PACKAGE INSERT

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

VELZOMY 3,5 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

Intravenous (IV) or subcutaneous (SC) use.

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

After reconstitution, 1 ml of solution for subcutaneous injection contains 2,5 mg bortezomib.

Contains sugar (35 mg mannitol). For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Powder for solution for injection.

White to off-white cake or powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

VELZOMY is indicated for:

Multiple myeloma:

- as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation;
- in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy with haematopoietic stem cell transplantation;
- in combination with melphalan and prednisone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell

transplantation.

Mantle cell lymphoma:

- treatment of relapsed or refractory mantle cell lymphoma for patients who have received at least 1 prior line of therapy, one of which should have included an anthracycline (or mitoxantrone) and/or rituximab as part of their chemotherapy regimen;
- treatment for newly diagnosed mantle cell lymphoma (MCL) in adults, in combination with rituximab, cyclophosphamide, doxorubicin and prednisone who are unsuitable for haematopoietic stem cell transplantation.

4.2 Posology and method of administration:

VELZOMY 3,5 mg powder for solution for injection is available for:

- intravenous administration at a concentration of 1 mg/ml (as a 3-5 second bolus injection) or
- subcutaneous administration at a concentration of 2,5 mg/ml.

Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

VELZOMY IS FOR INTRAVENOUS AND SUBCUTANEOUS USE ONLY and should not be given by other routes. Intrathecal administration has resulted in death.

See **section 6.6** for reconstitution instructions.

VELZOMY retreatment may be considered for multiple myeloma patients who had previously responded to treatment with VELZOMY (see below).

Monotherapy:

Relapsed multiple myeloma and relapsed mantle cell lymphoma:

Recommended dosage:

The recommended starting dose of VELZOMY is 1,3 mg/m^2 body surface area administered twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-day rest period (days 12-21). This 3-week period is considered a treatment cycle. This 3-week period is considered a treatment cycle. It is recommended that patients receive 2

cycles of VELZOMY following a confirmation of a complete response. It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of therapy. At least 72 hours should elapse between consecutive doses of VELZOMY.

Dose modification and re-initiation of treatment:

VELZOMY treatment must be withheld at the onset of any Grade 3 non-haematological or any Grade 4 haematological toxicities, excluding neuropathy as discussed below (see **section 4.4**). Once the symptoms of the toxicity have resolved, VELZOMY treatment may be re-initiated at a 25 % reduced dose (1,3 mg/m^2 reduced to 1,0 mg/m^2; 1,0 mg/m^2 reduced to 0,7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of VELZOMY must be considered unless the benefit of treatment clearly outweighs the risk.

The following table contains the recommended dose modification for the management of patients who experience VELZOMY-related neuropathic pain and/or peripheral sensory neuropathy (**Table 1**). Severe autonomic neuropathy resulting in treatment interruption or discontinuation has been reported. Patients with pre-existing severe neuropathy may be treated with VELZOMY only after careful risk/benefit assessment.

Table 1: Recommended* dose modifications for VELZOMY related neuropathic pain and/or peripheral sensory or motor neuropathy.

SEVERITY OF PERIPHERAL NEUROPATHY: Signs and Symptoms[a]	**MODIFICATION OF DOSE REGIMEN:**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paraesthesia without pain or loss of function).	No action.
Grade 1 with pain or **Grade 2** (moderate symptoms; limiting Instrumental Activities of Daily Living (ADL))[b].	Reduce VELZOMY to 1,0 mg/m^2 OR Change VELZOMY treatment schedule to 1,3 mg/m^2 once per week
Grade 2 with pain or **Grade 3** (severe symptoms; limiting self-care ADL[c]).	Withhold VELZOMY therapy until toxicity resolves. When toxicity resolves re-initiate

	with a reduced dose of VELZOMY 0,7 mg/m^2 once per week.
Grade 4 (life threatening consequences; urgent intervention indicated)	Discontinue **VELZOMY**.

***** Based on dose modifications in phase II and III multiple myeloma studies.

[a] Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

[b] *Instrumental ADL:* refers to preparing meals, shopping for groceries or clothes, using telephone, managing money or other such daily activities.

[c] *Self-care ADL:* refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Combination therapy:

Previously untreated multiple myeloma - patients who are not eligible for stem cell transplantation:

Recommended dosage in combination with melphalan and prednisone:

VELZOMY (bortezomib) for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in **Table 2**. In Cycles 1-4, VELZOMY is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, VELZOMY is administered once weekly (days 1, 8, 22 and 29).

Table 2: Recommended dosage regimen for VELZOMY when used in combination with melphalan and prednisone for patients with previously untreated multiple myeloma who are not eligible for stem cell transplantation.

TWICE WEEKLY VELZOMY (CYCLES 1-4)						
Week	**1**	**2**	**3**	**4**	**5**	**6**
VELZOMY (1,3 mg/m^2)	D - - D 1 4	D - - D 8 11	Rest period	D - - D 22 25	D - - D 29 32	Rest period
m (9 mg/m^2) **p (60 mg/m^2)**	D D D D 1 2 3 4	- -	Rest period	- -	- -	Rest period

ONCE WEEKLY VELZOMY (CYCLES 5-9)

Week	1	2	3	4	5	6
VELZOMY (1,3 mg/m^2)	D - - - 1	D 8	Rest period	D 22	D 29	Rest period
m (9 mg/m^2) p (60 mg/m^2)	D D D D 1 2 3 4	-	Rest period	-	-	Rest period

* D = Day; m = melphalan, p = prednisone

Dose management guidelines for combination therapy with melphalan and prednisone:

Dose modifications and re-initiation of therapy when VELZOMY is administered in combination with melphalan and prednisone:

Prior to initiating a new cycle of therapy:

- Platelet count should be ≥ 70 x 10^9/L and the ANC should be ≥ 1,0 x 10^9/L.
- Non-haematological toxicities should have resolved to Grade 1 or baseline.

Table 3: Dose modifications during subsequent cycles.

TOXICITY:	**DOSE MODIFICATIONS OR DELAY:**
Haematological toxicity during a cycle:	
• If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle.	Consider reduction of the melphalan dose by 25 % in the next cycle.
• If platelet count ≤ 30 x 10^9/L or ANC ≤ 0,75 x 10^9/L on a VELZOMY dosing day (other than day 1).	VELZOMY dose should be withheld.
• If several VELZOMY doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration).	VELZOMY dose should be reduced by 1 dose level (from 1,3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0,7 mg/m^2).
Grade ≥ 3 non-haematological toxicities.	VELZOMY therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline.

	Then, VELZOMY may be reinitiated with one dose level reduction (from 1,3 mg/m^2 to 1 mg/m^2 or from 1 mg/m^2 to 0,7 mg/m^2). For VELZOMY-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELZOMY as outlined in **Table 1**.

For additional information concerning melphalan and prednisone, see the respective professional information.

Previously untreated multiple myeloma – patients who are eligible for stem cell transplantation:

Recommended dosage:

The recommended starting dose of VELZOMY 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 10-18 days, which is considered a treatment cycle. Three to 6 cycles should be administered. At least 72 hours should elapse between consecutive doses of VELZOMY.

For VELZOMY dosage adjustments for transplant eligible patients follow dose modification guidelines described under monotherapy (**Table 1**) above.

For dosing instructions for other medicines combined with VELZOMY, see their respective professional information leaflets.

Relapsed multiple myeloma:

Recommended dosage in combination with pegylated liposomal doxorubicin:

For VELZOMY dosage and dose modifications, see **Monotherapy**.

Pegylated liposomal doxorubicin is administered at 30 mg/m² on day 4 of the VELZOMY 3-week regimen as a 1-hour intravenous infusion administered after the VELZOMY injection. For additional information concerning pegylated liposomal doxorubicin, see respective professional information leaflet.

Recommended dosage in combination with dexamethasone:

For VELZOMY dosage and dose modifications, see **Monotherapy**.

Dexamethasone is administered orally at 20 mg on the day of, and the day after, VELZOMY administration.

For additional information concerning dexamethasone, see respective professional information leaflet.

Retreatment for multiple myeloma:

Patients who have previously responded to treatment with VELZOMY (either alone or in combination) and who have relapsed should be started on retreatment at the last tolerated dose. Refer to **Monotherapy** for dosing schedule.

Previously untreated mantle cell lymphoma:

Recommended dosage in combination with rituximab, cyclophosphamide, doxorubicin and prednisone:

For VELZOMY dosage, see **Monotherapy**. Six VELZOMY cycles are administered. For patients with a response first documented at Cycle 6, two additional VELZOMY cycles are recommended.

The following medicines are administered on Day 1 of each VELZOMY 3-week 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 administered orally at 100 mg/m^2 on Days 1, 2, 3, 4 and 5 of each treatment cycle.

Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma:

Prior to the first day of each cycle (other than Cycle 1):

- Platelet count should be ≥ 100 x 10^9/L and absolute neutrophil count (ANC) should be ≥ 1,5 x 10^9/L
- Haemoglobin should be ≥ 8 g/dL (≥ 4,96 mmol/L)
- Non-haematologic toxicity should have recovered to Grade 1 or baseline.

VELZOMY treatment must be withheld at the onset of any Grade 3 non-haematological or Grade 3 haematological toxicities, excluding neuropathy (see **section 4.4**). For dose adjustments, see **Table 4** below.

Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration. Platelet transfusion for the treatment of thrombocytopenia should be considered

when clinically appropriate.

Table 4: Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma.

Toxicity:	**Posology modification or delay:**
Haematological toxicity • ≥ Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10 x 10^9/L	VELZOMY therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 0,75 x 10^9/L and a platelet count ≥ 25 x 10^9/L. • If, after VELZOMY has been held, the toxicity does not resolve, as defined above, then VELZOMY must be discontinued. • If toxicity resolves i.e., patient has an ANC ≥ 0,75 x 10^9/L and a platelet count ≥ 25 x 10^9/L, VELZOMY dose should be reduced by 1 dose level (from 1,3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0,7 mg/m^2).
• If platelet counts < 25 x 10^9/L or ANC < 0,75 x 10^9/L on a VELZOMY dosing day (other than Day 1) •	VELZOMY dose should be withheld
Grade ≥ 3 non-haematological toxicities	VELZOMY therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, VELZOMY may be reinitiated with one dose level reduction (from 1,3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0,7 mg/m^2). For VELZOMY-related neuropathic pain and/or peripheral neuropathy, hold and/or

	modify VELZOMY as outlined in **Table 1**.

For dosing instructions for rituximab, cyclophosphamide, doxorubicin, or prednisone, see the respective professional information leaflet.

Special populations:

Paediatric patients:

VELZOMY has not been studied in children and adolescents. Therefore, it should not be used in the paediatric age group.

Elderly patients:

There is no evidence to suggest that dose adjustments are necessary in the elderly (older than 65 years) with multiple myeloma or with mantle cell lymphoma (see **section 4.8**).

Patients with renal impairment:

The pharmacokinetics of VELZOMY are not influenced in patients with mild to moderate renal impairment (Creatinine Clearance [CrCL] > 20 ml/min/1,73 m^2). Therefore, dosing adjustments of VELZOMY are not necessary for patients with mild to moderate renal insufficiency. Since dialysis may reduce VELZOMY concentrations, VELZOMY should be administered after the dialysis procedure (see **section 5.2**).

Patients with hepatic impairment:

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended VELZOMY dose. Patients with moderate or severe hepatic impairment should be started on VELZOMY at a reduced dose of 0,7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1,0 mg/m^2 or further dose reduction to 0,5 mg/m^2 may be considered based on patient tolerance (see **Table 5**).

Table 5: Recommended starting dose modification for VELZOMY in patients with hepatic impairment.

Grade of hepatic impairment*	**Bilirubin Level**	**SGOT (AST) Levels**	**Modification of Starting Dose**

Mild	≤ 1,0 x ULN	> ULN	None
	> 1,0 x − 1,5 x ULN	Any	None
Moderate	> 1,5 x − 3 x ULN	Any	Reduce VELZOMY to 0,7 mg/m^2 in the first cycle. Consider dose escalation to 1,0 mg/m^2 or further dose reduction to 0,5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3 x ULN	Any	

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;

AST = aspartate aminotransferase, ULN = upper limit of the normal range.

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Method of administration:

Treatment must be initiated and administered under the supervision of a medical practitioner experienced in the use of chemotherapeutic medicines.

Administration precautions:

There have been fatal cases of inadvertent intrathecal administration of VELZOMY.

DO NOT ADMINISTER VELZOMY INTRATHECALLY.

Intravenous injection:

VELZOMY 3,5 mg reconstituted solution is administered as a 3 to 5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with sodium chloride 9 mg/ml (0,9 %) solution for injection.

At least 72 hours should elapse between consecutive doses of **VELZOMY.**

Subcutaneous injection:

The reconstituted solution is injected into 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 VELZOMY injection subcutaneously, a less concentrated VELZOMY solution (1 mg/ml instead of 2,5 mg/ml) may be administered subcutaneously or changed to IV injection.

4.3 Contraindications:

Hypersensitivity to bortezomib, to boron or to any of the excipients listed in **section 6.1**.

Acute diffuse infiltrative pulmonary and pericardial disease.

4.4 Special warnings and precautions for use:

There have been fatal cases of inadvertent intrathecal administration of VELZOMY.

Bortezomib 1 mg is for IV use only. VELZOMY 3,5 mg is for IV or SC use.

DO NOT ADMINISTER VELZOMY INTRATHECALLY.

When VELZOMY is given in combination with other medicines, the professional information of these other medicines must be consulted prior to initiation of treatment with VELZOMY.

Gastrointestinal toxicity:

Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with bortezomib treatment. Reactions usually occur early in treatment (Cycle 1 and 2) and may persist for several cycles. Cases of ileus have been reported (see **section 4.8**). Therefore, patients who experience constipation should be closely monitored. Patients experiencing treatment emergent gastrointestinal toxicity may benefit from administration of anti-emetics and anti-diarrhoeals. Fluid and electrolyte replacement should be administered to prevent or treat dehydration.

Haematological toxicity:

VELZOMY treatment is frequently associated with haematological toxicities (thrombocytopenia and neutropenia). However febrile neutropenia is a less frequent undesirable effect. The most frequent haematologic toxicity is transient thrombocytopenia, which generally resolves between treatment cycles. Platelets were lowest at Day 11 of each cycle of VELZOMY treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet decrease and recovery remained consistent over the 8 cycles of twice weekly dosing and there was no evidence of cumulative thrombocytopenia or neutropenia. In a multiple myeloma study with bortezomib and dexamethasone the mean platelet count nadir measured was approximately 40 % of baseline. Severe bleeding, including CNS and gastrointestinal bleeding, associated with thrombocytopenia, has been reported. In patients with advanced myeloma, the severity of thrombocytopenia was related to pre-treatment platelet count. Platelet counts should be monitored prior to each dose of VELZOMY. Therapy should be held when the platelet count is <25 000/µl or in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/µl, and re-initiated at a reduced dose after resolution (see **SIDE EFFECTS**). Potential benefit of the treatment should be carefully weighed against the risks. Platelet transfusions, red blood cell (RBC) transfusions and administration of growth factors may be utilised in the management of haematologic toxicities. Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

Herpes zoster virus reactivation:

Antiviral prophylaxis is recommended in patients being treated with VELZOMY. In studies in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was more frequent in patients treated with bortezomib+melphalan+prednisone compared with melphalan+prednisone (14 % versus 4 % respectively).

Hepatitis B virus (HBV) reactivation and infection:

When rituximab is administered in combination with VELZOMY, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with VELZOMY. Antiviral prophylaxis should be considered.

Progressive multifocal leukoencephalopathy (PML):

Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have

been reported in patients treated with VELZOMY. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of VELZOMY. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue VELZOMY if PML is diagnosed.

Peripheral neuropathy:

Treatment with VELZOMY is frequently associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy are likely to experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with VELZOMY. The incidence of peripheral neuropathy increases early in VELZOMY treatment and has been observed to peak during cycle 5.

It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperaesthesia, hypoaesthesia, paraesthesia, discomfort, neuropathic pain or weakness.

Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the dose or schedule. Neuropathy has been managed with supportive care and other therapies. Peripheral neuropathy may not be reversible.

Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving VELZOMY in combination with medicines known to be associated with neuropathy and appropriate dose reduction or treatment discontinuation should be considered.

In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.

Seizures:

Seizures have been less frequently reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

Hypotension:

VELZOMY treatment is frequently associated with orthostatic/postural hypotension. Most adverse reactions are mild to moderate in nature and are observed throughout treatment. Patients who developed orthostatic hypotension on VELZOMY (injected intravenously) did not have evidence of orthostatic hypotension prior to treatment with VELZOMY. Most patients required treatment for their orthostatic hypotension. A minority of patients with orthostatic hypotension experienced syncopal events.

Orthostatic/postural hypotension was not acutely related to bolus infusion of VELZOMY. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to VELZOMY or VELZOMY may aggravate an underlying condition such as diabetic or amyloidotic neuropathy. Caution is advised in these patients.
Caution is advised when treating patients with a history of syncope receiving medicines known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicines, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

Posterior Reversible Encephalopathy Syndrome (PRES):

There have been reports of *PRES* in patients receiving bortezomib. *PRES* is a rare, often reversible, rapidly evolving neurological condition, which can present with seizure, hypertension, headache, lethargy, confusion, blindness and other visual and neurological disturbances. Brain imaging, preferably Magnetic Resonance Imaging (MRI), is used to confirm the diagnosis. In patients developing PRES, VELZOMY should be discontinued.

Heart failure:

Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during VELZOMY treatment. Fluid retention may be a predisposing factor for

signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored.

Patients using angiotensin inhibitors, betablockers, antihypertensives, calcium channel blockers, angiotensin receptor blockers and diuretics may have a higher incidence of cardiac failure during VELZOMY treatment.

Electrocardiogram investigations:

There have been isolated cases of QT-interval prolongation in clinical studies, causality has not been established.

Pulmonary disorders:

There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration and acute respiratory distress syndrome (ARDS) in patients receiving VELZOMY (see **section 4.8**). Some of these events have been fatal. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes.

In the event of new or worsening pulmonary symptoms (e.g. cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients treated appropriately.

High-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours with daunorubicin and bortezomib has been associated with ARDS and death early in the course of therapy. Therefore, this specific regimen with VELZOMY and high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours is not recommended.

Renal impairment:

Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely (see **sections 4.2** and **5.2**).

Hepatic impairment:

Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with VELZOMY at reduced doses and closely monitored for toxicities (see **sections 4.2** and **5.2**).

Hepatic reactions:

Rare cases of hepatic failure have been reported in patients receiving VELZOMY and concomitant medicines and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia and hepatitis. Such changes may be reversible upon discontinuation of VELZOMY (see **section 4.8**).

Tumour lysis syndrome:

Because VELZOMY is a cytotoxic medicine and can rapidly kill malignant plasma cells and MCL cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. Symptoms of tumour lysis syndrome are weakness, vomiting, cramps, seizure, oedema and fluid overload, congestive heart failure, dysrhythmias and syncope. These patients should be monitored closely and appropriate precautions taken.

Concomitant medicines:

Patients should be closely monitored when given VELZOMY in combination with potent CYP3A4-inhibitors. Caution should be exercised when VELZOMY is combined with CYP3A4- or CYP2C19 substrates (see **section 4.5**).

Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycaemics (see **section 4.5**).

Potentially immunocomplex-mediated reactions:

Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported less frequently. VELZOMY should be discontinued if serious reactions occur.

4.5 Interaction with other medicines and other forms of interaction:

In vitro studies indicate that VELZOMY is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution (7 %) of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metaboliser phenotype is not expected to affect the overall disposition of VELZOMY.

A medicine interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of VELZOMY (injected intravenously), showed a mean bortezomib AUC increase of 35 % ($CI_{90\ \%}$ [1,032 to 1,772]) based on data from 12 patients. Therefore, patients should be closely monitored when given VELZOMY in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

In a medicine interaction study assessing the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of VELZOMY (injected intravenously), there was no significant effect on the pharmacokinetics of VELZOMY based on data from 17 patients.

Concomitant exposure to narcotics may increase the incidence of constipation, nausea and vomiting.

A medicine interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of VELZOMY (injected intravenously), showed a mean bortezomib AUC reduction of 45 % based on data from 6 patients. Therefore, the concomitant use of VELZOMY with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced.

In the same medicine interaction study assessing the effect of dexamethasone, a weaker CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), there was no significant effect on the pharmacokinetics of VELZOMY based on data from 7 patients.

A medicine interaction study assessing the effect of melphalan-prednisone on the pharmacokinetics of VELZOMY (injected intravenously), showed a mean bortezomib AUC increase of 17 % based on data from 21 patients. This is not considered clinically relevant.

During clinical trials, hypoglycaemia and hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics. Patients on oral antidiabetic medicines receiving VELZOMY treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medicines. Normal liver function should be confirmed and caution should be exercised in patients receiving oral hypoglycaemics.

Patients should be cautioned about the use of concomitant medications that may be associated with peripheral

neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

4.6 Fertility, pregnancy and lactation:

Contraception in males and females:

Male and female patients of childbearing potential must use effective contraceptive measures during and for 3 months following VELZOMY treatment.

Pregnancy:

No clinical data are available for VELZOMY with regard to exposure during pregnancy. The teratogenic potential of VELZOMY has not been fully investigated.

VELZOMY should not be used during pregnancy and if the patient becomes pregnant while receiving VELZOMY, the patient should be informed of the potential for hazard to the foetus.

Breastfeeding:

It is not known whether VELZOMY is excreted in human milk. Because of the potential for serious adverse reactions in breastfed infants, breastfeeding should be discontinued during treatment with VELZOMY.

Fertility:

Fertility studies were not conducted with VELZOMY (see **section 5.3**).

4.7 Effects on ability to drive and use machines:

VELZOMY may have a moderate influence on the ability to drive and use machines. VELZOMY may be associated with fatigue, dizziness, syncope and orthostatic/postural hypotension or blurred vision. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see **section 4.8**).

4.8 Undesirable effects:

Summary of the safety profile:

Serious adverse reactions less frequently reported during treatment with VELZOMY include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and autonomic neuropathy. The most frequently reported adverse reactions during treatment with VELZOMY are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Table 6: Adverse reactions in patients with multiple myeloma treated with bortezomib in clinical trials, and all post-marketing adverse reactions regardless of indication[#]:

SYSTEM ORGAN CLASS:	**INCIDENCE:**	**ADVERSE REACTION:**
Infections and infestations:	*Frequent:*	Herpes zoster (incl disseminated & ophthalmic), pneumonia*, herpes simplex*, fungal infection*
	Less frequent:	Infection*, bacterial infections*, viral infections*, sepsis (incl septic shock)*, bronchopneumonia, herpes virus infection*, meningoencephalitis herpetic[#], bacteraemia (incl staphylococcal), hordeolum, influenza, cellulitis, device related infection, skin infection*, ear infection*, staphylococcal infection, tooth infection*, meningitis (incl bacterial), Epstein-Barr virus infection, genital herpes, tonsillitis, mastoiditis, post viral fatigue syndrome
Neoplasms benign, malignant and unspecified (incl cysts and polyps):	*Less frequent:*	Neoplasm malignant, leukaemia plasmacytic, renal cell carcinoma, mass, mycosis fungoides, neoplasm benign*, cutaneous T-cell lymphoma
Blood and lymphatic system disorders:	*Frequent:*	Thrombocytopenia*, neutropenia*, anaemia*, leukopenia*, lymphopenia*

	Less frequent:	Pancytopenia*, febrile neutropenia, coagulopathy*, leukocytosis*, lymphadenopathy, haemolytic anaemia#, disseminated intravascular coagulation, thrombocytosis*, hyperviscosity syndrome, platelet disorder**, thrombocytopenic purpura, blood disorder**, haemorrhagic diathesis, lymphocytic infiltration, thrombotic microangiopathy (including thrombocytopenic purpura)#
Immune system disorders:	*Less frequent:*	Angioedema#, hypersensitivity*, anaphylactic shock, amyloidosis, type III immune complex mediated reaction
Endocrine disorders:	*Less frequent:*	Cushing's syndrome*, hyperthyroidism*, inappropriate antidiuretic hormone secretion, hypothyroidism
Metabolism and nutrition disorders:	*Frequent:*	Decreased appetite, dehydration, hypokalaemia*, hyponatraemia*, blood glucose abnormal*, hypocalcaemia*, enzyme abnormality*
	Less frequent:	Tumour lysis syndrome, failure to thrive*, hypomagnesaemia*, hypophosphataemia*, hyperkalaemia*, hypercalcaemia*, hypernatraemia*, uric acid abnormal*, diabetes mellitus*, fluid retention, hypermagnesaemia*, acidosis, electrolyte imbalance*, fluid overload, hypochloraemia*, hypovolaemia, hyperchloraemia*, hyperphosphataemia*, metabolic disorder, vitamin B complex deficiency, vitamin B12 deficiency, gout, increased appetite, alcohol intolerance
Psychiatric disorders:	*Frequent:*	Mood disorders and disturbances*, anxiety disorder*, sleep disorders and disturbances*
	Less frequent:	Mental disorder*, hallucination*, psychotic disorder*, confusion*, restlessness, suicidal ideation*, adjustment disorder, delirium, libido decreased

Nervous system disorders:	*Frequent:*	Neuropathies*, peripheral sensory neuropathy, dysaesthesia*, neuralgia*, motor neuropathy*, loss of consciousness (incl syncope), dizziness*, dysgeusia*, lethargy, headache*
	Less frequent:	Tremor, peripheral sensorimotor neuropathy, dyskinesia*, cerebellar coordination and balance disturbances*, memory loss (excl dementia)*, encephalopathy*, posterior reversible encephalopathy syndrome#, neurotoxicity, seizure disorders*, post herpetic neuralgia, speech disorder*, restless legs syndrome, migraine, sciatica, disturbance in attention, reflexes abnormal*, parosmia, cerebral haemorrhage*, haemorrhage intracranial (incl subarachnoid)*, brain oedema, transient ischaemic attack, coma, autonomic nervous system imbalance, autonomic neuropathy, cranial palsy*, paralysis*, paresis*, presyncope, brain stem syndrome, cerebrovascular disorder, nerve root lesion, psychomotor hyperactivity, spinal cord compression, cognitive disorder**, motor dysfunction, nervous system disorder**, radiculitis, drooling, hypotonia, Guillain-Barré syndrome#, demyelinating polyneuropathy#
Eye disorders:	*Frequent:*	Eye swelling*, vision abnormal*, conjunctivitis*
	Less frequent:	Eye haemorrhage*, eyelid infection*, eye inflammation*, diplopia, dry eye*, eye irritation*, eye pain, lacrimation increased, eye discharge, corneal lesion*, exophthalmos, retinitis, scotoma, eye disorder (incl eyelid)**, dacryoadenitis acquired, photophobia, photopsia, optic neuropathy#, different degrees of visual impairment (up to blindness)*, chalazion#, blepharitis#
Ear and labyrinth disorders:	*Frequent:*	Vertigo*
	Less frequent:	Dysacusis (incl tinnitus)*, hearing impaired (up to and incl deafness), ear discomfort*, ear haemorrhage, vestibular neuronitis, ear disorder**

Cardiac disorders:	*Less frequent:*	Cardiac tamponade[#], cardio-pulmonary arrest*, cardiac fibrillation (incl atrial), cardiac failure (incl left and right ventricular)*, dysrhythmia*, tachycardia*, palpitations, angina pectoris, pericarditis (incl pericardial effusion)*, cardiomyopathy*, ventricular dysfunction*, bradycardia, atrial flutter, myocardial infarction*, atrioventricular block*, cardiovascular disorder (incl cardiogenic shock), torsade de pointes, angina unstable, cardiac valve disorders*, coronary artery insufficiency, sinus arrest
Vascular disorders:	*Frequent:*	Hypotension*, orthostatic hypotension, hypertension*
	Less frequent:	Cerebrovascular accident[#], deep vein thrombosis*, haemorrhage*, thrombophlebitis (incl superficial), circulatory collapse (incl hypovolaemic shock), phlebitis, flushing*, haematoma (incl peri-renal)*, poor peripheral circulation*, vasculitis, hyperaemia (incl ocular)*, peripheral embolism, lymphoedema, pallor, erythromelalgia, vasodilatation, vein discolouration, venous insufficiency
Respiratory, thoracic and mediastinal disorders:	*Frequent:*	Dyspnoea*, epistaxis, upper/lower respiratory tract infection*, cough*
	Less frequent:	Pulmonary embolism, pleural effusion, pulmonary oedema (incl acute), pulmonary alveolar haemorrhage[#], bronchospasm, chronic obstructive pulmonary disease*, hypoxaemia*, respiratory tract congestion*, hypoxia, pleurisy*, hiccups, rhinorrhoea, dysphonia, wheezing, respiratory failure, acute respiratory distress syndrome, apnoea, pneumothorax, atelectasis, pulmonary hypertension, haemoptysis, hyperventilation, orthopnoea, pneumonitis, respiratory alkalosis, tachypnoea, pulmonary fibrosis, bronchial disorder*, hypocapnia*, interstitial lung disease, lung infiltration, throat tightness, dry throat, increased upper airway secretion, throat irritation, upper-airway cough syndrome

Gastrointestinal disorders:	*Frequent:*	Nausea and vomiting symptoms*, diarrhoea*, constipation, gastrointestinal haemorrhage (incl mucosal)*, dyspepsia, stomatitis*, abdominal distension, oropharyngeal pain*, abdominal pain (incl gastrointestinal and splenic pain)*, oral disorder*, flatulence
	Less frequent:	Pancreatitis (incl chronic)*, haematemesis, lip swelling*, gastrointestinal obstruction (incl small intestinal obstruction, ileus)*, abdominal discomfort, oral ulceration*, enteritis*, gastritis*, gingival bleeding, gastro-oesophageal reflux disease*, colitis (incl clostridium difficile)*, colitis ischaemic#, gastrointestinal inflammation*, dysphagia, irritable bowel syndrome, gastrointestinal disorder**, tongue coated, gastrointestinal motility disorder*, salivary gland disorder*, pancreatitis acute, peritonitis*, tongue oedema*, ascites, oesophagitis, cheilitis, faecal incontinence, anal sphincter atony, faecaloma*, gastrointestinal ulceration and perforation*, gingival hypertrophy, megacolon, rectal discharge, oropharyngeal blistering*, lip pain, periodontitis, anal fissure, change of bowel habit, proctalgia, abnormal faeces
Hepatobiliary disorders:	*Frequent:*	Hepatic enzyme abnormality*
	Less frequent:	Hepatotoxicity (incl liver disorder), hepatitis*, cholestasis, hepatic failure, hepatomegaly, Budd-Chiari syndrome, cytomegalovirus hepatitis, hepatic haemorrhage, cholelithiasis
Skin and	*Frequent:*	Rash*, pruritus*, erythema, dry skin

subcutaneous tissue disorders:	*Less frequent:*	Erythema multiforme, urticaria, acute febrile neutrophilic dermatosis, toxic skin eruption, toxic epidermal necrolysis#, Stevens-Johnson syndrome#, dermatitis*, hair disorder*, petechiae, ecchymosis, skin lesion, purpura, skin mass*, psoriasis, hyperhidrosis, night sweats, decubitus ulcer#, acne*, blister*, pigmentation disorder*, skin reaction, jessner's lymphocytic infiltration, palmar- plantar erythrodysaesthesia syndrome, haemorrhage subcutaneous, livedo reticularis, skin induration, papule, photosensitivity reaction, seborrhoea, cold sweat, skin disorder**, erythrosis, skin ulcer, nail disorder
Musculoskeletal and connective tissue disorders:	*Frequent:*	Musculoskeletal pain*, muscle spasms*, pain in extremity, muscular weakness
	Less frequent:	Muscle twitching, joint swelling, arthritis*, joint stiffness, myopathies*, sensation of heaviness, rhabdomyolysis, temporomandibular joint syndrome, fistula, joint effusion, pain in jaw, bone disorder, musculoskeletal and connective tissue infections and inflammations*, synovial cyst
Renal and urinary disorders:	*Frequent:*	Renal impairment*
	Less frequent:	Renal failure acute, renal failure chronic*, urinary tract infection*, urinary tract signs and symptoms*, haematuria*, urinary retention, micturition disorder*, proteinuria, uraemia, oliguria*, pollakiuria, bladder irritation

Reproductive system and breast disorders:	*Less frequent:*	Vaginal haemorrhage, genital pain*, erectile dysfunction, testicular disorder*, prostatitis, breast disorder female, epididymal tenderness, epididymitis, pelvic pain, vulval ulceration
Congenital, familial and genetic disorders:	*Less frequent:*	Aplasia, gastrointestinal malformation, ichthyosis
General disorders and administration site conditions:	*Frequent:*	Pyrexia*, fatigue, asthenia, oedema (incl peripheral), chills, pain*, malaise*
	Less frequent:	General physical health deterioration*, face oedema*, injection site reaction*, mucosal disorder*, chest pain, gait disturbance, feeling cold, extravasation*, catheter related complication*, change in thirst*, chest discomfort, feeling of body temperature change*, injection site pain*, death (incl sudden), multi-organ failure, injection site haemorrhage*, hernia (incl hiatus)*, impaired healing*, inflammation, injection site phlebitis*, tenderness, ulcer, irritability, non-cardiac chest pain, catheter site pain, sensation of foreign body
Investigations:	*Frequent:*	Weight decreased
	Less frequent:	Hyperbilirubinaemia*, protein analyses abnormal*, weight increased, blood test abnormal*, C-reactive protein increased, blood gases abnormal*, electrocardiogram abnormalities (incl QT prolongation)*, international normalised ratio abnormal*, gastric pH decreased, platelet aggregation increased, troponin I increased, virus identification and serology*, urine analysis abnormal*

Injury, poisoning and procedural complications:	*Less frequent:*	Fall, contusion, transfusion reaction, fractures*, rigors*, face injury, joint injury*, burns, laceration, procedural pain, radiation injuries*
Surgical and medical procedures:	*Less frequent:*	Macrophage activation

** Not otherwise specified

* Grouping of more than one MedDRA preferred term

Postmarketing adverse reaction regardless of indication

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the '**6.04 Adverse Drug Reactions Reporting Form**', found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

In patients, overdose more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes. There is no known specific antidote for VELZOMY overdose. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents,

ATC code: L01XX32.

Mechanism of action:

Bortezomib is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated

proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death.

Bortezomib is highly selective for the proteasome. At 10 µM concentrations, bortezomib does not inhibit any of a wide variety of receptors and proteases screened and is more than 1,500-fold more selective for the proteasome than for its next preferable enzyme. The kinetics of proteasome inhibition were evaluated *in vitro*, and bortezomib was shown to dissociate from the proteasome with a $t_{½}$ of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible.

Bortezomib mediated proteasome inhibition affects cancer cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumourigenesis, including cell growth and survival, angiogenesis, cell-cell interactions and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.

Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the pro-apoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth *in vivo* in many preclinical tumour models, including multiple myeloma.

5.2 Pharmacokinetic properties:

Absorption:

Following intravenous bolus administration of a 1,0 mg/m^2 and 1,3 mg/m^2 dose in eleven patients with multiple myeloma and creatinine clearance values greater than 50 ml/min, the mean first-dose maximum plasma concentrations of bortezomib were 57 and 112 ng/ml, respectively. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/ml for the 1,0 mg/m^2 dose and 89 to 120 ng/ml for the 1,3 mg/m^2 dose.

Following an intravenous bolus of a 1,3 mg/m^2 dose to patients with multiple myeloma, the total systemic exposure

after repeat dose administration (AUC_{last}) was equivalent for intravenous administrations. The C_{max} after subcutaneous administration (20,4 ng/ml) was lower than intravenous (223 ng/ml). The AUC_{last} geometric mean ratio was 0,99 and 90 % confidence intervals were 80,18 %-122,80 %.

Distribution:

The mean distribution volume (V_d) of bortezomib ranged from 1,659 L to 3,294 L following single-or repeated-dose intravenous administration of 1,0 mg/m^2 or 1,3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. Over a bortezomib concentration range of 0,01 to 1,0 µg/ml, the *in vitro* protein binding averaged 82,9 % in human plasma. The fraction of bortezomib bound to plasma proteins was not concentration-dependent.

Biotransformation:

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19 and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent molecule.

Elimination:

The mean elimination half-life ($t_{1/2}$) of bortezomib upon multiple dosing ranged from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively, and ranged from 15 to 32 L/h and 18 to 32 L/h following subsequent doses for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively.

Special populations:

Hepatic impairment:

Mild hepatic impairment did not alter dose-normalised bortezomib AUC. Dose-normalised mean AUC values were increased by approximately 60 % in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be closely

monitored (see **section 4.2**).

Renal impairment:

Bortezomib exposure is comparable in patients with various (mild, moderate to severe) degrees of renal impairment (see **section 4.2**).

5.3 Preclinical safety data:

Bortezomib was positive for clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary (CHO) cells at concentrations as low as 3,125 µg/ml, which was the lowest concentration evaluated. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames assay) and *in vivo* micronucleus assay in mice.

Developmental toxicity studies in the rat and rabbit have shown embryo-foetal lethality at maternally toxic doses, but no direct embryo-foetal toxicity below maternally toxic doses. Fertility studies were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the 6-month rat study, degenerative effects in both the testes and the ovary have been observed. It is, therefore, likely that bortezomib could have a potential effect on either male or female fertility. Peri- and postnatal development studies were not conducted.

In multi-cycle general toxicity studies conducted in the rat and monkey, the principal target organs included the gastrointestinal tract, resulting in vomiting and/or diarrhoea; haematopoietic and lymphatic tissues, resulting in peripheral blood cytopenias, lymphoid tissue atrophy and haematopoietic bone marrow hypocellularity; peripheral neuropathy (observed in monkeys, mice and dogs) involving sensory nerve axons; and mild changes in the kidneys. All these target organs have shown partial to full recovery following discontinuation of treatment.

Based on animal studies, the penetration of bortezomib through the blood-brain barrier appears to be limited, if any and the relevance to humans is unknown.

Cardiovascular safety pharmacology studies in monkeys and dogs show that intravenous doses approximately two to three times the recommended clinical dose on a mg/m^2 basis are associated with increases in heart rate, decreases in contractility, hypotension and death. In dogs, the decreased cardiac contractility and hypotension

responded to acute intervention with positive inotropic or pressor medicines. Moreover, in dog studies, a slight increase in the corrected QT interval was observed.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Mannitol (E421)

6.2 Incompatibilities:

VELZOMY must not be mixed with other medicines except those mentioned in **section 6.6**.

6.3 Shelf life:

Unopened vial:

3 years.

Reconstituted solution:

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25 °C stored in the original vial and/or a syringe.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, 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.

6.4 Special precautions for storage:

Store at or below 25 °C.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of VELZOMY, see **section 6.3**.

6.5 Nature and contents of container:

Type I colourless glass, 10 ml vial with a bromobutyl rubber stopper and sealed with an aluminium metallic cap with polypropylene disk, containing 3,5 mg bortezomib.

Each pack contains 1 single use vial.

6.6 Special precautions for disposal and other handling:

General precautions:

Bortezomib is a cytotoxic medicine. Therefore, caution should be used during handling and preparation of VELZOMY. Use of gloves and other protective clothing to prevent skin contact is recommended.

Aseptic technique must be strictly observed throughout the handling of VELZOMY, since it contains no preservative.

There have been fatal cases of inadvertent intrathecal administration of bortezomib. VELZOMY 1 mg powder for solution for injection is for intravenous use only, and VELZOMY 3,5 mg powder for solution for injection is for intravenous use or subcutaneous use. When administered subcutaneously, alternate sites for each injection (thigh or abdomen) should be used. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

VELZOMY should not be administered intrathecally.

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

VELZOMY is provided as a lyophilised powder in the form of a mannitol boronic ester. When reconstituted, the mannitol ester is in equilibrium with its hydrolysis product, the monomeric boronic acid.

Instructions for reconstitution:

VELZOMY must be reconstituted by a healthcare provider.

Intravenous injection:

Each 10 ml vial of VELZOMY must be reconstituted with 3,5 ml of sodium chloride 9 mg/ml (0,9 %) solution for injection. Dissolution of the lyophilised powder is completed in less than 2 minutes. After reconstitution, each ml solution contains 1 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The

reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

VELZOMY must not be mixed with any other medicinal products except for normal (0,9 %) saline, sodium chloride injection, USP.

Table 7: The contents of each vial should be reconstituted only with normal (0,9 %) saline according to the following instructions based on route of administration:

	IV	**SC**
	(3,5 mg bortezomib)	**(3,5 mg bortezomib)**
Volume of diluent (0,9 % sodium chloride) added to reconstitute one vial	3,5 ml	1,4 ml
Final concentration after reconstitution (mg/ml)	1,0 mg/ml	2,5 mg/ml

Dissolution is completed in less than 2 minutes. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted product must be discarded. 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 chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 25 °C stored in the original vial and/or a syringe prior to administration, with a maximum of 8 hours in the syringe.
Any unused product or waste material should be disposed of appropriately.

Disposal:

VELZOMY is for single use only.

Discard any unused portion.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park, Magwa Crescent West

Waterfall City

Midrand

Gauteng

2090

Tel: 011 055 0200

8. REGISTRATION NUMBER(S):

52/26/0471

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

24 March 2020

10. DATE OF REVISION OF THE TEXT:

20 February 2022