PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: **S4**

VELCADE® 3,5 mg

Powder for solution for injection for subcutaneous use.

Bortezomib

Contains sugar:

0,035 g mannitol per 3,5 mg vial.

Read all of this leaflet carefully before you are given VELCADE

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.

What is in this leaflet

1. What VELCADE is and what it is used for

VELCADE belongs to a group of medicines called *cytotoxic* medicines. These are used to

kill cancer cells.

VELCADE 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 for 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 receive VELCADE

VELCADE should not be administered to you:

- If you are allergic (hypersensitive) to the active substance or to any of the

other ingredients of VELCADE.

- If you have certain severe lung or heart problems.

Warnings and precautions

Tell your doctor or healthcare professional before being given the injection:

Special care should be taken with VELCADE:

- If you have a low level of red blood cells, platelets, or white blood cells, as these conditions may become worse during treatment with VELCADE.
- If you have had any bleeding problems.
- If you are suffering from diarrhoea, constipation or nausea and vomiting, as this may become worse during VELCADE treatment.
- If you have a history of fainting, dizziness or lightheadedness.
- If you have any problems with your kidneys.
- If you have any problems with your liver.
- If you have had any problems in the past with numbness, tingling, or pain in the hands or feet (neuropathy). This effect may become worse during VELCADE treatment.
- If you have any problems with your heart or with your blood pressure.
- If you have been diagnosed with a condition called amyloidosis (that results from the abnormal deposit of a particular protein (called amyloid), in various tissues of the body).
- If you have experienced or have new or increased shortness of breath or cough.
- If you have experienced or have new or increased weakness, vomiting, cramps, fits, excess fluid buildup, heart failure, irregular heart rhythm or fainting. These are symptoms of tumour lysis syndrome.
- If you have experienced or have new or increased memory loss, confusion, trouble thinking, difficulty with walking or loss of vision.
- Seizures

- Shingles (localised including around the eyes or spread across the body).

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking this medicine.

Children and adolescents

VELCADE has not been studied in children or adolescents and therefore should not be used in this patient population.

Other medicines and VELCADE

Always tell your healthcare provider if you are taking any other medicine. (This includes all complementary or traditional medicines.) The use of VELCADE with these medicines may cause undesirable interactions.

In particular tell your doctor if you are using medicines containing the following active substances:

- Ketoconazole and other azole antifungals used to treat fungal infections.
- rifampicin, an antibiotic used to treat bacterial infections.
- carbamazepine, phenytoin or phenobarbital used to treat epilepsy.
- St. John's Wort used for depression or other conditions.
- Oral anti-diabetics.
- Ritonavir used to treat HIV infection.

Pregnancy and Breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before receiving this medicine.

VELCADE must not be used if you are pregnant or breastfeeding.

You must make sure that you do not become pregnant while receiving VELCADE. Both men and women must ensure adequate birth control measures are taken whilst receiving VELCADE, and for 3 months after treatment.

If you wish to restart breastfeeding after VELCADE treatment, you must discuss this with your doctor, pharmacist or other healthcare professional, who will tell you when it is safe to do so.

Driving and using machines

VELCADE might cause low blood pressure that may lead to tiredness, dizziness, fainting, or blurred vision. Do not drive or operate tools or machines if you experience such side effects. Even if you have not felt these effects, you must still be cautious.

3. How to use VELCADE

Do not share medicines prescribed for you with any other person.

You will be given VELCADE 3,5 mg subcutaneously (under the skin).

VELCADE 3,5 mg is for subcutaneous use.

You will receive VELCADE in a specialised medical unit, under the supervision of a doctor experienced in the use of *cytotoxic* medicines.

VELCADE powder has to be dissolved before administration. This will be done by a healthcare professional. The resulting solution is then injected under the skin.

Injection under the skin is in either the thigh or the abdomen.

The dose will be calculated from your height and weight (body surface area).

Progressive multiple myeloma

When VELCADE is given alone, you will receive 4 doses of VELCADE 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) of treatment.

You may also be given VELCADE together with the medicines pegylated liposomal doxorubicin or dexamethasone.

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

When VELCADE is given together with dexamethasone, you will receive VELCADE 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 VELCADE, 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 VELCADE 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, VELCADE is administered twice weekly on days 1, 4, 8, 11, 22, 25, 29 and 32.
- In cycles 5 to 9, VELCADE 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 VELCADE subcutaneously together with the medicines dexamethasone, or dexamethasone and thalidomide, as induction treatment.

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

When VELCADE 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 VELCADE 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).

Progressive mantle cell lymphoma

When VELCADE is given alone, you will receive 4 doses of VELCADE 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 mantle cell lymphoma

If you have not been treated before for mantle cell lymphoma you will receive VELCADE subcutaneously together with the medicines rituximab, cyclophosphamide, doxorubicin and prednisone. VELCADE is given 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 medicines are given on day 1 of each VELCADE 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 VELCADE treatment cycle.

Your doctor will tell you how long your treatment with VELCADE will last. Do not stop any treatment unless your doctor tells you to do so. If you have the impression that the effect of VELCADE is too strong or too weak, tell your doctor or pharmacist.

If you are given more VELCADE than you should

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

If you forget to take VELCADE

Since a healthcare provider will administer VELCADE, it is unlikely that a dose will be missed.

4. Possible side effects

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

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

- severe itching of the skin or raised lumps on the skin, swelling around the eyes, face, lips, tongue and /or throat, which may cause difficulty in swallowing,
- muscle cramping, muscle weakness,
- confusion, visual loss or disturbances, blindness, fits (seizures), headaches,
- shortness of breath, swelling of your feet, ankles, wrists, arms or legs or changes in your heartbeat, high blood pressure, tiredness, feeling dizzy/faint, collapse,
- coughing and breathing difficulties, tightness in the chest or chest pain.

Treatment with VELCADE 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 VELCADE, 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 gums 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 VELCADE for the treatment of multiple myeloma, the side effects you may get are listed below and tell your doctor if you notice any of the following:

Frequent side effects:

- 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
- 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 rashes

- 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
- Changes in 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

Less frequent side effects

- Heart failure, heart attack, chest pain, chest discomfort, increased or reduced heart rate
- Failing of your kidneys
- Swelling of a vein, blood clots in your veins and lungs
- Problems with blood clotting
- Poor circulation
- Swelling 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 swelling 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 swollen eyes, excessively wet eyes, painful eyes, dry eyes, eye infections, lump in the eyelid (chalazion), red and swollen eyelids, discharge from the eyes, abnormal vision, bleeding of the eye
- Swelling of your lymph glands
- Joint or muscle stiffness, sense of heaviness, pain in your groin
- Hair loss and abnormal hair texture
- Allergic reactions

- Redness or pain at the injection site
- Mouth pain
- Infections or swelling 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
- Swelling of the pancreas, blockage of the bile duct
- Genital pain, problem having an erection
- Weight increase
- Thirst
- Hepatitis (liver swelling)
- Injection site or injection device related disorders
- Skin reactions and disorders (which may be severe and life threatening), skin ulcers
- Bruises, falls and injuries
- Swelling 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 (non-cancerous) cysts
- A severe reversible brain condition which includes seizures, high blood pressure, headaches, tiredness, confusion, blindness or other vision problems.
- Heart problems to include heart attack, angina
- Flushing
- Discolouration of the veins
- Swelling 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)
- Breast disorders
- Vaginal tears
- Genital swelling
- Inability to tolerate alcohol consumption
- Wasting, or loss of body mass
- Increased appetite
- Fistula (abnormal connection between two spaces)
- 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
- Blood clot in small blood vessels (thrombotic microangiopathy)
- 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

If you are given VELCADE together with the other medicines for the treatment of mantle cell lymphoma the side effects you may get are listed below and tell your doctor if you notice any of the following:

Frequent side effects:

- Pneumonia
- 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
- Shingles (localised including around the eyes or spread across the body)
- Herpes virus infections
- Bacterial and viral infections
- Respiratory infections, bronchitis, coughing with phlegm, flu like illness
- Fungal infections
- 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

Less frequent side effects

- Hepatitis (swelling of the liver)
- Severe allergic reaction
- Movement disorders, paralysis, twitching
- Vertigo
- Hearing loss, deafness

- 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
- Yellow discoloration of the eyes and skin (jaundice)
- Lump in the eyelid (chalazion), red and swollen eyelids
- Blood clot in small blood vessels (thrombotic microangiopathy)

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist as soon as possible.

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via "**6.04 Adverse Drug Reaction Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8
By reporting side effects, you can help provide more information on the safety of VELCADE.

Alternatively, you may report side effects experienced with VELCADE directly to Janssen Pharmaceutica (see section 'Holder of the Certificate of Registration' for contact details or visit www.janssen.com).

5 How to store VELCADE

VELCADE will be stored in the pharmacy.

Store all medicines out of reach of children.

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

Do not use after the expiry date stated on the vial and the carton.

The reconstituted solution may be stored for 8 hours at 25 °C when stored in the original vial and/or a syringe prior to administration with a maximum of 8 hours in the syringe.

6 Contents of the pack and other information

The active substance is bortezomib. Each vial contains 3,5 mg (as a mannitol boronic ester).
VELCADE will be dissolved in a sterile, sodium chloride (salt) solution.
After reconstitution, 1 mL of solution for subcutaneous injection contains 2,5 mg bortezomib.

The other ingredient of VELCADE is mannitol (E 421).

What VELCADE looks like and contents of the pack

A white to off-white cake or powder.

VELCADE is supplied as a single-use 10 mL clear, colourless glass vial with a grey bromobutyl stopper and an aluminium seal with royal blue flip-off cap (10 mL vial).
The 10 mL vial contains 38,5 mg powder for solution for injection.
Each vial is contained in a transparent blister pack (consisting of a tray with a lid) which is placed into an outer carton together with a professional information insert/patient information leaflet.

Holder of certificate of registration

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Access to the corresponding Professional Information

Included in the carton, accompanying this patient information leaflet.