertigo, light-headedness, a feeling of weakness or loss of consciousness
- 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
- 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
- Inflammation of a vein, blood clots in your veins and lungs
- Problems with blood clotting
- 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, vagin
- Paralysis, seizures, falling, movement disorders, abnormal or change in, or reduced sensation (feeling, hearing, tasting, smelling), attention disturbance, trembling, twitching
- 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
- 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 reactionsAğızda ağrı, öğürme
- 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
- Bacterial and viral infections
- Inflammation of the pancreas, obstruction of the bile duct
- Genital pain, problem having an erection
- Weight increase
- Thirst
- Death
- Inflammation of the liver (hepatitis), growth in the liver, bleeding from the liver
- 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
- Nail fragility or weakness

Seyrek (ilacı kullanan her 10.000 kullanıcıdan 1 - 10 kişisinde görülebilen yan etkiler)

- Heart problems to include heart attack, angina
- Flushing
- Discoloration of the veins
- Inadequate blood circulation
- 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)
- Viral infections
- 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 7 lumps on the skin, swelling of the face, lips, tongue and /or throat, which may cause difficulty in swallowing, collapse
- Breast disorders
- Vaginal tears
- Inability to tolerate alcohol consumption
- Wasting, or loss of body mass
- Insemination of the body can not produce enough insulin or body cells to develop insulin resistance
- Fistula
- Fluid buildup in joints
- Arthritis, including those in the hands, toes and jaw joints (joint inflammation)
- Cyst formation around the joints
- Cranial fractures
- Disruption of muscle fibers leading to other complications
- Benign cysts
- Kidney cancer
- Skin disease similar to psoriasis
- Skin cancer
- Increased number of peripheral plasma cells (a type of white blood cells)
- Abnormal reaction when blood is given
- Partial or complete loss of view
- Abnormal dreams
- Decrease in sexual desire
- Do not talk foolishly
- Eyes thrown out
- Quick respiration
- Pain in the rectal region
- Gallstones
- Abnormal smell of urine
- Hernia
- Injuries

If you encounter any side effects not mentioned in these instructions for use, please inform your doctor or pharmacist.

Reporting side effects

Talk to your doctor, pharmacist or nurse if you have any side effects that are included or not in the Instructions for Use. In addition, the side effects you are experiencing www.titck.gov.t is located in the sites' Drug Side Effects Statement 'by clicking on the icon or 0800314 00 08 number of side effects by calling the notification line Turkey Pharmacovigilance Center (TÜFAM). By reporting side effects, you will contribute to learning more about the safety of the medicine you are using.

5. How to store BİEMİB

Keep BİEMİB in places where children can not, can not reach, and in their packaging.

Store BİEMİB at room temperature below 25 ° C. To protect from light, store in outer carton packaging. When diluted with 0.9% sodium chloride, the resulting solution is stable at 25 ° C in the original vial and / or for 8 hours in a syringe prior to application.

Use in accordance with expiration dates.

Do not use BİEMİB after the expiry date of packaging.

The vial is only disposable; the increasing solution should be discarded properly.

The solution obtained by diluting the powder with 0.9% sodium chloride can be stored in the original vial at 25 ° C and / or for 8 hours in a syringe before application.

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

Do not throw away drugs that have expired or are not used! Give to the collection system determined by the Ministry of Environment and Urbanism.

Marketing Authorisation Holder

Biem İlaç San. ve Tic. A.Ş.

Anıttepe Mah. Turgut Reis Cad. No: 21 Tandoğan-Çankaya / Ankara

Manufacturer

PharmIdea 4 Rupnicu Str., Olaine-LETONYA

This package leaflet was approved on 02/09/2015.

The following information is intended for healthcare professionals only:

1. RECONSTITUTION FOR INTRAVENOUS INJECTION

Note: BİEMİB 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 BİEMİB 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 BİEMİB powder by using a syringe of the appropriate size 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. 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.

BİEMİB 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.

The following information is intended for healthcare professionals only:

Only the 3.5 mg vial can be administered subcutaneously, as described below.

1. RECONSTITUTION FOR SUBCUTANEOUS INJECTION

Note: BİEMİB 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 BİEMİB 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 BİEMİB powder by using a syringe of the appropriate size 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 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 BİEMİB injection subcutaneously, either a less concentrated BİEMİB solution (1 mg/ml instead of 2.5 mg/ml) may be administered subcutaneously or a switch to intravenous injection is recommended.

BİEMİB 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.