PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

VELCADE® 1,0 mg powder for solution for injection for intravenous use only.

VELCADE® 3,5 mg powder for solution for injection for intravenous and subcutaneous use.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VELCADE 1,0 mg vial contains 1,0 mg of bortezomib (as a mannitol boronic ester).

Intravenous (IV) use only.

Contains sugar: 0,01 g mannitol per vial.

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

Intravenous (IV) or subcutaneous (SC) use.

Contains sugar: 0,035 g mannitol per vial.

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.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilised powder for injection. White to off-white cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VELCADE for injection 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

Posology

VELCADE 1 mg powder for solution for injection is available for:

- intravenous administration only at a concentration of 1 mg/mL (as a 3-5 second bolus injection).

VELCADE 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 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.

VELCADE 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.

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

Monotherapy

Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Recommended dosage

The recommended starting dose of VELCADE 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. It is recommended that patients receive 2 cycles of VELCADE 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 VELCADE.

Dose modification and re-initiation of treatment

VELCADE 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 also section 4.4). Once the symptoms of the toxicity have resolved, VELCADE 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 VELCADE 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 VELCADE-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 VELCADE only after careful risk/benefit assessment.

Table 1: Recommended* Dose Modifications for VELCADE related Neuropathic Pain and/or Peripheral Sensory Neuropathy or Motor Neuropathy.

Severity of Peripheral Neuropathy Signs and Symptoms [a]	**Modification of Dose and 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 VELCADE to 1,0 mg/m^2 OR Change VELCADE 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 VELCADE therapy until toxicity resolves. When toxicity resolves re-initiate with a reduced dose of VELCADE at 0,7 mg/m^2 once per week.
Grade 4 (life threatening consequences; urgent intervention indicated)	Discontinue VELCADE

*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

VELCADE (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, VELCADE is administered twice weekly (days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5-9, VELCADE is administered once weekly (days 1, 8, 22 and 29).

Table 2: Recommended Dosage Regimen for VELCADE 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 VELCADE (Cycles 1-4)

Week	**1**				**2**		**3**	**4**		**5**		**6**
Vc (1,3 mg/m^2)	Day 1	--	--	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
m (9 mg/m^2) p (60 mg/m$^{2)}$	Day 1	Day 2	Day 3	Day 4	--	--	rest period	--	--	--	--	rest period

Once Weekly VELCADE (Cycles 5-9)

Week	**1**				**2**	**3**	**4**	**5**	**6**
Vc (1,3 mg/m$^{2)}$	Day 1	--	--	--	Day 8	rest period	Day 22	Day 29	rest period
m (9 mg/m^2) p (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	--	rest period	--	--	rest period

Vc = VELCADE; m = melphalan, p=prednisone

Dose Management Guidelines for Combination Therapy with Melphalan and Prednisone

Dose modification and re-initiation of therapy when VELCADE 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 absolute neutrophil count (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 modification 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 × 10^9/L or ANC ≤ 0,75 x 10^9/L on a VELCADE dosing day (other than day 1)	VELCADE dose should be withheld
- If several VELCADE doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	VELCADE 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	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, VELCADE 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 VELCADE-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELCADE as outlined in Table 1.

For additional information concerning melphalan and prednisone, refer to their respective professional information leaflets.

Previously Untreated Multiple Myeloma – Patients who are Eligible for Stem Cell Transplantation

Recommended Dosage

The recommended starting dose of VELCADE 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 VELCADE.

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

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

Relapsed Multiple Myeloma

Recommended Dosage in Combination with Pegylated Liposomal Doxorubicin

For VELCADE dosage and dose modifications, see Monotherapy.

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

Recommended Dosage in Combination with Dexamethasone

For VELCADE dosage and dose modifications, see Monotherapy.

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

For additional information concerning dexamethasone, see respective professional information leaflet

Retreatment for Multiple Myeloma

Patients who have previously responded to treatment with VELCADE (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 VELCADE dosage, see Monotherapy. Six VELCADE cycles are administered. For patients with a response first documented at Cycle 6, two additional VELCADE cycles are recommended.

The following medicines are administered on Day 1 of each VELCADE 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

VELCADE treatment must be withheld at the onset of any Grade 3 non-haematological or Grade 3 haematological toxicities, excluding neuropathy (see also 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	VELCADE 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 VELCADE has been held, the toxicity does not resolve, as defined above, then VELCADE must be discontinued. • If toxicity resolves i.e., patient has anANC ⩾ 0,75 x 10^9/L and a platelet count ⩾ 25 x 10^9/L, VELCADE 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 VELCADE dosing day (other than Day 1)	VELCADE dose should be withheld

Grade ⩾ 3 non-haematological toxicities	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, VELCADE 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 VELCADE-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELCADE as outlined in Table 1.

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

Special populations

Paediatric patients

VELCADE 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 VELCADE 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 VELCADE are not necessary for patients with mild to moderate renal insufficiency. Since dialysis may reduce VELCADE concentrations, VELCADE 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 VELCADE dose. Patients with moderate or severe hepatic impairment should be started on VELCADE at a reduced dose of 0,7 mg/m² 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 VELCADE 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 VELCADE 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 agents.

Administration Precautions

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

DO NOT ADMINISTER VELCADE INTRATHECALLY.

VELCADE 1 mg

VELCADE 1 mg is for IV use only.

The reconstituted solution is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0,9 % sodium chloride solution for injection.

At least 72 hours should elapse between consecutive doses of VELCADE.

VELCADE 3,5 mg

Intravenous injection:

The reconstituted solution is administered as a 3-5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0,9 % sodium chloride solution for injection.

At least 72 hours should elapse between consecutive doses of VELCADE.

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 VELCADE injection subcutaneously, a less concentrated VELCADE solution (1 mg/mL instead of 2,5 mg/mL) may be administered

subcutaneously or changed to IV injection.

4.3 Contraindications

Hypersensitivity to VELCADE, boron or to any of the excipients

(see 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 VELCADE. VELCADE 1 mg is for IV use only. VELCADE 3,5 mg is for IV or SC use.

DO NOT ADMINISTER VELCADE INTRATHECALLY.

Herpes Zoster Virus Reactivation

Medical practitioners should consider the need for antiviral prophylaxis in patients being treated with VELCADE. In the phase 3 study in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was very common in patients treated with Velcade, Melphalan and Prednisone (VcMP).

In patients with MCL (study LYM-3002), the incidence of herpes zoster infection was 6,7 % in the VcR-CAP arm and 1,2 % in the R-CHOP arm (see section 4.8).

Hepatitis B Virus (HBV) reactivation and infection

When rituximab is used in combination with VELCADE, 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 VELCADE.

Antiviral prophylaxis should be considered. Refer to the Professional Information of rituximab for more information.

Laboratory Tests

Complete blood counts (CBC) including platelet counts should be frequently monitored throughout treatment with VELCADE.

Gastrointestinal toxicity

Gastrointestinal toxicity, including diarrhoea, constipation, nausea and vomiting are very common with VELCADE treatment (see section 4.8). Reactions usually occur early in treatment (Cycles 1 and 2) and may persist for several cycles. 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. Cases of ileus have been reported therefore patients who experience constipation should be closely monitored.

Haematological toxicity

VELCADE treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). However, febrile neutropenia is an uncommon undesirable effect. The most common haematologic toxicity is transient thrombocytopenia, which generally resolves between treatment cycles. Platelets were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet count decrease, and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in any of the regimens studied.

Platelet counts should be monitored prior to each dose of VELCADE. Therapy should be withheld 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 (see sections 4.2 and 4.8). Severe bleeding, including central nervous system (CNS) and gastrointestinal bleeding, associated with thrombocytopenia, has been reported. 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 haematological toxicities. Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

In the multiple myeloma study of VELCADE vs dexamethasone, the mean platelet count nadir measured was approximately 40 % of baseline. The severity of thrombocytopenia related to pre-treatment platelet count is shown in Table 6. The incidence of significant bleeding events (≥ Grade 3) was similar on both the VELCADE (4 %) and dexamethasone (5 %) arms.

Table 6: Severity of Thrombocytopenia Related to Pre-treatment Platelet Count in the Phase 3 Multiple Myeloma Study of VELCADE vs Dexamethasone

Pre-treatment Platelet Count[a]	Number of Patients (N=331) [b]	Number of Patients with Platelet Count < 10,000/μL	Number of Patients with Platelet Count 10,000 -25,000/μL
≥ 75,000/μL	309	8 (3 %)	36 (12 %)
≥ 50,000/μL – < 75,000/μL	14	2 (14 %)	11 (79 %)
≥ 10,000/μL – < 50,000/μL	7	1 (14 %)	5 (71 %)

[a] A baseline platelet count of 50,000/μL was required for study eligibility.

[b] Data for one patient was missing at baseline.

In the combination study of VELCADE with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP) in previously untreated mantle cell lymphoma patients, the incidence of thrombocytopenia adverse events (≥ Grade 4) was 32 % VcR-CAP versus 2 % for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm. The incidence of bleeding adverse events (≥ Grade 3) was 1,7 % (4 patients) in the VcR-CAP arm and was 1,2 % (3 patients) in the R-CHOP arm.

There were no deaths due to bleeding events in either arm. There were no CNS bleeding events in the VcR-CAP arm; there was 1 bleeding event in the R-CHOP arm. Platelet transfusions were given to 23 % of the patients in the VcR-CAP arm and 3 % of the patients in the R-CHOP arm.

The incidence of neutropenia (≥ Grade 4) was 70 % in the VcR-CAP arm and 52 % in the R-CHOP arm. The incidence of febrile neutropenia (≥ Grade 4) was 5 % in the VcR-CAP arm and 6 % in the R-CHOP arm. Colony-stimulating factor support was provided at a rate of 78 % in the VcR-CAP arm and 61 % in the R-CHOP arm.

Peripheral Neuropathy

VELCADE treatment causes a peripheral neuropathy (PN) that 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 VELCADE. The incidence of peripheral neuropathy increases early in the 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. In the Phase 3 study comparing VELCADE IV vs SC the incidence of Grade ≥ 2 peripheral neuropathy events was 24 % for SC and 41 % for IV (p=0,0124). Grade ≥ 3 peripheral neuropathy occurred in 6 % of subjects in the SC treatment group, compared with 16 % in the IV treatment group (p=0,0264) (see section 4.8). Therefore, patients with pre-existing PN or at high risk of peripheral neuropathy may benefit from starting VELCADE subcutaneously.

Patients experiencing new or worsening peripheral neuropathy may require the dose, schedule or route of administration to SC to be modified (see section 4.2). Neuropathy has been managed with supportive care and other therapies. Peripheral neuropathy may not be reversible.

Improvement in, or resolution of, peripheral neuropathy was reported in 51 % of patients with ≥ Grade 2 peripheral neuropathy in the single agent phase 3 multiple myeloma study of VELCADE vs dexamethasone and 73 % of patients with grade 3 or 4 peripheral neuropathy or peripheral neuropathy leading to discontinuation of treatment in phase 2 studies, respectively.

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. The long-term outcome of peripheral neuropathy has not been studied in Mantle Cell Lymphoma.

Seizures

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

Hypotension

VELCADE treatment is commonly associated with orthostatic/postural hypotension. Most patients required treatment for their orthostatic hypotension. Patients with orthostatic hypotension experienced syncopal events. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to VELCADE or VELCADE may aggravate an underlying condition such as diabetic or amyloidotic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension is symptomatic and may include adjustment of antihypertensive medicinal products, 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.

Cardiac Disorders

Development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported. Patients with risk factors for, or existing heart disease should be closely monitored. Fluid retention may be a predisposing factor for signs and symptoms of heart failure.

There have been cases of QT-interval prolongation in clinical trials; causality has not been established.

Patients using angiotensin converting enzyme inhibitors, beta-blockers, antihypertensives, calcium channel blockers, angiotensin receptor blockers and diuretics may have a higher incidence of cardiac failure during VELCADE treatment.

Pulmonary Disorders

There have been 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 VELCADE. Some of these events have been fatal. A higher proportion of these events have been reported in Japan. In the event of new or worsening pulmonary symptoms, a prompt diagnostic evaluation should be performed, and patients treated appropriately.

In a clinical trial, the two patients given high doses cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours in combination with daunorubicin and VELCADE for relapsed acute myelogenous leukaemia died of ARDS early in the course of therapy. The trial was discontinued subsequently and this specific treatment regimen is not recommended.

Renal Events

Renal complications are frequent in patients with multiple myeloma. Such patients should be monitored closely.

Hepatic Events

Cases of acute liver failure have been reported. Other reported hepatic events include asymptomatic increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of VELCADE. There is limited re-challenge information in these patients.

Hepatic Impairment

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

Tumour lysis syndrome

Because VELCADE is a cytotoxic agent and can rapidly kill malignant plasma 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, dysrrhythmias and syncope. These patients should be monitored closely, and appropriate precautions taken.

Amyloidosis

The impact of proteasome inhibition by VELCADE on disorders associated with protein accumulation such as amyloidosis is unknown. Caution is advised in these patients.

Potentially immunocomplex-mediated reactions

Potentially immunocomplex-mediated reactions, such as serum-sickness–type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. VELCADE should be discontinued if severe reactions occur.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of PRES in patients receiving VELCADE. PRES is a rare, often reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably MRI (Magnetic Resonance Imaging), is used to confirm the diagnosis. In patients developing PRES, discontinue VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing PRES is not known.

Progressive multifocal leukoencephalopathy (PML)

Cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with VELCADE. Patients diagnosed with PML

had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of VELCADE. 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 VELCADE if PML is diagnosed.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies indicate that VELCADE 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 VELCADE, the CYP2D6 poor metaboliser phenotype is not expected to affect the overall disposition of VELCADE.

An interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of VELCADE, showed a bortezomib AUC mean increase of 35 %, based on data from 12 patients. Therefore, patients should be monitored closely when given VELCADE in combination with potent CYP3A4-inhibitors (e.g., ketoconazole, ritonavir).

In an interaction study assessing the effect of omeprazole, a potent inhibitor of CYP2C19, on the pharmacokinetics of VELCADE**,** there was no significant effect on the pharmacokinetics of bortezomib, based on data from 17 patients.

An interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of VELCADE (injected intravenously), showed a mean bortezomib AUC reduction of 45 % based on data from 6 patients. The concomitant use of VELCADE with strong CYP3A4 inducers is therefore not recommended, as efficacy may be reduced. Examples of CYP3A4 inducers are rifampicin, carbamazepine, phenytoin, phenobarbital and

St. John's Wort. In the same interaction study, the effect of dexamethasone, a weaker CYP3A4 inducer was assessed. There was no significant effect on bortezomib pharmacokinetics based on data from 7 patients.

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

An interaction study assessing the effect of melphalan-prednisone on VELCADE (injected intravenously), showed a 17 % increase in mean bortezomib AUC 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 agents receiving VELCADE treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medication. 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

Males and females of childbearing capacity must use effective contraceptive measures during treatment and for 3 months following VELCADE therapy.

Pregnancy

Safety in pregnancy has not been established.

If VELCADE is used during pregnancy, alone or in combination with other medicines, or if the patient becomes pregnant while receiving VELCADE, the patient needs to be informed of the potential hazards to the foetus.

Breastfeeding

Safety in lactation has not been established.

It is not known whether VELCADE is excreted in human milk. Because of the potential for serious undesirable effects in breastfed infants from mothers on VELCADE, women should not breastfeed their infants while receiving VELCADE.

4.7 Effects on ability to drive and use machines

VELCADE may have a moderate influence on the ability to drive and use machines. VELCADE may be associated with fatigue very commonly, dizziness commonly, syncope uncommonly, and orthostatic/postural hypotension or blurred vision commonly. 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

Clinical trial data

Summary of the safety profile

Serious adverse reactions uncommonly reported during treatment with VELCADE include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy. The most commonly reported adverse reactions during treatment with VELCADE

are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Tabulated summary of adverse reactions

Multiple Myeloma

The undesirable effects in Table 7 were considered by the investigators to have at least a possible or probable causal relationship to VELCADE. These adverse reactions are based on an integrated data set of 5,476 patients of whom 3,996 were treated with VELCADE at 1,3 mg/m^2 and included in Table 7.

Overall, VELCADE was administered for the treatment of multiple myeloma in 3,974 patients.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 7: Adverse reactions in patients with Multiple Myeloma treated with VELCADE in clinical trials

System Organ Class	Incidence	Adverse reaction
Infections and	Common	Herpes zoster (inc. disseminated & ophthalmic), Pneumonia*, Herpes simplex*, Fungal infection*

infestations	Uncommon	Infection*, Bacterial infections*, Viral infections*, Sepsis (inc. septic shock)*, Bronchopneumonia, Herpes virus infection*, Bacteraemia (inc. staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection*, Ear infection*, Staphylococcal infection, Tooth infection*
	Rare	Meningitis (inc. bacterial), Epstein-Barr virus infection, Genital herpes, Tonsillitis, Mastoiditis, Post viral fatigue syndrome
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rare	Neoplasm malignant, Leukaemia plasmacytic, Renal cell carcinoma, Mass, Mycosis fungoides, Neoplasm benign*
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Neutropenia*, Anaemia*
	Common	Leukopenia*, Lymphopenia*
	Uncommon	Pancytopenia*, Febrile neutropenia, Coagulopathy*, Leukocytosis*, Lymphadenopathy
	Rare	Disseminated intravascular coagulation, Thrombocytosis*, Hyperviscosity syndrome, Platelet disorder NOS, Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration
Immune system disorders	Uncommon	Hypersensitivity*
	Rare	Anaphylactic shock, Amyloidosis, Type III immune complex mediated reaction

Endocrine disorders	Uncommon	Cushing's syndrome*, Hyperthyroidism*, Inappropriate antidiuretic hormone secretion
	Rare	Hypothyroidism
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Dehydration, Hypokalaemia*, Hyponatraemia*, Abnormal blood glucose*, Hypocalcaemia*, Enzyme abnormality*
	Uncommon	Tumour lysis syndrome, Failure to thrive*, Hypomagnesaemia*, Hypophosphataemia*, Hyperkalaemia*, Hypercalcaemia*, Hypernatraemia*, Uric acid abnormal*, Diabetes mellitus*, Fluid retention
	Rare	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	Common	Mood disorders and disturbances*, Anxiety disorder*, Sleep disorders and disturbances*
	Uncommon	Mental disorder*, Hallucination*, Psychotic disorder*, Confusion*, Restlessness
	Rare	Suicidal ideation*, Adjustment disorder, Delirium, Decreased libido
Nervous system disorders	Very Common	Neuropathies*, Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*

	Common	Motor neuropathy*, Loss of consciousness (inc. syncope), Dizziness*, Dysgeusia*, Lethargy, Headache*
	Uncommon	Tremor, Peripheral sensorimotor neuropathy, Dyskinesia*, Cerebellar coordination and balance disturbances*, Memory loss (exc. dementia)*, Encephalopathy*, Neurotoxicity, Seizure disorders*, Post herpetic neuralgia, Speech disorder*, Restless legs syndrome, Migraine, Sciatica, Disturbance in attention, Abnormal reflexes*, Parosmia
	Rare	Cerebral haemorrhage*, Haemorrhage intracranial (inc. 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 NOS, Motor dysfunction, Nervous system disorder NOS, Radiculitis, Drooling, Hypotonia
Eye disorders	Common	Eye swelling*, Abnormal vision*, Conjunctivitis*
	Uncommon	Eye haemorrhage*, Eyelid infection*, Eye inflammation*, Diplopia, Dry eye*, Eye irritation*, Eye pain, Increased lacrimation, Eye discharge

	Rare	Corneal lesion*, Exophthalmos, Retinitis, Scotoma, Eye disorder (inc. eyelid) NOS, Dacryoadenitis acquired, Photophobia, Photopsia, Different degrees of visual impairment (up to blindness)*
Ear and labyrinth disorders	Common	Vertigo*
	Uncommon	Dysacusis (inc. tinnitus)*,Hearing impaired (up to and inc. deafness), Ear discomfort*
	Rare	Ear haemorrhage, Vestibular neuronitis, Ear disorder NOS
Cardiac disorders	Uncommon	Cardio-pulmonary arrest*, Cardiac fibrillation (inc atrial), Cardiac failure (inc. left and right ventricular)*, Arrhythmia*, Tachycardia*, Palpitations, Angina pectoris, Pericarditis (inc pericardial effusion)*, Cardiomyopathy*, Ventricular dysfunction*, Bradycardia
	Rare	Atrial flutter, Myocardial infarction*, Atrioventricular block*, Cardiovascular disorder (inc cardiogenic shock), Torsade de pointes, Angina unstable, Cardiac valve disorders*, Coronary artery insufficiency, Sinus arrest
Vascular disorders	Common	Hypotension*, Orthostatic hypotension, Hypertension*

	Uncommon	Deep vein thrombosis*, Haemorrhage*, Thrombophlebitis (inc. superficial), Circulatory collapse (inc. hypovolaemic shock), Phlebitis, Flushing*, Haematoma (inc. perirenal)*, Poor peripheral circulation*, Vasculitis, Hyperaemia (inc. ocular)*
	Rare	Peripheral embolism, Lymphoedema, Pallor, Erythromelalgia, Vasodilatation, Vein discolouration, Venous insufficiency
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Epistaxis, Upper/lower respiratory tract infection*, Cough*
	Uncommon	Pulmonary embolism, Pleural effusion, Pulmonary oedema (inc. acute), Bronchospasm, Chronic obstructive pulmonary disease*, Hypoxaemia*, Respiratory tract congestion*, Hypoxia, Pleurisy*, Hiccups, Rhinorrhoea, Dysphonia, Wheezing
	Rare	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	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Constipation
	Common	Gastrointestinal haemorrhage (inc. mucosal)*, Dyspepsia, Stomatitis*, Abdominal distension, Oropharyngeal pain*, Abdominal pain (inc. gastrointestinal and splenic pain)*, Oral disorder*, Flatulence

	Uncommon	Pancreatitis (inc. chronic)*, Haematemesis, Lip swelling*, Gastrointestinal obstruction (inc. small intestinal obstruction, ileus)*, Abdominal discomfort, Oral ulceration*, Enteritis*, Gastritis*, Gingival bleeding, Gastrooesophageal reflux disease*, Colitis (inc. clostridium difficile)*, Gastrointestinal inflammation*, Dysphagia, Irritable bowel syndrome, Gastrointestinal disorder NOS, Tongue coated, Gastrointestinal motility disorder*, Salivary gland disorder*
	Rare	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	Common	Hepatic enzyme abnormality*
	Uncommon	Hepatotoxicity (inc. liver disorder), Hepatitis*, Cholestasis

	Rare	Hepatic failure, Hepatomegaly, Budd-Chiari syndrome, Cytomegalovirus hepatitis, Hepatic haemorrhage, Cholelithiasis
Skin and Subcutaneous tissue disorders	Common	Rash*, Pruritus*, Erythema, Dry skin
	Uncommon	Erythema multiforme, Urticaria, Acute febrile neutrophilic dermatosis, Toxic skin eruption, Dermatitis*, Hair disorder*, Petechiae, Ecchymosis, Skin lesion, Purpura, Skin mass*, Psoriasis, Hyperhidrosis, Night sweats, Acne*, Blister*, Pigmentation disorder*
	Rare	Skin reaction, Jessner's lymphocytic infiltration, Palmar-plantar erythrodysaesthesia syndrome, Haemorrhage subcutaneous, Livedo reticularis, Skin induration, Papule, Photosensitivity reaction, Seborrhoea, Cold sweat, Skin disorder NOS, Erythrosis, Skin ulcer, Nail disorder
Musculoskeletal and connective tissue disorders	Very Common	Musculoskeletal pain*
	Common	Muscle spasms*, Pain in extremity, Muscular weakness
	Uncommon	Muscle twitching, Joint swelling, Arthritis*, Joint stiffness, Myopathies*, Sensation of heaviness

	Rare	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	Common	Renal impairment*
	Uncommon	Renal failure acute, Renal failure chronic*, Urinary tract infection*, Urinary tract signs and symptoms*, Haematuria*, Urinary retention, Micturition disorder*, Proteinuria, Azotaemia, Oliguria*, Pollakiuria
	Rare	Bladder irritation
Reproductive system and breast disorders	Uncommon	Vaginal haemorrhage, Genital pain*, Erectile dysfunction,
	Rare	Testicular disorder*, Prostatitis, Female Breast disorder, Epididymal tenderness, Epididymitis, Pelvic pain, Vulval ulceration
Congenital, familial and genetic disorders	Rare	Aplasia, Gastrointestinal malformation, Ichthyosis
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia

	Common	Oedema (inc. peripheral), Chills, Pain*, Malaise*
	Uncommon	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*
	Rare	Death (inc. sudden), Multi-organ failure, Injection site haemorrhage*, Hernia (inc. hiatus)*, Impaired healing*, Inflammation, Injection site phlebitis*, Tenderness, Ulcer, Irritability, Non-cardiac chest pain, Catheter site pain, Sensation of foreign body
Investigations	Common	Decreased weight
	Uncommon	Hyperbilirubinaemia*, Abnormal protein analyses*, Increased weight, Abnormal blood test*, Increased C-reactive protein
	Rare	Abnormal blood gases*, Electrocardiogram abnormalities (inc QT prolongation)*, Abnormal International Normalised Ratio* (INR), Decreased gastric pH, Increased platelet aggregation, Increased Troponin I, Virus identification and serology*, Abnormal urine analysis*

Injury, poisoning and procedural complications	Uncommon	Fall, Contusion
	Rare	Transfusion reaction, Fractures*, Rigors*, Face injury, Joint injury*, Burns, Laceration, Procedural pain, Radiation injuries*
Surgical and medical procedures	Rare	Macrophage activation

NOS=not otherwise specified

* Grouping of more than one MedDRA preferred term.

Mantle Cell Lymphoma (MCL)

Summary of the Clinical Trial in Patients with Relapsed Mantle Cell Lymphoma

Safety data for patients with relapsed mantle cell lymphoma were evaluated in a phase 2 study, which included 155 patients treated with VELCADE at the recommended dose of 1,3 mg/m^2. The safety profile of VELCADE in these patients was similar to that observed in patients with multiple myeloma. Notable differences between the two patient populations were that thrombocytopenia, neutropenia, anaemia, nausea, vomiting and pyrexia were reported more often in the patients with multiple myeloma than in those with mantle cell lymphoma; whereas peripheral neuropathy, rash and pruritus were higher among patients with mantle cell lymphoma compared to patients with multiple myeloma.

Summary of Clinical Trial in Patients with Previously Untreated Mantle Cell Lymphoma

The safety profile of VELCADE in study LYM-3002 in 240 MCL patients treated with VELCADE at 1,3 mg/m^2 in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP), versus 242 patients treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] was relatively consistent to that

observed in patients with multiple myeloma with main differences described below. Additional adverse drug reactions identified associated with the use of the combination therapy (VcR-CAP) were hepatitis B infection (< 1 %) and myocardial ischaemia (1,3 %). The similar incidences of these events in both treatment arms, indicated that these adverse drug reactions are not attributable to VELCADE alone. Notable differences in the MCL patient population as compared to patients in the multiple myeloma studies were a ≥ 5 % higher incidence of the haematological adverse reactions (neutropenia, thrombocytopenia, leukopenia, anaemia, lymphopenia), peripheral sensory neuropathy, hypertension, pyrexia, pneumonia, stomatitis, and hair disorders.

Adverse drug reactions identified as those with a ≥ 1 % incidence, similar or higher incidence in the VcR-CAP arm and with at least a possible or probable causal relationship to the components of the VcR-CAP arm, are listed in Table 8 below. Also included are adverse drug reactions identified in the VcR-CAP arm that were considered by investigators to have at least a possible or probable causal relationship to VELCADE based on historical data in the multiple myeloma studies.

Adverse reactions are listed below by system organ class and frequency grouping. Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Table 8 has been generated using Version 16 of the MedDRA.

Table 8: Adverse reactions in patients with Mantle Cell Lymphoma treated with VcR-CAP in a clinical trial

System Organ Class	Incidence	Adverse reaction
Infections and infestations	Very Common	Pneumonia*
	Common	Sepsis (inc. septic shock)*, Herpes zoster (inc. disseminated & ophthalmic), Herpes virus infection*, Bacterial infections*, Upper/lower respiratory tract infection*, Fungal infection*, Herpes simplex*
	Uncommon	Hepatitis B, Infection*, Bronchopneumonia
Blood and lymphatic system disorders	Very Common	Thrombocytopenia*, Febrile neutropenia, Neutropenia*, Leukopenia*, Anaemia*, Lymphopenia*
	Uncommon	Pancytopenia*
Immune system disorders	Common	Hypersensitivity*
	Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	Very Common	Decreased appetite
	Common	Hypokalaemia*, Abnormal blood glucose*, Hyponatraemia*, Diabetes mellitus*, Fluid retention
	Uncommon	Tumour lysis syndrome
Psychiatric disorders	Common	Sleep disorders and disturbances*
Nervous system disorders	Very Common	Peripheral sensory neuropathy, Dysaesthesia*, Neuralgia*
	Common	Neuropathies*, Motor neuropathy*, Loss of consciousness (inc. syncope), Encephalopathy*, Peripheral sensorimotor neuropathy, Dizziness*, Dysgeusia*, Autonomic neuropathy

	Uncommon	Autonomic nervous system imbalance
Eye disorders	Common	Abnormal vision*
Ear and labyrinth disorders	Common	Dysacusis (inc. tinnitus)*
	Uncommon	Vertigo*, Hearing impaired (up to and inc. deafness)
Cardiac disorders	Common	Cardiac fibrillation (inc. atrial), Arrhythmia*, Cardiac failure (inc. left and right ventricular)*, Myocardial ischaemia, Ventricular dysfunction*
	Uncommon	Cardiovascular disorder (inc. cardiogenic shock)
Vascular disorders	Common	Hypertension*, Hypotension*, Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea*, Cough*, Hiccups
	Uncommon	Acute respiratory distress syndrome, Pulmonary embolism, Pneumonitis, Pulmonary hypertension, Pulmonary oedema (inc. acute)
Gastrointestinal disorders	Very Common	Nausea and vomiting symptoms*, Diarrhoea*, Stomatitis*, Constipation
	Common	Gastrointestinal haemorrhage (inc. mucosal)*, Abdominal distension, Dyspepsia, Oropharyngeal pain*, Gastritis*, Oral ulceration*, Abdominal discomfort, Dysphagia, Gastrointestinal inflammation*, Abdominal pain (inc. gastrointestinal and splenic pain)*, Oral disorder*
	Uncommon	Colitis (inc. clostridium difficile)*
Hepatobiliary disorders	Common	Hepatotoxicity (inc liver disorder)
	Uncommon	Hepatic failure
	Very Common	Hair disorder*

Skin and subcutaneous tissue disorders	Common	Pruritus*, Dermatitis*, Rash*
Musculoskeletal and connective tissue disorders	Common	Muscle spasms*, Musculoskeletal pain*, Pain in extremity
Renal and urinary disorders	Common	Urinary tract infection*
General disorders and administration site conditions	Very Common	Pyrexia*, Fatigue, Asthenia
	Common	Oedema (inc. peripheral), Chills, Injection site reaction*, Malaise*
Investigations	Common	Hyperbilirubinaemia*, Abnormal protein analyses*, Decreased weight, Increased weight

* Grouping of more than one MedDRA preferred term.

Description of selected adverse reactions

Herpes zoster virus reactivation

Multiple Myeloma

Antiviral prophylaxis was administered to 26 % of the patients in the Vc+M+P arm. The incidence of herpes zoster among patients in the Vc+M+P treatment group was 17 % for patients not administered antiviral prophylaxis compared to 3 % for patients administered antiviral prophylaxis.

Mantle cell lymphoma

Antiviral prophylaxis was administered to 137 of 240 patients (57 %) in the VcR-CAP arm in

study LYM-3002. The incidence of herpes zoster among patients in the VcR-CAP arm was 10,7 % for patients not administered antiviral prophylaxis compared to 3,6 % for patients administered antiviral prophylaxis (see section 4.4).

Hepatitis B Virus (HBV) reactivation and infection

Mantle cell lymphoma

HBV infection with fatal outcomes occurred in 0,8 % (n=2) of patients in the non-VELCADE treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP) and 0,4 % (n=1) of patients receiving VELCADE in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) in study LYM-3002 . The overall incidence of hepatitis B infections was similar in patients treated with VcR-CAP or with R-CHOP (0,8 % vs 1,2 % respectively).

Peripheral neuropathy in combination regimens

Multiple Myeloma

In trials in which VELCADE was administered as induction treatment in combination with dexamethasone (study IFM-2005-01), and dexamethasone-thalidomide (study MMY-3010), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 9: Incidence of peripheral neuropathy during induction treatment by toxicity and treatment discontinuation due to peripheral neuropathy

	IFM-2005-01		MMY-3010	
	VDDx (N=239)	VcDx (N=239)	TDx (N=126)	VcTDx (N=130)
Incidence of PN (%)				
All Grade PN	3	15	12	45

≥ Grade 2 PN	1	10	2	31
≥ Grade 3 PN	< 1	5	0	5
Discontinuation due to PN (%)	< 1	2	1	5

VDDx=vincristine, doxorubicin, dexamethasone; VcDx=VELCADE, dexamethasone; TDx=thalidomide, dexamethasone; VcTDx=VELCADE, thalidomide, dexamethasone; PN=peripheral neuropathy

Note: Peripheral neuropathy included the preferred terms: neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

Mantle cell lymphoma

In study LYM-3002 in which VELCADE was administered with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CAP), the incidence of peripheral neuropathy in the combination regimens is presented in the table below:

Table 10: Incidence of peripheral neuropathy in study LYM-3002 by toxicity and treatment discontinuation due to peripheral neuropathy

	VcR-CAP (N=240)	R-CHOP (N=242)
Incidence of PN (%)		
All Grade PN	30	29
≥ Grade 2 PN	18	9
≥ Grade 3 PN	8	4
Discontinuation due to PN (%)	2	< 1

VcR-CAP=VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PN=peripheral

neuropathy

Peripheral neuropathy included the preferred terms: peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy, and peripheral sensorimotor neuropathy

Elderly MCL patients

42,9 % and 10,4 % of patients in the VcR-CAP arm in study LYM-3002 were in the range 65-74 years and ≥ 75 years of age, respectively. Although in patients aged ≥ 75 years, both VcR-CAP and R-CHOP were less tolerated, the serious adverse event rate in the VcR-CAP groups was 68 %, compared to 42 % in the R-CHOP group.

Notable differences in the safety profile of VELCADE administered subcutaneously versus intravenously as single agent

In the Phase III study patients who received VELCADE subcutaneously compared to intravenous administration had 13 % lower overall incidence of treatment emergent adverse reactions that were Grade 3 or higher in toxicity, and a 5 % lower incidence of discontinuation of VELCADE. The overall incidence of diarrhoea, gastrointestinal and abdominal pain, asthenic conditions, upper respiratory tract infections and peripheral neuropathies were 12 %- 15 % lower in the subcutaneous group than in the intravenous group. In addition, the incidence of Grade 3 or higher peripheral neuropathies was 10 % lower, and the discontinuation rate due to peripheral neuropathies was 8 % lower for the subcutaneous group as compared to the intravenous group.

Six percent of patients had an adverse local reaction to subcutaneous administration, mostly redness. Cases resolved in a median of 6 days; dose modification was required in two patients. Two (1 %) of the patients had severe reactions; 1 case of pruritus and 1 case of redness.

The incidence of death on treatment was 5 % in the subcutaneous treatment group and 7 %

in the intravenous treatment group. Incidence of death from “Progressive disease” was 18 % in the subcutaneous group and 9 % in the intravenous group.

Retreatment of patients with relapsed multiple myeloma

In a study in which VELCADE retreatment was administered in 130 patients with relapsed multiple myeloma, who previously had at least partial response on a VELCADE-containing regimen, the most common all-grade adverse events occurring in at least 25 % of patients were thrombocytopenia (55 %), neuropathy (40 %), anaemia (37 %), diarrhoea (35 %), and constipation (28 %). All grade peripheral neuropathy and grade ≥ 3 peripheral neuropathy were observed in 40 % and 8,5 % of patients, respectively.

Post-marketing

Clinically significant adverse reactions are listed here if they have not been reported above.

The frequencies provided in the table below reflect reporting rates of adverse drug reactions from the worldwide post-marketing experience with VELCADE. The frequencies provided below reflect reporting rates as precise estimates of incidence cannot be made. These adverse drug reactions are ranked by frequency, using the following convention: Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1000 and < 1/100), rare (≥ 1/10,000 and < 1/1000), very rare (<1/10,000, including isolated reports).

Table 11: Post-marketing Reports of Adverse Reactions

Blood and lymphatic system disorders	
Haemolytic anaemia	Uncommon
Thrombotic microangiopathy (inc thrombocytopenic purpura)	Rare

Cardiac disorders	
Cardiac tamponade	Uncommon
Eye disorders	
Chalazion	Uncommon
Blepharitis	
Optic neuropathy	Rare
Gastrointestinal disorders	
Ischaemic colitis	Uncommon
Infections and infestations	
Herpetic meningoencephalitis	Uncommon
Immune system disorders	
Angioedema	Uncommon
Nervous system disorders	
Posterior Reversible Encephalopathy Syndrome	Uncommon
Respiratory, thoracic and mediastinal disorders	
Pulmonary alveolar haemorrhage	Uncommon
Skin and subcutaneous tissue disorders	
Toxic epidermal necrolysis	Uncommon
Stevens-Johnson syndrome	
Decubitus ulcer	
Vascular disorders	
Cerebrovascular accident	Uncommon

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

professionals are asked to report any suspected adverse reactions via "**6.04 Adverse Drug Reaction Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com).

4.9 Overdose

One case of overdosage (more than twice the recommended dose) in the setting of concurrent sepsis has been reported with VELCADE. Overdosage was associated with acute onset of symptomatic hypotension and the patient subsequently died. It is recommended that in the event of overdosage, patients should undergo careful haemodynamic monitoring, and hypotension should be treated aggressively with intravenous hydration and other clinically appropriate measures.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION

A 26 Cytostatic agents

Mechanism of action

Bortezomib is a selective proteasome inhibitor. It specifically inhibits the chymotrypsin-like activity of the 26S proteasome in mammalian cells.

Bortezomib mediated proteasome inhibition affects 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 tumourogenesis, 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 to eleven patients with multiple myeloma, the mean maximum plasma concentrations of bortezomib were 57 and 112 mg/mL respectively after the first dose. 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. The mean elimination half-life 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 following subsequent doses for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively.

Distribution

The mean distribution volume of bortezomib was variable and ranged from 1659 litres to 3294 liters following single- or repeat-dose 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. The binding of bortezomib to human plasma averaged 83 % over the concentration range 100 – 1000 mg/mL.

Metabolism

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. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. 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.

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:

Age, Gender and Race

The pharmacokinetics of bortezomib were characterised following twice weekly intravenous bolus administration of 1,3 mg/m^2 doses to 104 paediatric patients (2 - 16 years old) with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). Based on a population

pharmacokinetic analysis, clearance of bortezomib increased with increasing body surface area (BSA). Geometric mean (% CV) clearance was 7,79 (25 %) L/hr/m^2, volume of distribution at steady state was 834 (39 %) L/m^2, and the elimination half-life was 100 (44 %) hours. After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalised clearance of bortezomib in paediatric patients was similar to that observed in adults.

The effects of gender and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic Impairment

The effect of hepatic impairment (see Table 2 for hepatic impairment classification) on the pharmacokinetics of bortezomib was assessed in 61 cancer patients at bortezomib doses ranging from 0,5 to 1,3 mg/m^2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose- normalised bortezomib AUC. However, the 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 monitored closely (see Table 5).

Renal Impairment

A pharmacokinetic study was conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL ≥ 60 mL min/1,73 m^2, n=12), Mild (CrCL =40-59 mL/min/1,73 m^2, n=10), Moderate (CrCL =20-39 mL/min/1,73 m^2, n=9), and Severe (CrCL < 20 mL/min/1,73 m^2, n=3). A group of dialysis patients who were dosed after dialysis was also included in the study (n=8). Patients were administered intravenous doses of 0,7 to 1,3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalised AUC and Cmax) was

comparable among all the groups (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421)

Nitrogen

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

36 months.

Reconstituted solution

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.

6.4 Special precautions for storage

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

KEEP OUT OF REACH OF CHILDREN.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

VELCADE is supplied as a single-use 5 mL or 10 mL clear, colourless glass vial with a grey bromobutyl stopper and an aluminium seal with green flip-off cap (5 mL vial) or royal blue flip-off cap (10 mL vial).

The 5 mL vial contains 11 mg powder for solution for injection and 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.

6.6 Special precautions for disposal and other handling

For single use only.

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

Reconstitution Instructions

VELCADE 1 mg is for IV use only.

VELCADE 3,5 mg is for IV or SC 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.

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

VELCADE 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.

Reconstitution for intravenous administration

Prior to use, the contents of each 5 mL vial must be reconstituted with 1 mL of normal (0,9 %) saline, Sodium Chloride Injection, USP. The contents of each 10 mL vial must be reconstituted with 3,5 mL of normal (0,9 %) saline.

VELCADE must not be mixed with any other medicinal products except for normal (0,9 %) saline, Sodium Chloride Injection, USP.

Table 12: 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**
	(1 mg bortezomib)	**(3,5 mg bortezomib)**	**(3,5 mg bortezomib)**
Volume of diluent (0,9 % Sodium Chloride) added to reconstitute one vial	1,0 mL	3,5 mL	1,4 mL

Final Concentration after reconstitution (mg/mL)	1,0 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

1 mg/vial: 43/26/0427

3,5 mg/vial: A40/26/0005

9 DATE OF FIRST AUTHORISATION

- Date of registration:
  - Velcade 1 mg - 05 August 2011.
  - Velcade 3,5 mg – 07 July 2006.

10 DATE OF REVISION OF THE TEXT

Date of the most recently revised Professional Information as approved by SAHPRA: 25 May 2022.