Dr. Reddy's Laboratories (Pty) Ltd.
APPROVED PATIENT INFORMATION LEAFLET:
BERTRED 3,5
(Powder for solution for injection - Vial)

SCHEDULING STATUS

S4

BERTRED 3,5, lyophilised powder for solution for injection

bortezomib

Contains sugar (mannitol)

Each vial contains 35,0 mg mannitol

Read all of this leaflet carefully before you are given BERTRED 3,5

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse or other healthcare provider.
- BERTRED 3,5 has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours. The injection will be given to you by your medical doctor or by a qualified healthcare professional under her/his supervision.

What is in this leaflet

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

1. What BERTRED 3,5 is and what it is used for

The active substance, bortezomib, is an anticancer medicine.

BERTRED 3,5 is used for the treatment of:

Multiple Myeloma (a cancer of the bone marrow) in adults:

- 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 other medicines (melphalan and prednisone), for patients who have 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).

Mantle Cell Lymphoma (a blood cancer in the lymph glands) in adults:

- whose disease is worsening (progressive) after receiving at least one prior treatment, one of which should have included the medicine anthracycline (or mitoxantrone) and/or rituximab as part of their chemotherapy treatment.
- 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 are given BERTRED 3,5

You should not be given BERTRED 3,5

- if you are hypersensitive (allergic) to bortezomib, boron or any of the other ingredients of BERTRED 3,5.
- if you have acute diffuse interstitial lung disease (lung disorders in which the tissues of the lungs become inflamed).
- if you have pericardial disease (disease that affects the sac that encloses the heart).

Warnings and precautions

Take special care BERTRED 3,5:

Tell your doctor or healthcare professional, before you are given a BERTRED 3,5 injection if you have or ever had any of the following conditions:

- liver problems.
- diabetes or high blood sugar (doses of medicines for diabetes may have to be changed if you

receive BERTRED 3,5).

- low numbers of red or white blood cells.
- numbness, burning feeling, tingling, or pain in the hands or feet (neuropathy).
- bleeding problems and/or low number of platelets in your blood.
- diarrhoea, constipation, nausea or vomiting.
- fits (seizures) or epilepsy.
- dizziness/light-headedness or fainting when rising from a sitting or lying position (postural low blood pressure).
- heart or blood pressure problems.
- lung problems, shortness of breath.
- kidney problems.
- shingles (localised including around the eyes or spread across the body).
- hepatitis B virus infection.
- 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.
- a rare disease called amyloidosis which occurs when a substance called amyloid builds up in your organs.
- a history of allergies and a type of arthritis called polyarthritis.

Use in children

BERTRED 3,5 has not been studied, and should therefore not be used in children and adolescents.

Blood monitoring

Your doctor will do regular blood tests before and during your treatment with BERTRED 3,5 to check your blood cells, including the number of platelets in your blood. Platelets are responsible for normal clotting of blood. BERTRED 3,5 often lowers the platelet numbers and this can cause severe bleeding.

Other medicines with BERTRED 3,5

Always tell your healthcare professional if you are taking any other medicine.

(This includes complementary or traditional medicines).

In particular, tell your doctor if you are using medicines containing any of the following with BERTRED 3,5

- ketoconazole used to treat fungal infections.
- ritonavir used to treat HIV infection.
- rifampicin, chloramphenicol, clarithromycin - antibiotics used to treat bacterial infections.
- pain medicines e.g., codeine (will increase risk of constipation, nausea and vomiting).
- carbamazepine, phenytoin or phenobarbitone used to treat epilepsy.
- oral anti-diabetic medicines.
- St. John's Wort (*Hypericum perforatum*) used to treat depression or other conditions.
- medication for high blood pressure or for heart problems (such as angiotensin inhibitors, beta-blockers, antihypertensive medicine, calcium channel blockers, angiotensin receptor blockers and diuretics (water pills)).
- amiodarone used for heart rhythm problems.
- isoniazid, an antibiotic used in the treatment of tuberculosis (TB)
- nitrofurantoin, an antibiotic used in the treatment of bladder infections
- statins, used to control blood cholesterol levels

BERTRED 3,5 with food and drink

BERTRED 3,5 is not known to be affected by food.

Drinking of alcohol with BERTRED 3,5 is not advised as the risk of liver damage can increase.

Pregnancy, breastfeeding and fertility

You should not receive BERTRED 3,5 if you are pregnant, or planning to be pregnant, unless treatment is clearly necessary.

If you are pregnant or plan to become pregnant or are breastfeeding your baby please consult your doctor, pharmacist or other healthcare professional for advice before receiving BERTRED 3,5.

If you are a woman who can become pregnant you should use a highly effective method of contraception while using BERTRED 3,5 and for 8 months after stopping treatment with BERTRED 3,5. If, despite these measures, pregnancy occurs, tell doctor immediately. Talk to your doctor if you wish to freeze your eggs before starting treatment.

If you are a man you should not father a child while receiving treatment with BERTRED 3,5. You should use an effective method of contraception while using BERTRED 3,5 for 5 months after stopping treatment with BERTRED 3,5. Talk to your doctor if you wish to conserve your sperm before starting treatment.

You should not breastfeed while receiving BERTRED 3,5. Discuss with your doctor when it is safe to restart breastfeeding after finishing your treatment.

Driving and using machines

It is not always possible to predict to what extent BERTRED 3,5 may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which BERTRED 3,5 affects them.

BERTRED 3,5 may cause low blood pressure and may lead to tiredness, dizziness, fainting, blurred vision or may have other effects that may make it unsafe for you to drive vehicles or operate machinery safely.

Do not drive or operate any tools or machines unless you are certain that it is safe for you to do so while receiving BERTRED 3,5.

Even if you have not felt these effects, you must still be cautious.

3. How to use BERTRED 3,5

- BERTRED 3,5 is for intravenous and subcutaneous use.

- You will not be expected to give yourself injections of BERTRED 3,5. It will be given to you by a person who is qualified to do so.
- Always go for your injection of BERTRED 3,5 exactly as your doctor has instructed you.
- You should check with your doctor, pharmacist or healthcare professional if you are unsure.

BERTRED 3,5 is for single use only and discard any unused portions.

BERTRED 3,5 lyophilised powder has to be dissolved before administration. The resulting solution is then either injected into a vein or injected into the thighs or abdomen.

Your doctor will work out your dose of BERTRED 3,5 according to your height and weight (body surface area) and determine further treatment.

Monotherapy

Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

When BERTRED 3,5 is given alone, you will receive 4 doses of BERTRED 3,5 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) of treatment.

Combination therapy

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 BERTRED 3,5 intravenously together with two other medicines; melphalan and prednisone.

In this case, the duration of a cycle is 42 days (6 weeks). The treatment consists of a total of 9 cycles (54 weeks).

- In cycles 1 to 4, BERTRED 3,5 is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.
- In cycles 5 to 9, BERTRED 3,5 is administered once weekly on days 1, 8, 22 and 29.

Melphalan and prednisone 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 BERTRED 3,5 intravenously together with the medicines dexamethasone, or dexamethasone and thalidomide, as induction treatment.

The recommended starting dose of BERTRED 3,5 in combination with other medicines used for the treatment of multiple myeloma is 1,3 mg/m^2 to be administered twice weekly on Days 1, 4, 8, and 11, followed by a rest period of 10 to 18 days, which is considered a treatment cycle.
Three to six cycles should be administered. At least 72 hours should elapse between consecutive doses of BERTRED 3,5.

Relapsed Multiple Myeloma

If you have been treated before for multiple myeloma and you are unsuitable for blood stem cell transplantation or if you have already received a blood stem cell transplantation, you will receive BERTRED 3,5 together with
a medicine called pegylated liposomal doxorubicin or a medicine called dexamethasone.

When BERTRED 3,5 is given together with pegylated liposomal doxorubicin, you will receive BERTRED 3,5 as a 21-day treatment cycle and pegylated liposomal doxorubicin 30 mg/m^2 is given on day 4 of the BERTRED 3,5 21-day treatment cycle as an intravenous infusion after the BERTRED 3,5 injection. You might receive up to 8 cycles (24 weeks).

When BERTRED 3,5 is given together with dexamethasone, you will receive BERTRED 3,5as a 21-day treatment cycle and dexamethasone 20 mg is given orally on the day of and the day after the BERTRED 3,5 injection.

<u>Retreatment for Multiple Myeloma</u>

If you have previously responded to treatment with BERTRED 3,5 (either alone or in combination) and if you have relapsed you should be started on retreatment at the last tolerated dose. Refer to "Monotherapy" for dosing schedule*.*

Previously untreated Mantle Cell Lymphoma

If you have not been treated before for Mantle Cell Lymphoma you will receive BERTRED 3,5 intravenously together with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone.
BERTRED 3,5 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 medicines are given on day 1 of each BERTRED 3,5 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 BERTRED 3,5 treatment cycle.

Your doctor will tell you how long your treatment with BERTRED 3,5 will last. Do not stop treatment early without discussing this with your doctor.

If you have the impression that the effect of BERTRED 3,5 is too strong or too weak, tell your doctor or pharmacist.

If you receive more BERTRED 3,5 than you should

Since a healthcare professional will administer BERTRED 3,5 he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If you forget to receive BERTRED 3,5

If you forget to receive BERTRED 3,5 for any reason, discuss this with your doctor as soon as possible.

If you stop taking BERTRED 3,5

Do not stop taking BERTRED 3,5 unless your doctor tells you to.

4. Possible side effects

BERTRED 3,5 can have side effects.

Not all side effects reported for BERTRED 3,5 are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking BERTRED 3,5, please consult your doctor, pharmacist or other health care professional for advice.

If any of the following happens, stop taking BERTRED 3,5 and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Swelling and redness of the hands, feet, ankles, face, mouth, lips, gums, tongue, throat and neck which may cause difficulty in swallowing or breathing or throat tightness;

- Shortness of breath and wheezing;
- Rash, hives (raised bumps), blisters or itching;
- Fainting;
- A serious hypersensitivity reaction causing kidney problems or failure, joint pain, fever and a rash.

Allergic reactions can happen in patients taking BERTRED 3,5 even after only one dose.

These are all very serious side effects. If you have them, you may have had a serious allergic reaction to BERTRED 3,5.

You may need urgent medical attention or hospitalisation.

Tell your doctor immediately or go to the casualty department at your nearest hospital if you notice any of the following:

- Difficulty passing stools (constipation), inability to pass gas, belching, vomiting, feeling sick (nausea), severe stomach pain.
- Numbness, prickling or tingling sensations in your toes, fingers, feet or hands and burning, freezing, throbbing and/or shooting pain that is often worse at night.
- Loss of the ability to move and to feel anything in one or more parts of the body (paralysis).
- Confusion, visual loss or disturbances, blindness, fits (seizures), headaches.
- Abnormal tiredness, changes in heartbeat (faster or irregular), chest pain which may indicate heart problems.
- Rapid breathing or gasping for breath, coughing, wheezing, restlessness, confusion and rapid pulse. These are symptoms of a medical emergency as a result of fluid accumulating and/or inflammation in the lungs, and which may indicate lung problems.
- Feeling sick (nausea), vomiting, passing only small amounts of urine or no urine, pain in the back and swelling may indicate kidney problems. Sudden or gradual change in kidney functioning can lead to kidney failure and death.
- High fever, shaking, chills, confusion, joint aches, stiff neck, severe headaches, extreme tiredness, rapid pulse, flu-like symptoms, or any general feeling of being unwell due to infection in any part of the body that can be fatal.
- Blood clot in the leg (thrombosis) or bleeding throughout the body leading to organ failure, due to a life-threatening condition that prevents normal blood clotting.

- Severe pain in the upper middle or upper left part of the belly, nausea, fever or chills, swollen abdomen and tender to touch which may indicate problems with your pancreas.
- Bruising or bleeding anywhere in your body without obvious injury e.g., bleeding from your bowels, mouth, gums, vomiting blood, blood in your urine or stools.
- Muscle cramping, muscle weakness.

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.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

If you are given BERTRED 3,5 for the treatment of multiple myeloma the side-effects you may get are listed below*:*

Frequent:

- Shingles (itching, tingling or severe burning pain with painful, rash that develops into blisters on one side of the body and may occur on the forehead, cheek, nose, and around the eye and may also spread throughout the body).
- Cold sores.
- Pneumonia (infection in lungs).
- Bacterial and fungal infections.
- Decreased appetite.
- Dehydration.
- Low levels of potassium, salt, and calcium in the circulating blood.
- Abnormal sugar and enzyme levels in the blood (picked up in blood tests).
- Problems with your mood and sleep.
- Feeling anxious, troubled/nervous.
- Weakness, numbness and pain, usually in the hands and feet.

- A sensation which is painful, itchy, burning, or restrictive
- Nerve pain.
- Muscle weakness of the arms and legs.
- Fainting.
- Dizziness.
- Sour, sweet, bitter or metallic taste in mouth.
- Tiredness.
- Headache.
- Swelling or bulging of the eye.
- Vision problems.
- "Pink eye" (conjunctivitis).
- Vertigo (the sensation of spinning while stationary).
- High or low blood pressure.
- A drop in blood pressure on standing or sitting up.
- Shortness of breath.
- Nose bleeds.
- Sneezing, nasal discharge and congestion, persistent watery runny nose.
- Cough.
- Nausea (feeling sick) vomiting (throwing up).
- Vomiting of blood.
- Runny tummy (loose watery stools).
- Inflamed and sore lips and mouth.
- Reflux or indigestion.
- Sensation of elevated abdominal pressure and volume.
- Pain in the throat/upper airway.
- Stomach pain.
- Passing of gas/belching.
- Liver problems.
- Rash.

- Itching.
- Redness of the skin.
- Dry skin.
- Pain in the bones, joints, ligaments, tendons or muscles.
- Kidney problems.
- Fever.
- Feeling weak with no energy and a general feeling of discomfort.
- Swelling including in the face.
- Chills.
- Pain.
- Decrease in weight.

Less frequent:

- Various types of bacterial and viral infections which include urinary tract infections, the flu, ear infections, tooth infections, skin infections, cold sores, sexually transmitted infection marked by genital pain and sores.
- Inflammation of the tonsils.
- Inflammation of the mastoid bone, located behind the ear.
- Extreme tiredness, sleep abnormalities, pain and other symptoms that are made worse by exertion which is experienced after having a viral infection.
- Severe reversible brain condition caused by a virus which includes seizures, high blood pressure, headaches, tiredness, confusion, blindness or other vision problems.
- An infection of the brain and brain covering (meninges) caused by the herpes simplex virus
- Different types of cancers of the blood and cancer of the kidneys.
- Fever when your white blood cell are very low.
- Swelling of your lymph nodes.
- Inflammation or bleeding 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.

- A rare disease that occurs when a protein called amyloid builds up in organs (you may experience feeling very weak or tired, losing weight without trying, swelling in the belly, legs, ankles or feet, numbness, pain or tingling in hands or feet, skin that bruises easily, purple spots (purpura) or bruised-looking areas of skin around the eyes, bleeding more than usual after an injury).
- Swelling of the deeper layers of the skin, caused by a build-up of fluid.
- Passing excessive amounts of urine.
- Low or high thyroid hormone levels.
- High levels of a hormone called cortisol.
- Large amounts of tumour cells are killed off at the same time by the treatment, releasing their contents into the bloodstream (Tumour lysis syndrome).
- Decreased levels of magnesium, phosphate and chlorine in the circulating blood.
- Increased levels of potassium, salt, magnesium, chlorine and phosphate in the circulating blood.
- Higher than normal levels of uric acid which can cause kidney problems or gout.
- Vitamin B12 and B complex deficiency symptoms.
  This may present with loss of appetite, vomiting, tiredness, weakness.
  nausea with or without vomiting, lack of appetite and fatigue, dark urine, reduced urine output, or flank pain, numbness, seizures, or hallucinations, muscle cramps and spasms, heart palpitations (symptoms of Tumour lysis syndrome).
- Increased appetite.
- Unable to tolerate alcohol.
- Having a disturbed state of mind.
- Feeling or experiencing things that seem real, but that do not in fact really
- happen (hallucinations).
- Feeling confused, disorientated, and restless.
- Thoughts of killing oneself.
- Feeling stressed, sad and hopeless.
- Decreased sex drive.
- Shaking

- Pins-and-needles, pricks, tingling and numbness.
- Jerky and/ or involuntary movements.
- Unable to balance properly
- Memory loss
- Fits (seizures).
- Problems with speaking.
- Headache that can cause severe throbbing pain or a pulsing sensation, usually on one side of the head.
- Pain, weakness, numbness, or tingling in the leg.
- Restless leg syndrome - disorder that causes a strong urge to move your legs.
- A distorted sense of smell.
- Pain, numbness, and/or weakness that radiate along the sciatic nerve from the lower back to the legs.
- Paralysis.
- Coma.
- Weakened muscle movement.
- Drooling.
- Decreased muscle tone.
- Visual disturbance, seizure, headaches, and altered thinking.
- Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barré syndrome).
- Progressive weakness and decreased feeling in the arms and legs.
- Bleeding, infection, swelling in the eye
- Double vision.
- Dry eyes, irritated or light sensitive eyes.
- Discharge or watery eyes.
- Eye pain.
- Lump in the eyelid.
- Red, swollen, irritated and itchy eyelids.

- When blood does not flow properly to your eye's optic nerve, which cause you to suddenly lose your vision in one or both of your eyes.
- Being overly sensitive to sound.
- Ringing in the ears.
- Hearing problems may include deafness.
- Bleeding in the ear, ear pain.
- Heart problems to include heart attack, angina, heart failure, chest pain, chest discomfort, increased or reduced heart rate, heart muscle disease, specific type of abnormal heart rhythm that can lead to sudden cardiac death, fluid builds up in the heart.
- Blood clots in the legs.
- Bleeding.
- Sudden, rapid heartbeat, loss of consciousness., weak pulse, low blood pressure.
- Inflammation of the veins.
- Flushing (red in the face).
- A pale appearance.
- Redness, warmth, and burning pain of the hands and legs.
- Discoloration of the veins.
- Insufficient blood circulation,
- Improper functioning of the vein valves in the leg, causing swelling and skin changes.
- Stroke.
- Blood clot that forms in the leg and travel to the lung.
- Accumulation of fluid in the lungs.
- Low levels of oxygen in blood and tissue.
- A type of high blood pressure that affects the lungs.
- Temporary inability to breath.
- Hiccups.
- Runny nose.
- Difficulty in speaking due to a physical disorder of the mouth, tongue, throat, or vocal cords
- Wheezing.

- Rapid and shallow breathing.
- Dry throat.
- Throat tightness, dry throat, throat irritation.
- Bleeding in the lung and coughing up blood.
- Swelling of the lips, lip pain.
- Vomiting blood.
- Swelling of the tongue.
- Bleeding gums.
- Problems swallowing.
- Stomach pain.
- Mouth ulcers and blisters in the mouth and throat.
- Inflammation of the pancreas, stomach and colon.
- Gum infection.
- Sharp, sudden pain you feel in your anus.
- Changes of bowel habit and abnormal faeces.
- Liver problems including inflammation, bleeding and liver failure.
- A condition in which the flow of bile from the liver stops or slows.

  which causes intense itching, dark urine and light-coloured bowel movements.
- Budd-Chiari syndrome (the clinical symptoms caused by blockage of the hepatic veins).
- Gall stones.
- "Hives"
- Hair loss.
- Dry or discolouration or ulcers of the skin.
- Pimples.
- Blisters.
- Oversensitivity to sunlight resulting in sunburn.
- Increased sweating, night and cold sweats.
- Changes in nails.
- A potentially life-threatening skin disorder characterised by the peeling of the skin leading to

possible infection and/or death.

- A reaction to medication that starts with flu-like symptoms, followed by a painful rash that spreads and blisters.
- Damage to an area of the skin caused by constant pressure on the area for a long time.
- Twitching of the muscles.
- Joint swelling and inflammation, pain and stiffness, a sense of heaviness.
- Jaw pain.
- Cysts in the lining of joints (synovial cysts).

- Urinary tract infections.
- Blood in the urine.
- Unable to empty all the urine from the bladder.
- Frequent, abnormal urination during the day.
- Increased amounts of protein in the urine (picked up using a urine test).
- Low amounts of urine.
- Bladder irritation.
- Vaginal problems including bleeding.
- Genital pain.
- Problems to maintain an erection.
- Problems with testes.
- Inflammation of the prostate.
- Breast problems in females.
- Pelvic pain.
- An organ, tissue or body part didn't develop normally.
- Undeveloped or incorrectly positioned organs that prevent the digestive system from functioning.
- A condition that causes widespread and persistent thick, dry, "fish-scale" skin.
- Worsening of general health.
- Swelling of the face.
- Pain and bleeding at the injection site.

- Inflammation of the vein at the injection site.
- Chest pain and discomfort.
- Abnormal walking.
- Feeling cold.
- Change in thirst.
- Changes in body temperature.
- Death.
- Multi-organ failure
- Hernia (happens when an internal organ pushes through a weak spot in your muscle or tissue).
- Delayed healing.
- Tenderness.
- Ulcers.
- Catheter site pain.
- Feeling of a foreign body.
- Increased weight.
- Abnormal tests e.g., increase in bilirubin, increased weight, protein analysis abnormal, increased C-reactive protein, abnormal urine analysis, abnormal ECG, abnormal blood gases.
- Transfusion reactions.
- Falls and fractures.
- A sudden feeling of cold with shivering accompanied by a rise in temperature.
- Injury to face and joints.
- Cuts and bruises.
- Burns.
- Injuries due to radiation.
- Macrophage activation syndrome is a severe, potentially life-threatening, complication of several chronic rheumatic diseases of childhood.

If you are given BERTRED 3,5 together with other medicines for the treatment of mantle cell lymphoma the side-effects you may get are listed below:

Frequent:

- Infection in the lung (pneumonia).
- Various bacterial, viral and fungal infections.
- Decreased appetite.
- Decreased levels of potassium and salt in the circulating blood.
- Abnormal sugar levels.
- Fluid retention.
- Difficulty or problems sleeping.
- Sensitivity, numbness, tingling or burning sensation of the skin, or pain in the hands or feet, due to nerve damage.
- Abnormal sense of touch.
- Loss of consciousness or fainting.
- Dizziness.
- Altered taste.
- Abnormal vision.
- Impaired hearing including ringing in the ears.
- Heart problems.
- High or low blood pressure.
- A drop in blood pressure on standing or sitting up.
- Difficulty breathing.
- Cough.
- Hiccups.
- Feeling sick and throwing up.
- Runny or hard stools.
- Swelling of the tongue.
- Indigestion.
- Mouth and throat pain.

- Mouth ulcers and blisters in the mouth and throat.
- Problems swallowing.
- Stomach pain.
- Liver failure.
- Hair problems.
- Itching.
- Rash.
- Swelling and irritation of the skin.
- Muscle pain and spasms
- Pain in arms and legs.
- Urinary tract infection.
- Fever.
- Tiredness.
- Weakness and lack energy.
- Swelling.
- Chills.
- Reactions at the injection site.
- Abnormal blood tests (abnormal levels of bilirubin, abnormal protein analysis).
- Increased or decreased weight.

Less frequent:

- Inflammation of the liver (Hepatitis B).
- Bronchopneumonia
- An infection of the brain and brain covering (meninges) caused by the herpes simplex virus.
- Low counts for all three types of blood cells.

  You may experience symptoms associated with low levels of each type, including anaemia, increased risk of infection and excessive bruising or bleeding.
- 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
- Swelling of the deeper layers of the skin, caused by a build-up of fluid.

- Large amounts of tumour cells are killed off at the same time by the treatment, releasing their contents into the bloodstream (Tumour lysis syndrome).
- A dysfunction of the nerves that regulate non-voluntary body functions, such as heart rate, blood pressure and sweating.
- Serious nerve inflammation, which may cause paralysis and difficulty breathing (Guillain-Barre syndrome)
- Progressive weakness and reduced sensation in the arms and legs.
- Lump in the eyelid.
- Red, swollen, irritated and itchy eyelids.
- When blood does not flow properly to your eye's optic nerve, which cause you to suddenly lose your vision in one or both of your eyes.
- Vertigo (the sensation of spinning while stationary).
- Problems hearing.
- Heart problems including when fluid builds up in the heart.
- 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.
- Bleeding in the lungs.
- Inflammation of colon.
- Liver failure.
- A potentially life-threatening skin disorder characterised by the peeling of the skin leading to possible infection and/or death.
- A reaction to medication that starts with flu-like symptoms, followed by a painful rash that spreads and blisters.
- Damage to an area of the skin caused by constant pressure on the area for a long time.

If you notice any side effects not mentioned in the leaflet, please inform your doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor or pharmacist or nurse. You can also report side effects to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

By reporting side effects, you can help provide more information on the safety of BERTRED 3,5.

5. How to store BERTRED 3,5

Store at or below 30 ˚C. Keep the vial in the outer carton in order to protect from light.

Reconstituted solution:

The reconstituted solution should be used immediately after preparation.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8° C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

However, the chemical and physical in-use stability of reconstituted/ diluted solution has been demonstrated for 8 hours at 30 °C and for 15 days at 2 °C to 8 °C, stored in the original vial and/or a syringe prior to administration.

Do not use this medicine after the expiry date.

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

Do not dispose medicines in drains or sewerage systems (e.g., toilets).

6. Contents of the pack and other information

The active ingredient is bortezomib.

Each vial contains 3,5 mg bortezomib (as a mannitol boronic ester).

The other ingredients are nitrogen, tertiary butanol and water for injection.

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 BERTRED 3,5 looks like and contents of the pack

BERTRED 3,5: lyophilised powder for solution for injection is a sterile white to off- white freeze-dried powder in a 10 ml vial.

BERTRED 3,5 is supplied in a single-use 10 ml type I, clear, colourless, flint tubular glass vial, stoppered with a 13 mm dark grey coloured bromobutylrubber stopper and sealed with 13 mm royal blue coloured aluminium flip-off seal, packed in an outer printed cardboard carton.

Holder of Certificate of Registration

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

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For any information about this medicine, please contact the local representative of the Holder of Certificate of Registration:

Dr. Reddy's Laboratories (Pty) Ltd. Tel: +27 11 324 2100

Access to the corresponding Professional Information

Detailed information on this medicine is available on the Dr. Reddy's Laboratories (Pty) Ltd. website:

http://www.drreddys.co.za