FULL PRESCRIBING INFORMATION

1 NAME OF THE MEDICINAL PRODUCT

VELCADE 3.5MG

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3.5 mg of **bortezomib** (as a mannitol boronic ester).

After reconstitution, 1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

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

For the full list of excipients, see section 12.

Powder for solution for injection I.V., S.C.

3 THERAPUETIC INDICATIONS

3.1 Multiple Myeloma

VELCADE is indicated for the treatment of adult patients with multiple myeloma.

3.2 Mantle Cell Lymphoma

VELCADE (bortezomib) for Injection is indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

VELCADE in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

4 DOSAGE AND ADMINISTRATION

General Dosing Guidelines

VELCADE IS FOR INTRAVENOUS OR SUBCUTANEOUS USE ONLY. VELCADE must not be administered by any other route. Intrathecal administration has resulted in death. Intrathecal administration has resulted in death.

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

The recommended starting dose of VELCADE is 1.3 mg/m^2. VELCADE may be administered intravenously at a concentration of 1mg/mL, or subcutaneously at a concentration of 2.5 mg/mL (see reconstitution /preparation for intravenous and subcutaneous administration section 4.8). When administered intravenously, VELCADE is administered as a 3 to 5 second bolus intravenous injection.

4.1 Dosage in Previously Untreated Multiple Myeloma

VELCADE is administered in combination with oral melphalan and oral prednisone for 9, six week treatment cycles as shown in *Table 1*. In Cycles 1 to 4, VELCADE is administered twice weekly (Days 1, 4, 8, 11, 22, 25, 29 and 32). In Cycles 5 to 9, VELCADE is administered once weekly (Days 1, 8, 22 and 29). At least 72 hours should elapse between consecutive doses of VELCADE.

Table 1: Dosage Regimen for Patients with Previously Untreated Multiple Myeloma
Twice Weekly VELCADE (Cycles 1 to 4)

Week	1				2		3	4		5		6
VELCADE (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
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4			rest period					rest period
Once Weekly VELCADE (Cycles 5 to 9 when used in combination with Melphalan and Prednisone)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
VELCADE (1.3 mg/m^2)	Day 1				Day 8		rest period	Day 22		Day 29		rest period
Melphalan (9 mg/m^2) Prednisone (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4			rest period					rest period

4.2 Dose Modification Guidelines for Combination Therapy with VELCADE Melphalan and Prednisone

Prior to initiating any cycle of therapy with VELCADE in combination with melphalan and prednisone:

- Platelet count should be ≥70 x 10^9/L and the absolute neutrophil count (ANC) should be ≥ 1.0 x 10^9/L
- Nonhematological toxicities should have resolved to Grade 1 or baseline

Table 2: Dose Modifications During Cycles of Combination VELCADE, Melphalan and Prednisone Therapy

Toxicity	Dose Modification or Delay
Hematological 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 is not above 30 x 10^9/L or ANC is not above 0.75 x 10^9/L on a VELCADE dosing day (other than Day 1)	Withhold VELCADE dose
If several VELCADE doses in consecutive cycles are withheld due to toxicity	Reduce VELCADE dose by one 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 or higher nonhematological toxicities	Withhold VELCADE therapy until symptoms of 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 or modify VELCADE as outlined in *Table 5*.

For information concerning melphalan and prednisone, see manufacturer's prescribing information.

Dose modifications guidelines for peripheral neuropathy are provided *[see Dosage and Administration (*4.5*)]*.

4.3 Posology for patients with previously untreated mantle cell lymphoma (MCL)

Combination therapy with rituximab, cyclophosphamide, doxorubicin and prednisone (VcR-CAP) VELCADE *3*.5mg powder for solution for injection is administered via intravenous injection at the recommended dose of 1.3 mg/m^2 body surface area twice weekly for two weeks on days 1, 4, 8, and 11 followed by a 10-day rest period on days 1221. This 3-week period is considered a treatment cycle. Six VELCADE cycles are recommended, although for patients with a response first documented at cycle 6, two additional VELCADE cycles may be given. At least 72 hours should elapse between consecutive doses of VELCADE.

The following medicinal products 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 VELCADE treatment cycle.
Dose adjustments during treatment for patients with previously untreated mantle cell lymphoma Prior to initiating a new cycle of therapy:

- Platelet counts should be ≥ 100,000 cells/µL and the absolute neutrophils count (ANC) should be ≥ 1,500 cells/µL
- Platelet counts should be ≥ 75,000 cells/µL in patients with bone marrow infiltration or splenic sequestration
- Haemoglobin ≥ 8 g/dL
- Non-haematological toxicities should have resolved to Grade 1 or baseline.

VELCADE treatment must be withheld at the onset of any ≥ Grade 3 VELCADE-related non-haematological toxicities (excluding neuropathy) or ≥ Grade 3 haematological toxicities. For dose adjustments, see Table 3 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 3: 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 < 10,000 cells/µL	VELCADE therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 750 cells/µL and a platelet count ≥ 25,000 cells/µL. • 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 an ANC ≥ 750 cells/µL and a platelet count ≥ 25,000 cells/µL, VELCADE may be reinitiated at a dose reduced by one 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 < 25,000 cells/µL. or ANC < 750 cells/µL on a VELCADE dosing day (other than Day 1 of each cycle)	VELCADE therapy should be withheld
If several VELCADE doses in consecutive cycles are withheld due to toxicity	Reduce VELCADE dose by one dose level (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m2))
Grade ≥ 3 non-haematological toxicities considered to be related to VELCADE	VELCADE therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, VELCADE may be reinitiated at a dose reduced by one 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). For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold and/or modify VELCADE as outlined in Table 1.

In addition, when **VELCADE** is given **in** combination **with** other chemotherapeutic medicinal products, appropriate dose reductions for these medicinal products should be considered in the event of toxicities, according to the recommendations in the respective Summary of Product Characteristics.

4.4 Dosage in Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

VELCADE (1.3 mg/m^2/dose) is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a ten day rest period (Days 12 to 21). For extended therapy of more than eight cycles, VELCADE may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for four weeks (Days 1, 8, 15, and 22) followed by a 13 day

rest period (Days 23 to 35) *[see Clinical Studies* section (13) for a description of dose administration during the trials]. At least 72 hours should elapse between consecutive doses of VELCADE.

4.5 Dose Modification Guidelines for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or Grade 4 hematological toxicities excluding neuropathy as discussed below *[see Warnings and Precautions (7)]*. Once the symptoms of the toxicity have resolved, VELCADE therapy may be reinitiated at a 25% reduced dose (1.3 mg/m^2/dose reduced to 1 mg/m^2/dose; 1 mg/m^2/dose reduced to 0.7 mg/m^2/dose.
For dose modifications guidelines for peripheral neuropathy, see Management of peripheral neuropathy section 4.5)

4.6 Dose Modifications of Peripheral Neuropathy
Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy. Patients with pre-existing severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment.
Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may require a decrease in the dose and/or a less dose-intense schedule.
For dose or schedule modification guidelines for patients who experience VELCADE-related neuropathic pain and/or peripheral neuropathy, see *Table* **4***.*

Table 4 – Recommended Dose Modification for VELCADE -Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms*	**Modification of Dose and Regimen**
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL))**	Reduce VELCADE to 1 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 ***)	Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate 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

*Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

** *Instrumental ADL*: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc.

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

4.7 Dosage in Patients with Hepatic Impairment
Patients with mild hepatic impairment do not require a 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/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). *[see Warnings and Precautions (7.8), Use in Specific Populations (10.7) and Clinical Pharmacology (13.3)]*

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	less than or equal to 1.0x ULN	> ULN	None
	More than 1.0x to 1.5x ULN	Any	None
Moderate	More than 1.5x to 3x ULN	Any	Reduce VELCADE to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	More than 3x 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).**

4.8 Administration Precautions

The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose. (see reconstitution /preparation for intravenous and subcutaneous administration section 4.8).

VELCADE is authorized for intravenous or subcutaneous use only. Intrathecal administration has resulted in death.

When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated. New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

If local injection site reactions occur following VELCADE administration subcutaneously, a less concentrated VELCADE solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously *[see* reconstitution /preparation for intravenous *and* subcutaneous administration section *4.*8) and follow reconstitution instructions for 1 mg/mL]. Alternatively, the intravenous route of administration should be considered *[see* reconstitution /preparation for intravenous and subcutaneous administration section *4.*8].

VELCADE is a cytotoxic drug. Follow applicable special handling and disposal procedures [See ***How Supplied/Storage and Handling (16)***].

4.9 Reconstitution/Preparation for Intravenous and Subcutaneous Administration

Use proper aseptic technique. Reconstitute **only with 0.9% sodium chloride**. The reconstituted product should be a clear and colorless solution.

Different volumes of 0.9% sodium chloride are used to reconstitute the product for the different routes of administration. The reconstituted concentration of bortezomib for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration of bortezomib for intravenous administration (1 mg/mL). **Because each route of administration has a different reconstituted concentration, use caution when calculating the volume to be administered** (*see Administration* Precautions section 4.8).

For each 3.5 mg single-dose vial of bortezomib, reconstitute with the following volume of 0.9% sodium chloride based on route of administration *(Table* 6*)*:**Table 6: Reconstitution Volumes and Final Concentration for Intravenous and Subcutaneous Administration**

Route of Administration	Bortezomib (mg/vial)	Diluent (0.9% Sodium Chloride)	Final Bortezomib Concentration (mg/mL)
Intravenous	3.5 mg	3.5 mL	1 mg/mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL

Dose must be individualized to prevent overdosage. After determining patient body surface area (BSA) in square meters, use the following equations to calculate the total volume (mL) of reconstituted VELCADE to be administered:

- **Intravenous Administration [1 mg/mL concentration]**

VELCADE dose (mg/m^2) x patient BSA (m^2)

_____ = Total VELCADE volume (mL) to be administered

1 mg/mL

- **Subcutaneous Administration [2.5 mg/mL concentration]**

VELCADE dose (mg/m^2) x patient BSA (m^2)

_____ = Total VELCADE volume (mL) to be administered

2.5 mg/mL

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If any discoloration or particulate matter is observed, the reconstituted product should not be used.

Stability

Unopened vials of VELCADE are stable until the date indicated on the package when stored in the original package protected from light. Do not store above 30°C.

VELCADE contains no antimicrobial preservative.

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.

The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration.

5 DOSAGE FORMS AND STRENGTHS

Each single dose vial of VELCADE contains 3.5 mg of bortezomib as a sterile lyophilized white to off-white powder for reconstitution and withdrawal of the appropriate individual patient dose *[see Dosage and Administration (section 4)]*.

6 CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity (not including local reactions) to bortezomib, boron or mannitol. Reactions have included anaphylactic reactions *[see Adverse Reactions (8.1)]*.

VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

7 WARNINGS AND PRECAUTIONS

7.1 Peripheral Neuropathy

VELCADE treatment causes a peripheral neuropathy that is predominantly sensory; however, cases of severe sensory and motor 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 may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. In the Phase 3 relapsed multiple myeloma trial comparing VELCADE subcutaneous vs intravenous, the incidence of Grade ≥2 peripheral neuropathy was 24% for subcutaneous and 39% for intravenous.Grade ≥3 peripheral neuropathy occurred in 6% of patients in the subcutaneous treatment group, compared with 15% in

the intravenous treatment group *[see Adverse Reactions (8.1)]*. Starting VELCADE subcutaneously may be considered for patients with pre-existing or at high risk of peripheral neuropathy.

Patients experiencing new or worsening peripheral neuropathy during VELCADE therapy may require a decrease in the dose and/or a less dose-intense schedule *[see Dosage and Administration (4)*].

In the VELCADE vs dexamethasone Phase 3 relapsed multiple myeloma study, improvement in or resolution of peripheral neuropathy was reported in 48% of patients with ≥Grade 2 peripheral neuropathy following dose adjustment or interruption. Improvement in or resolution of peripheral neuropathy was reported in 73% of patients who discontinued due to Grade 2 neuropathy or who had ≥Grade 3 peripheral neuropathy in the Phase 2 multiple myeloma studies. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

7.2 Hypotension

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8% *[see Adverse Reactions (8.1)]*. These events are observed throughout therapy. Patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated may be at increased risk of hypotension. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics.

7.3 Cardiac Toxicity

Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have occurred during VELCADE therapy, including reports in patients with no risk factors for decreased left ventricular ejection fraction *[see Adverse Reactions (8.1)]*. Patients with risk factors for, or existing heart disease should be frequently monitored. In the relapsed multiple myeloma study of VELCADE vs dexamethasone, the incidence of any treatment-related cardiac disorder was 8% and 5% in the VELCADE and dexamethasone groups, respectively. The incidence of adverse reactions suggestive of heart failure (acute pulmonary edema, pulmonary edema, cardiac failure, congestive cardiac failure, cardiogenic shock) was ≤1% for each individual reaction in the VELCADE group. In the dexamethasone group the incidence was ≤1% for cardiac failure and congestive cardiac failure; there were no reported reactions of acute pulmonary edema, pulmonary edema, or cardiogenic shock. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

7.4 Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration have occurred in patients receiving VELCADE. Some of these events have been fatal.

In a clinical trial, the first two patients given high-dose cytarabine (2 g/m^2 per day) by continuous infusion with daunorubicin and VELCADE for relapsed acute myelogenous leukemia died of ARDS early in the course of therapy.

There have been reports of pulmonary hypertension associated with VELCADE administration in the absence of left heart failure or significant pulmonary disease.

In the event of new or worsening cardiopulmonary symptoms, consider interrupting VELCADE until a prompt and comprehensive diagnostic evaluation is conducted.

7.5 Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior Reversible Encephalopathy Syndrome (PRES; formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS)) has occurred in patients receiving VELCADE. PRES is a rare, 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.

7.6 Gastrointestinal Toxicity

VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting *[see Adverse Reactions (8.1)]* sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration. Interrupt VELCADE for severe symptoms.

7.7 Thrombocytopenia/Neutropenia

VELCADE is associated with thrombocytopenia and neutropenia that follow a cyclical pattern with nadirs occurring following the last dose of each cycle and typically recovering prior to initiation of the subsequent cycle. The cyclical pattern of platelet and neutrophil decreases and recovery remain consistent in the studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in the treatment regimens studied.

Monitor complete blood counts (CBC) frequently during treatment with VELCADE. Measure platelet counts prior to each dose of VELCADE. Adjust dose/schedule for thrombocytopenia *[see Tables 6 and 7, Dosage and Administration (5.6)]*. Gastrointestinal and intracerebral hemorrhage has occurred during thrombocytopenia in association with VELCADE. Support with transfusions and supportive care, according to published guidelines.

In the single agent, relapsed multiple myeloma study of VELCADE vs dexamethasone, the mean platelet count nadir measured was approximately 40% of baseline. The severity of thrombocytopenia related to pretreatment platelet count is shown in *Table* 7. The incidence of bleeding (≥Grade 3) was 2% on the VELCADE arm and was <1% in the dexamethasone arm.

Table 7 Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Relapsed Multiple Myeloma Study of VELCADE vs Dexamethasone

Pretreatment Platelet Count*	Number of Patients (N=331)‡	Number (%) of Patients with Platelet Count <10,000/µL	Number (%) of Patients with Platelet Count 10,000 to 25,000/µL
≥75,000/µL	309	8 (3%)	36 (12%)
≥50,000/µL to <75,000/µL	14	2 (14%)	11 (79%)
≥10,000/µL to <50,000/µL	7	1 (14%)	5 (71%)

* A baseline platelet count of 50,000/µL was required for study eligibility ‡ Data were missing at baseline for one patient

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 (≥Grade 4) was 32% vs 1% for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm as shown in *Table 12*. The incidence of bleeding events (≥Grade 3) was 1.7% in the VcR-CAP arm (four patients) and was 1.2% in the R-CHOP arm (three patients).

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

7.8 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 VELCADE at reduced doses and closely monitored for toxicities (see sections 4.6 and 13.3).

7.9 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with VELCADE therapy. Patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor patients closely and take appropriate precautions.

7.10 Hepatic Toxicity

Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia. Interrupt VELCADE therapy to assess reversibility. There is limited rechallenge information in these patients.

7.11 Thrombotic Microangiopathy

Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in the postmarketing setting in patients who received VELCADE. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop VELCADE and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting VELCADE. The safety of reinitiating VELCADE therapy in patients previously experiencing TTP/HUS is not known.

7.12 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, VELCADE can cause fetal harm when administered to a pregnant woman. Bortezomib administered to rabbits during organogenesis at a dose approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area caused postimplantation loss and a decreased number of live fetuses *[see Use in Specific Populations (10.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with VELCADE and for seven months following treatment. Advise males with female partners of reproductive potential to use effective contraception during treatment with VELCADE and for four months following treatment. If VELCADE is used during pregnancy or if the patient becomes pregnant during VELCADE treatment, the patient should be apprised of the potential risk to the fetus *[see Use in Specific Populations (10.1, 10.3), Nonclinical Toxicology (14.1)]*.

7.13 Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with VELCADE.

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.

7.14 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 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.

7.15 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.

7.16 Renal impairment

Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely.

7.17 Concomitant medicinal products

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates.

Normal liver function should be confirmed, and caution should be exercised in patients receiving oral hypoglycemics.

7.18 Potentially immunocomplex-mediated reactions

Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis

with rash and proliferative glomerulonephritis have been reported uncommonly. Bortezomib should be discontinued if serious reactions occur.

7.19 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 Summary of Product Characteristics of rituximab for more information.

7.20 Haematological toxicity

VELCADE treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia). In studies in patients with relapsed multiple myeloma treated with VELCADE and in patients with previously untreated MCL treated with VELCADE in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP), one of the most common haematologic toxicity was transient thrombocytopenia. Platelets were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. There was no evidence of cumulative thrombocytopenia. The mean platelet count nadir measured was approximately 40% of baseline in the single-agent multiple myeloma studies and 50% in the MCL study. In patients with advanced myeloma the severity of thrombocytopenia was related to pre-treatment platelet count: for baseline platelet counts < 75,000/μl, 90% of 21 patients had a count ≤ 25,000/μl during the study, including 14% < 10,000/μl; in contrast, with a baseline platelet count > 75,000/μl, only 14% of 309 patients had a count ≤ 25,000/μl during the study.

In patients with MCL (study LYM-3002), there was a higher incidence (56.7% versus 5.8%) of Grade ≥ 3 thrombocytopenia in the VELCADE treatment group (VcR-CAP) as compared to the non-VELCADE treatment group (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]). The two treatment groups were similar with regard to the overall incidence of all-grade bleeding events (6.3% in the VcR-CAP group and 5.0% in the R-CHOP group) as well as Grade 3 and higher bleeding events (VcR-CAP: 4 patients [1.7%]; R-CHOP: 3 patients [1.2%]). In the VcR-CAP group, 22.5% of patients received platelet transfusions compared to 2.9% of patients in the R-CHOP group.

Gastrointestinal and intracerebral haemorrhage, have been reported in association with VELCADE treatment. Therefore, platelet counts should be monitored prior to each dose of VELCADE. 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 section 5.3). Potential benefit of the treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding.

Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with VELCADE. Platelet transfusion should be considered when clinically appropriate (see section 4.3).

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Neutrophils were lowest at Day 11 of each cycle of VELCADE treatment and typically recovered to baseline by the next cycle. In study LYM-3002, colony stimulating factor support was given to 78% of patients in the VcR-CAP arm and 61% of patients in the R-CHOP arm. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. 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 (see section 4.3).

7.21 Intrathecal administration

There have been fatal cases of inadvertent intrathecal administration of VELCADE. VELCADE 1 mg powder for solution for injection is for intravenous use only, while VELCADE 3.5 mg powder for solution for injection is for intravenous or subcutaneous use. VELCADE should not be administered intrathecally.

7.22 Electrocardiogram investigations

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

8 ADVERSE REACTIONS

The following clinically significant adverse reactions are also discussed in other sections of the labeling:

- Peripheral Neuropathy *[see Warnings and Precautions (7.1)]*
- Hypotension *[see Warnings and Precautions (7.2)]*
- Cardiac Toxicity *[see Warnings and Precautions (7.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (7.4)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (7.5)]*
- Gastrointestinal Toxicity *[see Warnings and Precautions (7.6)]*
- Thrombocytopenia/Neutropenia *[see Warnings and Precautions (7.7)]*
- Hepatic impairment *[see Warnings and Precautions (7.8)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (7.9)]*
- Hepatic Toxicity *[see Warnings and Precautions (7.10)]*
- Thrombotic Microangiopathy *[see Warnings and Precautions (7.11)]*

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Summary of Clinical Trial in Patients with Previously Untreated Multiple Myeloma

Table 8 describes safety data from 340 patients with previously untreated multiple myeloma who received VELCADE (1.3 mg/m^2) administered intravenously in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in a prospective randomized study.

The safety profile of VELCADE in combination with melphalan/prednisone is consistent with the known safety profiles of both VELCADE and melphalan/prednisone.

Table 8: Most Commonly Reported Adverse Reactions (≥10% in the VELCADE, Melphalan and Prednisone Arm) with Grades 3 and ≥4 Intensity in the Previously Untreated Multiple Myeloma Study						
	VELCADE, Melphalan and Prednisone			Melphalan and Prednisone		
	(n=340)			(n=337)		
Body System	**Total**	**Toxicity Grade, n (%)**		**Total**	**Toxicity Grade, n (%)**	
Adverse Reaction	**n (%)**	**3**	**≥4**	**n (%)**	**3**	**≥4**
Blood and Lymphatic System Disorders						
Thrombocytopenia	164 (48)	60 (18)	57 (17)	140 (42)	48 (14)	39 (12)
Neutropenia	160 (47)	101 (30)	33 (10)	143 (42)	77 (23)	42 (12)
Anemia	109 (32)	41 (12)	4 (1)	156 (46)	61 (18)	18 (5)
Leukopenia	108 (32)	64 (19)	8 (2)	93 (28)	53 (16)	11 (3)
Lymphopenia	78 (23)	46 (14)	17 (5)	51 (15)	26 (8)	7 (2)
Gastrointestinal Disorders						
Nausea	134 (39)	10 (3)	0	70 (21)	1 (<1)	0
Diarrhea	119 (35)	19 (6)	2 (1)	20 (6)	1 (<1)	0
Vomiting	87 (26)	13 (4)	0	41 (12)	2 (1)	0
Constipation	77 (23)	2 (1)	0	14 (4)	0	0
Abdominal pain upper	34 (10)	1 (<1)	0	20 (6)	0	0
Nervous System Disorders						
Peripheral neuropathy*	156 (46)	42 (12)	2 (1)	4 (1)	0	0
Neuralgia	117 (34)	27 (8)	2 (1)	1 (<1)	0	0
Paresthesia	42 (12)	6 (2)	0	4 (1)	0	0
General Disorders and Administration Site Conditions						
Fatigue	85 (25)	19 (6)	2 (1)	48 (14)	4 (1)	0
Asthenia	54 (16)	18 (5)	0	23 (7)	3 (1)	0
Pyrexia	53 (16)	4 (1)	0	19 (6)	1 (<1)	1 (<1)
Infections and Infestations						
Herpes Zoster	39 (11)	11 (3)	0	9 (3)	4 (1)	0
Metabolism and Nutrition Disorders						
Anorexia	64 (19)	6 (2)	0	19 (6)	0	0
Skin and Subcutaneous Tissue Disorders						
Rash	38 (11)	2 (1)	0	7 (2)	0	0
Psychiatric Disorders						
Insomnia	35 (10)	1 (<1)	0	21 (6)	0	0

* Represents High Level Term Peripheral Neuropathies NEC

Relapsed Multiple Myeloma Randomized Study of VELCADE vs Dexamethasone

The safety data described below and in *Table 10* reflect exposure to either VELCADE (n=331) or dexamethasone (n=332) in a study of patients with relapsed multiple myeloma. VELCADE was administered intravenously at doses of 1.3 mg/m^2 twice weekly for two out of three weeks (21 day cycle). After eight, 21 day cycles patients continued therapy for three, 35 day cycles on a weekly schedule. Duration of treatment was up to 11 cycles (nine months) with a median duration of six cycles (4.1 months). For inclusion in the trial, patients must have had measurable disease and one to three prior therapies. There was no upper age limit for entry. Creatinine clearance could be as low as 20 mL/min and bilirubin levels as high as 1.5 times the upper limit of normal. The overall frequency of adverse reactions was similar in men and women, and in patients <65 and ≥65 years of age. Most patients were

Caucasian *[see Clinical Studies (**15**.1)]*.

Among the 331 VELCADE-treated patients, the most commonly reported (>20%) adverse reactions overall were nausea (52%), diarrhea (52%), fatigue (39%), peripheral neuropathies (35%), thrombocytopenia (33%), constipation (30%), vomiting (29%), and anorexia (21%). The most commonly reported (>20%) adverse reaction reported among the 332 patients in the dexamethasone group was fatigue (25%). Eight percent (8%) of patients in the VELCADE-treated arm experienced a Grade 4 adverse reaction; the most common reactions were thrombocytopenia (4%) and neutropenia (2%). Nine percent (9%) of dexamethasone-treated patients experienced a Grade 4 adverse reaction. All individual dexamethasone-related Grade 4 adverse reactions were less than 1%.

Serious Adverse Reactions and Adverse Reactions Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of VELCADE vs Dexamethasone

Serious adverse reactions are defined as any reaction that results in death, is life-threatening, requires hospitalization or prolongs a current hospitalization, results in a significant disability, or is deemed to be an important medical event. A total of 80 (24%) patients from the VELCADE treatment arm experienced a serious adverse reaction during the study, as did 83 (25%) dexamethasone-treated patients. The most commonly reported serious adverse reactions in the VELCADE treatment arm were diarrhea (3%), dehydration, herpes zoster, pyrexia, nausea, vomiting, dyspnea, and thrombocytopenia (2% each). In the dexamethasone treatment group, the most commonly reported serious adverse reactions were pneumonia (4%), hyperglycemia (3%), pyrexia, and psychotic disorder (2% each). A total of 145 patients, including 84 (25%) of 331 patients in the VELCADE treatment group and 61 (18%) of 332 patients in the dexamethasone treatment group were discontinued from treatment due to adverse reactions. Among the 331 VELCADE-treated patients, the most commonly reported adverse reaction leading to discontinuation was peripheral neuropathy (8%). Among the 332 patients in the dexamethasone group, the most commonly reported adverse reactions leading to treatment discontinuation were psychotic disorder and hyperglycemia (2% each).

Four deaths were considered to be VELCADE-related in this relapsed multiple myeloma study: one case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest. Four deaths were considered dexamethasone-related: two cases of sepsis, one case of bacterial meningitis, and one case of sudden death at home.

Most Commonly Reported Adverse Reactions in the Relapsed Multiple Myeloma Study of VELCADE vs Dexamethasone

The most common adverse reactions from the relapsed multiple myeloma study are shown in *Table* 9. All adverse reactions with incidence ≥10% in the VELCADE arm are included.

Table 9: Most Commonly Reported Adverse Reactions ((≥10% in VELCADE Arm), with Grades 3 and 4 Intensity in the Relapsed Multiple Myeloma Study of VELCADE vs Dexamethasone (N=663)

	VELCADE (N=331)			**Dexamethasone (N=332)**		
Adverse Reactions	**All**	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**
Any Adverse Reactions	324 (98)	193 (58)	28 (8)	297 (89)	110 (33)	29 (9)
Nausea	172 (52)	8 (2)	0	31 (9)	0	0
Diarrhea NOS	171 (52)	22 (7)	0	36 (11)	2 (<1)	0
Fatigue	130 (39)	15 (5)	0	82 (25)	8 (2)	0
Peripheral neuropathies*	115 (35)	23 (7)	2 (<1)	14 (4)	0	1 (<1)
Thrombocytopenia	109 (33)	80 (24)	12 (4)	11 (3)	5 (2)	1 (<1)
Constipation	99 (30)	6 (2)	0	27 (8)	1 (<1)	0
Vomiting NOS	96 (29)	8 (2)	0	10 (3)	1 (<1)	0
Anorexia	68 (21)	8 (2)	0	8 (2)	1 (<1)	0
Pyrexia	66 (20)	2 (<1)	0	21 (6)	3 (<1)	1 (<1)
Paresthesia	64 (19)	5 (2)	0	24 (7)	0	0
Anemia NOS	63 (19)	20 (6)	1 (<1)	21 (6)	8 (2)	0
Headache NOS	62 (19)	3 (<1)	0	23 (7)	1 (<1)	0

Table 9: Most Commonly Reported Adverse Reactions ((≥10% in VELCADE Arm), with Grades 3 and 4 Intensity in the Relapsed Multiple Myeloma Study of VELCADE vs Dexamethasone (N=663)						
	VELCADE (N=331)			**Dexamethasone (N=332)**		
Adverse Reactions	**All**	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**
Neutropenia	58 (18)	37 (11)	8 (2)	1 (<1)	1 (<1)	0
Rash NOS	43 (13)	3 (<1)	0	7 (2)	0	0
Appetite decreased NOS	36 (11)	0	0	12 (4)	0	0
Dyspnea NOS	35 (11)	11 (3)	1 (<1)	37 (11)	7 (2)	1 (<1)
Abdominal pain NOS	35 (11)	5 (2)	0	7 (2)	0	0
Weakness	34 (10)	10 (3)	0	28 (8)	8 (2)	0

* Represents High Level Term Peripheral Neuropathies NEC

Safety Experience from the Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma

In the Phase 2 extension study of 63 patients, no new cumulative or new long-term toxicities were observed with prolonged VELCADE treatment. These patients were treated for a total of 5.3 to 23months, including time on VELCADE in the prior VELCADE study *[see Clinical Studies (15.1)]*.

Safety Experience from the Phase 3 Open-Label Study of VELCADE Subcutaneous vs Intravenous in Relapsed Multiple Myeloma

The safety and efficacy of VELCADE administered subcutaneously were evaluated in one Phase 3 study at the recommended dose of 1.3 mg/m^2. This was a randomized, comparative study of VELCADE subcutaneous vs intravenous in 222 patients with relapsed multiple myeloma. The safety data described below and in *Table* 10 reflect exposure to either VELCADE subcutaneous (N=147) or VELCADE intravenous (N=74) *[see Clinical Studies (*15*.1)]*.

Table 10: Most Commonly Reported Adverse Reactions (≥10%), with Grade 3 and ≥4 Intensity in the Relapsed Multiple Myeloma Study (N=221) of VELCADE Subcutaneous vs Intravenous

	Subcutaneous (N=147)			Intravenous (N=74)		
Body System	**Total**	**Toxicity Grade, n (%)**		**Total**	**Toxicity Grade, n (%)**	
Adverse Reaction	**n (%)**	**3**	**≥4**	**n (%)**	**3**	**≥4**
Blood and Lymphatic System Disorders						
Anemia	28 (19)	8 (5)	0	17 (23)	3 (4)	0
Leukopenia	26 (18)	8 (5)	0	15 (20)	4 (5)	1 (1)
Neutropenia	34 (23)	15 (10)	4 (3)	20 (27)	10 (14)	3 (4)
Thrombocytopenia	44 (30)	7 (5)	5 (3)	25 (34)	7 (9)	5 (7)
Gastrointestinal Disorders						
Diarrhea	28 (19)	1 (1)	0	21 (28)	3 (4)	0
Nausea	24 (16)	0	0	10 (14)	0	0
Vomiting	13 (9)	3 (2)	0	8 (11)	0	0
General Disorders and Administration Site Conditions						
Asthenia	10 (7)	1 (1)	0	12 (16)	4 (5)	0
Fatigue	11 (7)	3 (2)	0	11 (15)	3 (4)	0
Pyrexia	18 (12)	0	0	6 (8)	0	0
Nervous System Disorders						
Neuralgia	34 (23)	5 (3)	0	17 (23)	7 (9)	0
Peripheral neuropathies*	55 (37)	8 (5)	1 (1)	37 (50)	10 (14)	1 (1)

Note: Safety population: 147 patients in the subcutaneous treatment group and 74 patients in the intravenous treatment group who received at least one dose of study medication

* Represents High Level Term Peripheral Neuropathies NEC

In general, safety data were similar for the subcutaneous and intravenous treatment groups. Differences were observed in the rates of some Grade ≥3 adverse reactions. Differences of ≥5% were reported in neuralgia (3% subcutaneous vs 9% intravenous), peripheral neuropathies (6% subcutaneous vs 15% intravenous), neutropenia (13% subcutaneous vs 18% intravenous), and thrombocytopenia (8% subcutaneous vs 16% intravenous).

A local reaction was reported in 6% of patients in the subcutaneous group, mostly redness. Only two (1%) patients were reported as having severe reactions, one case of pruritus and one case of redness. Local reactions led to reduction in injection concentration in one patient and drug discontinuation in one patient. Local reactions resolved in a median of six days.

Dose reductions occurred due to adverse reactions in 31% of patients in the subcutaneous treatment group compared with 43% of the intravenously-treated patients. The most common adverse reactions leading to a dose reduction included peripheral sensory neuropathy (17% in the subcutaneous treatment group compared with 31% in the intravenous treatment group); and neuralgia (11% in the subcutaneous treatment group compared with 19% in the intravenous treatment group).

Serious Adverse Reactions and Adverse Reactions Leading to Treatment Discontinuation in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous vs Intravenous.

The incidence of serious adverse reactions was similar for the subcutaneous treatment group (20%) and the intravenous treatment group (19%). The most commonly reported serious adverse reactions in the subcutaneous treatment arm were pneumonia and pyrexia (2% each). In the intravenous treatment group, the most commonly reported serious adverse reactions were pneumonia, diarrhea, and peripheral sensory neuropathy (3% each).

In the subcutaneous treatment group, 27 patients (18%) discontinued study treatment due to an adverse reaction compared with 17 patients (23%) in the intravenous treatment group. Among the 147 subcutaneously-treated patients, the most commonly reported adverse reactions leading to discontinuation were peripheral sensory neuropathy (5%) and neuralgia (5%). Among the 74 patients in the intravenous treatment group, the most commonly reported adverse reactions leading to treatment discontinuation were

peripheral sensory neuropathy (9%) and neuralgia (9%).
Two patients (1%) in the subcutaneous treatment group and one (1%) patient in the intravenous treatment group died due to an adverse reaction during treatment. In the subcutaneous group the causes of death were one case of pneumonia and one case of sudden death. In the intravenous group the cause of death was coronary artery insufficiency.

Safety Experience from the Clinical Trial in Patients with Previously Untreated Mantle Cell Lymphoma
Table 11 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received VELCADE (1.3 mg/m^2) administered intravenously in combination with rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), and prednisone (100 mg/m^2) (VcR-CAP) in a prospective randomized study.
Infections were reported for 31% of patients in the VcR-CAP arm and 23% of the patients in the comparator (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) arm, including the predominant preferred term of pneumonia (VcR-CAP 8% vs R-CHOP 5%).

Table 11: Most Commonly Reported Adverse Reactions (≥5%) with Grades 3 and ≥4 Intensity in the Previously Untreated Mantle Cell Lymphoma Study

	VcR-CAP (n=240)			R-CHOP (n=242)		
Body System Adverse Reactions	**All n (%)**	**Toxicity Grade 3 n (%)**	**Toxicity Grade ≥4 n (%)**	**All n (%)**	**Toxicity Grade 3 n (%)**	**Toxicity Grade ≥4 n (%)**
Blood and Lymphatic System Disorders						
Neutropenia	209 (87)	32 (13)	168 (70)	172 (71)	31 (13)	125 (52)
Leukopenia	116 (48)	34 (14)	69 (29)	87 (36)	39 (16)	27 (11)
Anemia	106 (44)	27 (11)	4 (2)	71 (29)	23 (10)	4 (2)
Thrombocytopenia	172 (72)	59 (25)	76 (32)	42 (17)	9 (4)	3 (1)
Febrile neutropenia	41 (17)	24 (10)	12 (5)	33 (14)	17 (7)	15 (6)
Lymphopenia	68 (28)	25 (10)	36 (15)	28 (12)	15 (6)	2 (1)
Nervous System Disorders						
Peripheral neuropathy*	71 (30)	17 (7)	1 (<1)	65 (27)	10 (4)	0
Hypoesthesia	14 (6)	3 (1)	0	13 (5)	0	0
Paresthesia	14 (6)	2 (1)	0	11 (5)	0	0
Neuralgia	25 (10)	9 (4)	0	1 (<1)	0	0
General Disorders and Administration Site Conditions						
Fatigue	43 (18)	11 (5)	1 (<1)	38 (16)	5 (2)	0
Pyrexia	48 (20)	7 (3)	0	23 (10)	5 (2)	0
Asthenia	29 (12)	4 (2)	1 (<1)	18 (7)	1 (<1)	0
Edema peripheral	16 (7)	1 (<1)	0	13 (5)	0	0
Gastrointestinal Disorders						
Nausea	54 (23)	1 (<1)	0	28 (12)	0	0
Constipation	42 (18)	1 (<1)	0	22 (9)	2 (1)	0
Stomatitis	20 (8)	2 (1)	0	19 (8)	0	1 (<1)
Diarrhea	59 (25)	11 (5)	0	11 (5)	3 (1)	1 (<1)
Vomiting	24 (10)	1 (<1)	0	8 (3)	0	0
Abdominal distension	13 (5)	0	0	4 (2)	0	0
Infections and Infestations						
Pneumonia	20 (8)	8 (3)	5 (2)	11 (5)	5 (2)	3 (1)

Skin and Subcutaneous Tissue Disorders						
Alopecia	31 (13)	1 (<1)	1 (<1)	33 (14)	4 (2)	0
Metabolism and Nutrition Disorders						
Hyperglycemia	10 (4)	1 (<1)	0	17 (7)	10 (4)	0
Decreased appetite	36 (15)	2 (1)	0	15 (6)	1 (<1)	0
Vascular Disorders						
Hypertension	15 (6)	1 (<1)	0	3 (1)	0	0
Psychiatric Disorders						
Insomnia	16 (7)	1 (<1)	0	8 (3)	0	0

Key: R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VcR-CAP = VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.
* Represents High Level Term Peripheral Neuropathies NEC

The incidence of herpes zoster reactivation was 4.6% in the VcR-CAP arm and 0.8% in the R-CHOP arm. Antiviral prophylaxis was mandated by protocol amendment.
The incidences of Grade ≥3 bleeding events were similar between the two arms (four patients in the VcR-CAP arm and three patients in the R-CHOP arm). All of the Grade ≥3 bleeding events resolved without sequelae in the VcR-CAP arm.
Adverse reactions leading to discontinuation occurred in 8% of patients in VcR-CAP group and 6% of patients in R-CHOP group. In the VcR-CAP group, the most commonly reported adverse reaction leading to discontinuation was peripheral sensory neuropathy (1%; three patients). The most commonly reported adverse reaction leading to discontinuation in the R-CHOP group was febrile neutropenia (<1%; two patients).

Mantle Cell Lymphoma (MCL)

The safety profile of VELCADE 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, anemia, 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 12 has been generated using Version 16 of the MedDRA.

Table 12: 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*, Blood glucose abnormal*, 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	Vision abnormal*
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
Skin and subcutaneous tissue disorders	Very Common	Hair disorder*
	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*, Protein analyses abnormal*, Weight decreased, Weight increased

* Grouping of more than one MedDRA preferred term.

Integrated Summary of Safety (Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma)

Safety data from Phase 2 and 3 studies of single agent VELCADE 1.3 mg/m^2/dose twice weekly for two weeks followed by a ten day rest period in 1163 patients with previously-treated multiple myeloma (N=1008) and previously-treated mantle cell lymphoma (N=155) were integrated and tabulated. This analysis does not include data from the Phase 3 open-label study of VELCADE subcutaneous vs intravenous in relapsed multiple myeloma. In the integrated studies, the safety profile of VELCADE was similar in patients with multiple myeloma and mantle cell lymphoma. [*see Clinical Studies (15)*].

In the integrated analysis, the most commonly reported (>20%) adverse reactions were nausea (49%), diarrhea (46%), asthenic conditions including fatigue (41%) and weakness (11%), peripheral neuropathies (38%), thrombocytopenia (32%), vomiting (28%), constipation (25%), and pyrexia (21%). Eleven percent (11%) of patients experienced at least one episode of ≥Grade 4 toxicity, most commonly thrombocytopenia (4%) and neutropenia (2%).

In the Phase 2 relapsed multiple myeloma clinical trials of VELCADE administered intravenously, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not associated with tissue damage.

Serious Adverse Reactions and Adverse Reactions Leading to Treatment Discontinuation in the Integrated Summary of Safety

A total of 26% of patients experienced a serious adverse reaction during the studies. The most commonly reported serious adverse reactions included diarrhea, vomiting and pyrexia (3% each), nausea, dehydration, and thrombocytopenia (2% each) and pneumonia, dyspnea, peripheral neuropathies, and herpes zoster (1% each).

Adverse reactions leading to discontinuation occurred in 22% of patients. The reasons for discontinuation included peripheral neuropathy (8%), and fatigue, thrombocytopenia, and diarrhea (2% each).

In total, 2% of the patients died and the cause of death was considered by the investigator to be possibly related to study drug: including reports of cardiac arrest, congestive heart failure, respiratory failure, renal failure, pneumonia and sepsis.

Most Commonly Reported Adverse Reactions in the Integrated Summary of Safety

The most common adverse reactions are shown in *Table 13*. All adverse reactions occurring at ≥10% are included. In the absence of a randomized comparator arm, it is often not possible to distinguish between adverse events that are drug-caused and those that reflect the patient's underlying disease. Please see the discussion of specific adverse reactions that follows.

Table 13: Most Commonly Reported (≥10% Overall) Adverse Reactions in Integrated Analyses of Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma Studies Using the 1.3 mg/m^2 Dose (N=1163)

	All Patients (N=1163)		Multiple Myeloma (N=1008)		Mantle Cell Lymphoma (N=155)	
Adverse Reactions	**All**	**≥Grade 3**	**All**	**≥Grade 3**	**All**	**≥Grade 3**
Nausea	567 (49)	36 (3)	511 (51)	32 (3)	56 (36)	4 (3)
Diarrhea NOS	530 (46)	83 (7)	470 (47)	72 (7)	60 (39)	11 (7)
Fatigue	477 (41)	86 (7)	396 (39)	71 (7)	81 (52)	15 (10)
Peripheral neuropathies *	443 (38)	129 (11)	359 (36)	110 (11)	84 (54)	19 (12)
Thrombocytopenia	369 (32)	295 (25)	344 (34)	283 (28)	25 (16)	12 (8)
Vomiting NOS	321 (28)	44 (4)	286 (28)	40 (4)	35 (23)	4 (3)
Constipation	296 (25)	17 (1)	244 (24)	14 (1)	52 (34)	3 (2)
Pyrexia	249 (21)	16 (1)	233 (23)	15 (1)	16 (10)	1 (<1)
Anorexia	227 (20)	19 (2)	205 (20)	16 (2)	22 (14)	3 (2)
Anemia NOS	209 (18)	65 (6)	190 (19)	63 (6)	19 (12)	2 (1)
Headache NOS	175 (15)	8 (<1)	160 (16)	8 (<1)	15 (10)	0
Neutropenia	172 (15)	121 (10)	164 (16)	117 (12)	8 (5)	4 (3)
Rash NOS	156 (13)	8 (<1)	120 (12)	4 (<1)	36 (23)	4 (3)
Paresthesia	147 (13)	9 (<1)	136 (13)	8 (<1)	11 (7)	1 (<1)
Dizziness (excl vertigo)	129 (11)	13 (1)	101 (10)	9 (<1)	28 (18)	4 (3)
Weakness	124 (11)	31 (3)	106 (11)	28 (3)	18 (12)	3 (2)

* Represents High Level Term Peripheral Neuropathies NEC

Description of Selected Adverse Reactions from the Integrated Phase 2 and 3 Relapsed Multiple Myeloma and Phase 2 Relapsed Mantle Cell Lymphoma Studies

Gastrointestinal Toxicity

A total of 75% of patients experienced at least one gastrointestinal disorder. The most common gastrointestinal disorders included nausea, diarrhea, constipation, vomiting, and appetite decreased. Other gastrointestinal disorders included dyspepsia and dysgeusia. Grade 3 adverse reactions occurred in 14% of patients; ≥Grade 4 adverse reactions were ≤1%. Gastrointestinal adverse reactions were considered serious in 7% of patients. Four percent (4%) of patients discontinued due to a gastrointestinal adverse reaction. Nausea was reported more often in patients with multiple myeloma (51%) compared to patients with mantle cell lymphoma (36%).

Thrombocytopenia

Across the studies, VELCADE-associated thrombocytopenia was characterized by a decrease in platelet count during the dosing period (Days 1 to 11) and a return toward baseline during the ten day rest period during each treatment cycle. Overall, thrombocytopenia was reported in 32% of patients. Thrombocytopenia was Grade 3 in 22%, ≥Grade 4 in 4%, and serious in 2% of patients, and the reaction resulted in VELCADE discontinuation in 2% of patients *[see Warnings and Precautions (7.7)]*. Thrombocytopenia was reported more often in patients with multiple myeloma (34%) compared to patients with mantle cell lymphoma (16%). The incidence of ≥Grade 3 thrombocytopenia also was higher in patients with multiple myeloma (28%) compared to patients with mantle cell lymphoma (8%).

Peripheral Neuropathy
Overall, peripheral neuropathies occurred in 38% of patients. Peripheral neuropathy was Grade 3 for 11% of patients and ≥Grade 4 for <1% of patients. Eight percent (8%) of patients discontinued VELCADE due to peripheral neuropathy. The incidence of peripheral neuropathy was higher among patients with mantle cell lymphoma (54%) compared to patients with multiple myeloma (36%).
In the VELCADE vs dexamethasone Phase 3 relapsed multiple myeloma study, among the 62 VELCADE-treated patients who experienced ≥Grade 2 peripheral neuropathy and had dose adjustments, 48% had improved or resolved with a median of 3.8 months from first onset.
In the Phase 2 relapsed multiple myeloma studies, among the 30 patients who experienced Grade 2 peripheral neuropathy resulting in discontinuation or who experienced ≥Grade 3 peripheral neuropathy, 73% reported improvement or resolution with a median time of 47 days to improvement of one grade or more from the last dose of VELCADE.

Hypotension
The incidence of hypotension (postural, orthostatic and hypotension NOS) was 8% in patients treated with VELCADE. Hypotension was Grade 1 or 2 in the majority of patients and Grade 3 in 2% and≥Grade 4 in <1%. Two percent (2%) of patients had hypotension reported as a serious adverse reaction, and 1% discontinued due to hypotension. The incidence of hypotension was similar in patients with multiple myeloma (8%) and those with mantle cell lymphoma (9%). In addition, <1% of patients experienced hypotension associated with a syncopal reaction.

Neutropenia
Neutrophil counts decreased during the VELCADE dosing period (Days 1 to 11) and returned toward baseline during the ten day rest period during each treatment cycle. Overall, neutropenia occurred in 15% of patients and was Grade 3 in 8% of patients and ≥Grade 4 in 2%. Neutropenia was reported as a serious adverse reaction in <1% of patients and <1% of patients discontinued due to neutropenia. The incidence of neutropenia was higher in patients with multiple myeloma (16%) compared to patients with mantle cell lymphoma (5%). The incidence of ≥Grade 3 neutropenia also was higher in patients with multiple myeloma (12%) compared to patients with mantle cell lymphoma (3%).

Asthenic Conditions (Fatigue, Malaise, Weakness, Asthenia)
Asthenic conditions were reported in 54% of patients. Fatigue was reported as Grade 3 in 7% and ≥Grade 4 in <1% of patients. Asthenia was reported as Grade 3 in 2% and ≥Grade 4 in <1% of patients. Two percent (2%) of patients discontinued treatment due to fatigue and <1% due to weakness and asthenia. Asthenic conditions were reported in 53% of patients with multiple myeloma and 59% of patients with mantle cell lymphoma.

Pyrexia
Pyrexia (>38ºC) was reported as an adverse reaction for 21% of patients. The reaction was Grade 3 in 1% and ≥Grade 4 in <1%. Pyrexia was reported as a serious adverse reaction in 3% of patients and led to VELCADE discontinuation in <1% of patients. The incidence of pyrexia was higher among patients with multiple myeloma (23%) compared to patients with mantle cell lymphoma (10%). The incidence of ≥Grade 3 pyrexia was 1% in patients with multiple myeloma and <1% in patients with mantle cell lymphoma.

Herpes Virus Infection
Consider using antiviral prophylaxis in subjects being treated with VELCADE. In the randomized studies in previously untreated and relapsed multiple myeloma, herpes zoster reactivation was more common in subjects treated with VELCADE (ranging between 6 to 11%) than in the control groups (3 to 4%). Herpes simplex was seen in 1 to 3% in subjects treated with VELCADE and 1 to 3% in the control groups. In the previously untreated multiple myeloma study, herpes zoster virus reactivation in the VELCADE, melphalan and prednisone arm was less common in subjects receiving prophylactic antiviral therapy (3%) than in subjects who did not receive prophylactic antiviral therapy (17%).

<u>Retreatment in Relapsed Multiple Myeloma</u>
A single-arm trial was conducted in 130 patients with relapsed multiple myeloma to determine the efficacy and safety of retreatment with intravenous VELCADE. The safety profile of patients in this trial is consistent with the known safety profile of VELCADE-treated patients with relapsed multiple myeloma as demonstrated in *Tables 10, 11,* and *13*; no cumulative toxicities were observed upon retreatment. The most common adverse drug reaction was thrombocytopenia which occurred in 52% of the patients. The incidence of ≥Grade 3 thrombocytopenia was 24%. Peripheral neuropathy occurred in 28% of patients, with the incidence of ≥Grade 3 peripheral neuropathy reported at 6%. The incidence of serious adverse reactions was 12.3%. The most commonly reported serious adverse reactions were thrombocytopenia (3.8%), diarrhea (2.3%), and herpes zoster and pneumonia (1.5% each).
Adverse reactions leading to discontinuation occurred in 13% of patients. The reasons for discontinuation included peripheral neuropathy (5%) and diarrhea (3%).

Two deaths considered to be VELCADE-related occurred within 30 days of the last VELCADE dose; one in a patient with cerebrovascular accident and one in a patient with sepsis.

Additional Adverse Reactions from Clinical Studies

The following clinically important serious adverse reactions that are not described above have been reported in clinical trials in patients treated with VELCADE administered as monotherapy or in combination with other chemotherapeutics. These studies were conducted in patients with hematological malignancies and in solid tumors.

Blood and Lymphatic System Disorders: Anemia, disseminated intravascular coagulation, febrile neutropenia, lymphopenia, leukopenia

Cardiac Disorders: Angina pectoris, atrial fibrillation aggravated, atrial flutter, bradycardia, sinus arrest, cardiac amyloidosis, complete atrioventricular block, myocardial ischemia, myocardial infarction, pericarditis, pericardial effusion, *Torsades de pointes*, ventricular tachycardia

Ear and Labyrinth Disorders: Hearing impaired, vertigo

Eye Disorders: Diplopia and blurred vision, conjunctival infection, irritation

Gastrointestinal Disorders: Abdominal pain, ascites, dysphagia, fecal impaction, gastroenteritis, gastritis hemorrhagic, hematemesis, hemorrhagic duodenitis, ileus paralytic, large intestinal obstruction, paralytic intestinal obstruction, peritonitis, small intestinal obstruction, large intestinal perforation, stomatitis, melena, pancreatitis acute, oral mucosal petechiae, gastroesophageal reflux

General Disorders and Administration Site Conditions: Chills, edema, edema peripheral, injection site erythema, neuralgia, injection site pain, irritation, malaise, phlebitis

Hepatobiliary Disorders: Cholestasis, hepatic hemorrhage, hyperbilirubinemia, portal vein thrombosis, hepatitis, liver failure

Immune System Disorders: Anaphylactic reaction, drug hypersensitivity, immune complex mediated hypersensitivity, angioedema, laryngeal edema

Infections and Infestations: Aspergillosis, bacteremia, bronchitis, urinary tract infection, herpes viral infection, listeriosis, nasopharyngitis, pneumonia, respiratory tract infection, septic shock, toxoplasmosis, oral candidiasis, sinusitis, catheter-related infection

Injury, Poisoning and Procedural Complications: Catheter-related complication, skeletal fracture, subdural hematoma

Investigations: Weight decreased

Metabolism and Nutrition Disorders: Dehydration, hypocalcemia, hyperuricemia, hypokalemia, hyperkalemia, hyponatremia, hypernatremia

Musculoskeletal and Connective Tissue Disorders: Arthralgia, back pain, bone pain, myalgia, pain in extremity

Nervous System Disorders: Ataxia, coma, dizziness, dysarthria, dysesthesia, dysautonomia, encephalopathy, cranial palsy, grand mal convulsion, headache, hemorrhagic stroke, motor dysfunction, neuralgia, spinal cord compression, paralysis, postherpetic neuralgia, transient ischemic attack

Psychiatric Disorders: Agitation, anxiety, confusion, insomnia, mental status change, psychotic disorder, suicidal ideation

Renal and Urinary Disorders: Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria, hemorrhagic cystitis, urinary incontinence, urinary retention, renal failure (acute and chronic), glomerular nephritis proliferative

Respiratory, Thoracic and Mediastinal Disorders: Acute respiratory distress syndrome, aspiration pneumonia, atelectasis, chronic obstructive airways disease exacerbated, cough, dysphagia, dyspnea, dyspnea exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion, pneumonitis, respiratory distress, pulmonary hypertension

Skin and Subcutaneous Tissue Disorders: Urticaria, face edema, rash (which may be pruritic), leukocytoclastic vasculitis, pruritus

Vascular Disorders: Cerebrovascular accident, cerebral hemorrhage, deep venous thrombosis, hypertension, peripheral embolism, pulmonary embolism, pulmonary hypertension

Mantle cell lymphoma

Antiviral prophylaxis was administered to 137 of 240 patients (57%) in the VcR-CAP arm. 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 7.13).

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). 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).

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 14: 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 GradePN	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 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.

8.2 Postmarketing Experience

The following adverse reactions have been identified from the worldwide postmarketing experience with VELCADE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Cardiac Disorders: Cardiac tamponade

Ear and Labyrinth Disorders: Deafness bilateral

Eye Disorders: Optic neuropathy, blindness, chalazion/blepharitis

Gastrointestinal Disorders: Ischemic colitis

Infections and Infestations: Progressive multifocal leukoencephalopathy (PML), ophthalmic herpes, herpes meningoencephalitis

Nervous System Disorders: Posterior reversible encephalopathy syndrome (PRES, formerly RPLS), Guillain-Barré syndrome, demyelinating polyneuropathy

Respiratory, Thoracic and Mediastinal Disorders: Acute diffuse infiltrative pulmonary disease

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute febrile neutrophilic dermatosis (Sweet's syndrome)

Reportingof suspected adverse reactions Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form *http://sideeffects.health.gov.il*

9 DRUG INTERACTIONS

9.1 Effects of Other Drugs on VELCADE

Strong CYP3A4 Inducers

Coadministration with a strong CYP3A4 inducer decreases the exposure of bortezomib *[see Clinical Pharmacology (13.3)]* which may decrease VELCADE efficacy. Avoid coadministration with strong CYP3A4 inducers.

Strong CYP3A4 Inhibitors

Coadministration with a strong CYP3A4 inhibitor increases the exposure of bortezomib *[see Clinical Pharmacology (13.3)]* which may increase the risk of VELCADE toxicities. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors.

9.2 Drugs Without Clinically Significant Interactions with VELCADE

No clinically significant drug interactions have been observed when VELCADE was coadministered with dexamethasone, omeprazole, or melphalan in combination with prednisone *[see Clinical Pharmacology (13.3)]*.

During clinical trials, hypoglycemia and hyperglycemia were uncommonly and commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving VELCADE treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetics.

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

Based on its mechanism of action *[see Clinical Pharmacology (13.1)]* and findings in animals, VELCADE can cause fetal harm when administered to a pregnant woman. There are no studies with the use of VELCADE in pregnant women to inform drug-associated risks. Bortezomib caused embryo-fetal lethality in rabbits at doses lower than the clinical dose *(see Data)*. Advise pregnant women of the potential risk to the fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m^2 in the rat and 0.05 mg/kg; 0.6 mg/m^2 in the rabbit) when administered during organogenesis. These dosages are approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area.

Bortezomib caused embryo-fetal lethality in rabbits at doses lower than the clinical dose (approximately 0.5 times the clinical dose of 1.3 mg/m^2 based on body surface area). Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05 mg/kg (0.6 mg/m^2) experienced significant postimplantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight.

10.2 Lactation

Risk Summary

There are no data on the presence of bortezomib or its metabolites in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. Because many drugs are excreted in human milk and because the potential for serious adverse reactions in a breastfed child from VELCADE is unknown, advise nursing women not to breastfeed during treatment with VELCADE and for two months after treatment.

10.3 Females and Males of Reproductive Potential

Based on its mechanism of action and findings in animals, VELCADE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (10.1)]*.

Pregnancy Testing

Conduct pregnancy testing in females of reproductive potential prior to initiating VELCADE treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with VELCADE and for seven months after the last dose.

Males

Males with female partners of reproductive potential should use effective contraception during treatment with VELCADE and for four months after the last dose.

Infertility

Based on the mechanism of action and findings in animals, VELCADE may have an effect on either male or female fertility *[see Nonclinical Toxicology (14.1)]*.

10.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

The activity and safety of VELCADE in combination with intensive reinduction chemotherapy was evaluated in pediatric and young adult patients with lymphoid malignancies (pre-B cell ALL 77%, 16% with T-cell ALL, and 7% T-cell lymphoblastic lymphoma (LL)), all of whom relapsed within 36 months of initial diagnosis in a single-arm multicenter, nonrandomized cooperative group trial. An effective reinduction multiagent chemotherapy regimen was administered in three blocks. Block 1 included vincristine, prednisone, doxorubicin and pegaspargase; Block 2 included cyclophosphamide, etoposide and methotrexate; Block 3 included high-dose cytosine arabinoside and asparaginase. VELCADE was administered at a dose of 1.3 mg/m^2 as a bolus intravenous injection on Days 1, 4, 8, and 11 of Block 1 and Days 1, 4, and 8 of Block 2. There were 140 patients with ALL or LL enrolled and evaluated for safety. The median age was ten years (range: 1 to 26), 57% were male, 70% were white, 14% were black, 4% were Asian, 2% were American Indian/Alaska Native, 1% were Pacific Islander.

The activity was evaluated in a prespecified subset of the first 60 evaluable patients enrolled on the study with pre-B ALL ≤21 years and relapsed <36 months from diagnosis. The complete remission (CR) rate at day 36 was compared to that in a historical control set of patients who had received the identical backbone therapy without VELCADE. There was no evidence that the addition of VELCADE had any impact on the CR rate.

No new safety concerns were observed when VELCADE was added to a chemotherapy backbone regimen as compared with a historical control group in which the backbone regimen was given without VELCADE.

The BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

10.5 Geriatric Use

Of the 669 patients enrolled in the relapsed multiple myeloma study, 245 (37%) were 65 years of age or older: 125 (38%) on the VELCADE arm and 120 (36%) on the dexamethasone arm. Median time to progression and median duration of response for patients ≥65 were longer on VELCADE compared to dexamethasone [5.5 mo vs 4.3 mo, and 8.0 mo vs 4.9 mo, respectively]. On the VELCADE arm, 40% (n=46) of evaluable patients aged ≥65 experienced response (CR + PR) vs 18% (n=21) on the dexamethasone arm. The

incidence of Grade 3 and 4 events was 64%, 78% and 75% for VELCADE patients ≤50, 51 to 64 and ≥65 years old, respectively *[see Adverse Reactions (9.1); Clinical Studies (15)*]

No overall differences in safety or effectiveness were observed between patients ≥age 65 and younger patients receiving VELCADE; but greater sensitivity of some older individuals cannot be ruled out.

10.5 Renal Impairment

No starting dosage adjustment of VELCADE is recommended for patients with renal impairment. In patients requiring dialysis, VELCADE should be administered after the dialysis procedure *[see Clinical Pharmacology (*13.*3*)]

10.6 Hepatic Impairment

No starting dosage adjustment of VELCADE is recommended for patients with mild hepatic impairment (total bilirubin ≤1x ULN and AST > ULN, or total bilirubin >1 to 1.5x ULN and any AST). The exposure of bortezomib is increased in patients with moderate (total bilirubin ≥1.5 to 3x ULN and any AST) and severe (total bilirubin >3x ULN and any AST) hepatic impairment. Reduce the starting dose in patients with moderate or severe hepatic impairment *[see Dosage and Administration (4.6), Clinical Pharmacology (13.3)]*.

10.7 Patients with Diabetes

During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. 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.

11 OVERDOSAGE

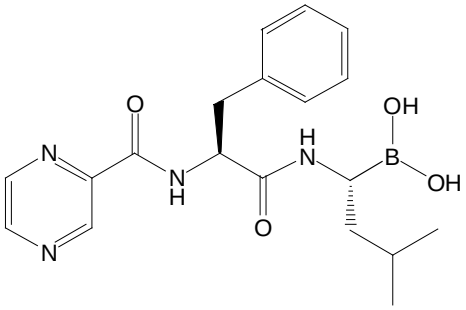
There is no known specific antidote for VELCADE overdosage. In humans, fatal outcomes following the administration of more than twice the recommended therapeutic dose have been reported, which were associated with the acute onset of symptomatic hypotension (5.2) and thrombocytopenia (7.7). In the event of an overdosage, the patient's vital signs should be monitored and appropriate supportive care given.

Studies in monkeys and dogs showed that intravenous bortezomib doses as low as two times the recommended clinical dose on a mg/m^2 basis were associated with increases in heart rate, decreases in contractility, hypotension, and death. In dog studies, a slight increase in the corrected QT interval was observed at doses resulting in death. In monkeys, doses of 3.0 mg/m^2 and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at one hour postadministration, with progression to death in 12 to 14 hours following drug administration**.**

12 DESCRIPTION

VELCADE® for Injection, a proteasome inhibitor, contains bortezomib which is an antineoplastic agent. Bortezomib is a modified dipeptidyl boronic acid. The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl) amino]propyl]amino]butyl] boronic acid.

Bortezomib has the following chemical structure:



The molecular weight is 384.24. The molecular formula is $C_{19}H_{25}BN_4O_4$. The solubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2 to 6.5.

VELCADE is available for intravenous injection or subcutaneous use. Each single-dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. It also contains the inactive ingredient: 35 mg mannitol, USP. The product is provided as a mannitol boronic ester

which, in reconstituted form, consists of the mannitol ester in equilibrium with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its cyclic anhydride form as a trimeric boroxine.

13 CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Bortezomib is a reversible inhibitor of 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 intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in nonclinical tumor models, including multiple myeloma.

13.2 Pharmacodynamics

Following twice weekly administration of 1 mg/m^2 and 1.3 mg/m^2 bortezomib doses, the maximum inhibition of 20S proteasome activity (relative to baseline) in whole blood was observed five minutes after drug administration. Comparable maximum inhibition of 20S proteasome activity was observed between 1 and 1.3 mg/m^2 doses. Maximal inhibition ranged from 70% to 84% and from 73% to 83% for the 1 mg/m^2 and 1.3 mg/m^2 dose regimens, respectively.

13.3 Pharmacokinetics

Following intravenous administration of 1 mg/m^2 and 1.3 mg/m^2 doses, the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose (Day 1) were 57 and 112 ng/mL, respectively. When administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose.

Following an intravenous bolus or subcutaneous injection 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 subcutaneous and intravenous administration. The AUC_{last} geometric mean ratio (90% confidence interval) was 0.99 (0.80 to 1.23). The C_{max} after subcutaneous administration (20.4 ng/mL) was lower than after intravenous administration (223 ng/mL) with repeat dose administration.

Distribution

The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m^2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.

Elimination

The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m^2 dose and 76 to 108 hours after the 1.3 mg/m^2 dose. The mean total body clearances were 102 and 112 L/h following the first dose for doses of 1 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 and 1.3 mg/m^2, respectively.

Metabolism

Bortezomib is primarily oxidatively metabolized to several inactive metabolites *in vitro* via cytochrome P450 (CYP) enzymes 3A4, CYP2C19, and CYP1A2, and to a lesser extent by CYP2D6 and CYP2C9.

Excretion

The pathways of elimination of bortezomib have not been characterized in humans.

Specific Populations

No clinically significant differences in the pharmacokinetics of bortezomib were observed based on age, sex, or renal impairment (including patients administered VELCADE after dialysis). The effect of race on bortezomib pharmacokinetics is unknown.

Patients with Hepatic Impairment

Following administration of bortezomib doses ranging from 0.5 to 1.3 mg/m^2, mild (total bilirubin ≤1x ULN and AST >ULN, or total bilirubin >1 to 1.5x ULN and any AST) hepatic impairment did not alter dose-normalized bortezomib AUC when compared to patients with normal hepatic function. Dose normalized mean bortezomib AUC increased by approximately 60% in patients with moderate (total

bilirubin >1.5 to 3x ULN and any AST) or severe (total bilirubin >3x ULN and any AST) hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment.

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 < 20mL/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-normalized AUC and Cmax) was comparable among all the groups. **[*See Use in Specific Populations (10.6)*]**

Drug Interaction Studies

Clinical Studies

No clinically significant differences in bortezomib pharmacokinetics were observed when coadministered with dexamethasone (weak CYP3A4 inducer), omeprazole (strong CYP2C19 inhibitor), or melphalan in combination with prednisone.

In vitro studies indicate that bortezomib 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 bortezomib.

A drug-drug interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib (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 bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

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

A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. Therefore, the concomitant use of bortezomib 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 drug-drug 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 bortezomib based on data from 7 patients.

Strong CYP3A4 Inhibitor

Coadministration with ketoconazole (strong CYP3A4 inhibitor) increased bortezomib exposure by 35%.

Strong CYP3A4 Inducer

Coadministration with rifampin (strong CYP3A4 inducer) decreased bortezomib exposure by approximately 45%.

In Vitro Studies

Bortezomib may inhibit CYP2C19 activity and increase exposure to drugs that are substrates for this enzyme.

14 NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with bortezomib.

Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo* micronucleus assay in mice.

Fertility studies with bortezomib were not performed but evaluation of reproductive tissues has been performed in the general toxicity studies. In the six month rat toxicity study, degenerative effects in the ovary were observed at doses ≥0.3 mg/m^2 (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m^2.

14.2 Animal Toxicology and/or Pharmacology

Cardiovascular Toxicity

Studies in monkeys showed that administration of dosages approximately twice the recommended clinical dose resulted in heart rate elevations, followed by profound progressive hypotension, bradycardia, and death 12 to 14 hours postdose. Doses ≥1.2 mg/m^2 induced dose-proportional changes in cardiac parameters. Bortezomib has been shown to distribute to most tissues in the body, including the myocardium. In a repeated dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis were also observed.

Chronic Administration

In animal studies at a dose and schedule similar to that recommended for patients (twice weekly dosing for two weeks followed by one week rest), toxicities observed included severe anemia and thrombocytopenia, and gastrointestinal, neurological and lymphoid system toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord. Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were observed.

15 CLINICAL STUDIES

15.1 Multiple Myeloma

Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma

A prospective, international, randomized (1:1), open-label clinical study of 682patients was conducted to determine whether VELCADE administered intravenously (1.3 mg/m^2) in combination with melphalan (9 mg/m^2) and prednisone (60 mg/m^2) resulted in improvement in time to progression (TTP) when compared to melphalan (9 mg/m^2) and prednisone (60 mg/m^2) in patients with previously untreated multiple myeloma. Treatment was administered for a maximum of nine cycles (approximately 54 weeks) and was discontinued early for disease progression or unacceptable toxicity. Antiviral prophylaxis was recommended for patients on the VELCADE study arm.

The median age of the patients in the study was 71 years (48;91), 50% were male, 88% were Caucasian and the median Karnofsky performance status score for the patients was 80 (60;100). Patients had IgG/IgA/Light chain myeloma in 63%/25%/8% instances, a median hemoglobin of 105 g/L (64;165), and a median platelet count of 221,500/microliter (33,000;587,000).

Efficacy results for the trial are presented in *Table* 15. At a prespecified interim analysis (with median follow-up of 16.3 months), the combination of VELCADE, melphalan and prednisone therapy resulted in significantly superior results for time to progression, progression-free survival, overall survival and response rate. Further enrollment was halted, and patients receiving melphalan and prednisone were offered VELCADE in addition. A later, prespecified analysis of overall survival (with median follow-up of 36.7 months with a hazard ratio of 0.65, 95% CI: 0.51, 0.84) resulted in a statistically significant survival benefit for the VELCADE, melphalan and prednisone treatment arm despite subsequent therapies including VELCADE based regimens. In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for the VELCADE, melphalan and prednisone treatment arm was 56.4 months and for the melphalan and prednisone treatment arm was 43.1 months, with a hazard ratio of 0.695 (95% CI: 0.57, 0.85).

Table 15: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study		
Efficacy Endpoint	**VELCADE, Melphalan and Prednisone (n=344)**	**Melphalan and Prednisone (n=338)**
Time to Progression		
Events n (%)	101 (29)	152 (45)
Median* (months) (95% CI)	20.7 (17.6, 24.7)	15.0 (14.1, 17.9)
Hazard ratio† (95% CI)	0.54 (0.42, 0.70)	
p-value‡	0.000002	
Progression-Free Survival		
Events n (%)	135 (39)	190 (56)
Median* (months) (95% CI)	18.3 (16.6, 21.7)	14.0 (11.1, 15.0)
Hazard ratio† (95% CI)	0.61 (0.49, 0.76)	
p-value ‡	0.00001	
Response Rate		
CR§ n (%)	102 (30)	12 (4)
PR§ n (%)	136 (40)	103 (30)
nCR n (%)	5 (1)	0
CR + PR§ n (%)	238 (69)	115 (34)
p-value¶	$<10^{-10}$	
Overall Survival at Median Follow-Up of 36.7 Months		
Events (deaths) n (%)	109 (32)	148 (44)
Median* (months) (95% CI)	Not Reached (46.2, NR)	43.1 (34.8, NR)
Hazard ratio† (95% CI)	0.65 (0.51, 0.84)	
p-value‡	0.00084	

Note: All results are based on the analysis performed at a median follow-up duration of 16.3 months except for the overall survival analysis.

* Kaplan-Meier estimate

† Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: $beta_2$-microglobulin, albumin, and region. A hazard ratio less than one indicates an advantage for VELCADE, melphalan and prednisone

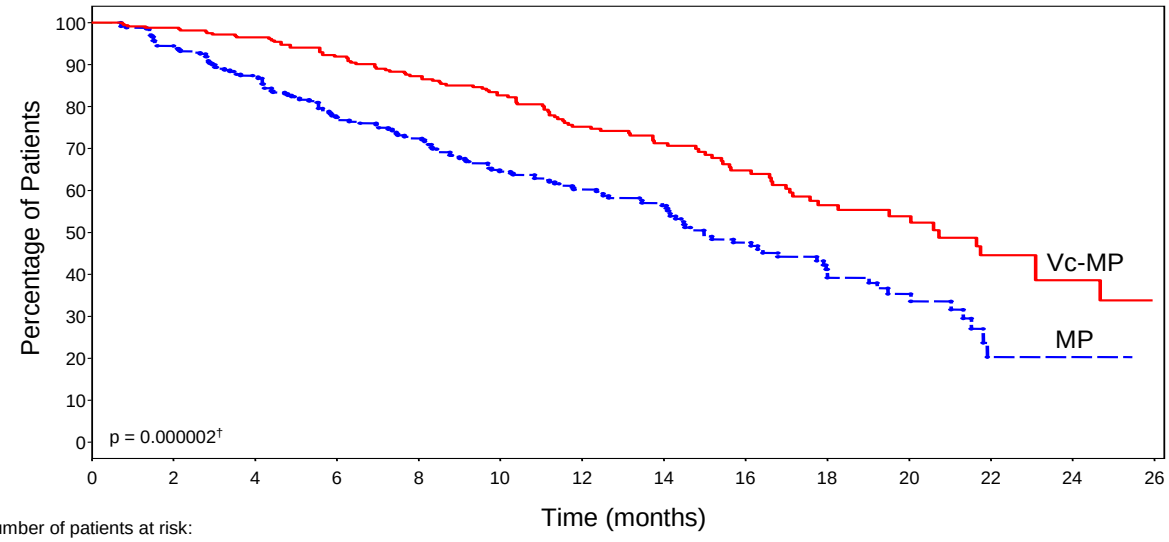
‡ p-value based on the stratified log-rank test adjusted for stratification factors: $beta_2$-microglobulin, albumin, and region

§ EBMT criteria

¶ p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors

TTP was statistically significantly longer on the VELCADE, melphalan and prednisone arm *(see Figure 1)*. (median follow-up 16.3 months)

Figure 1: Time to Progression VELCADE, Melphalan and Prednisone vs Melphalan and Prednisone



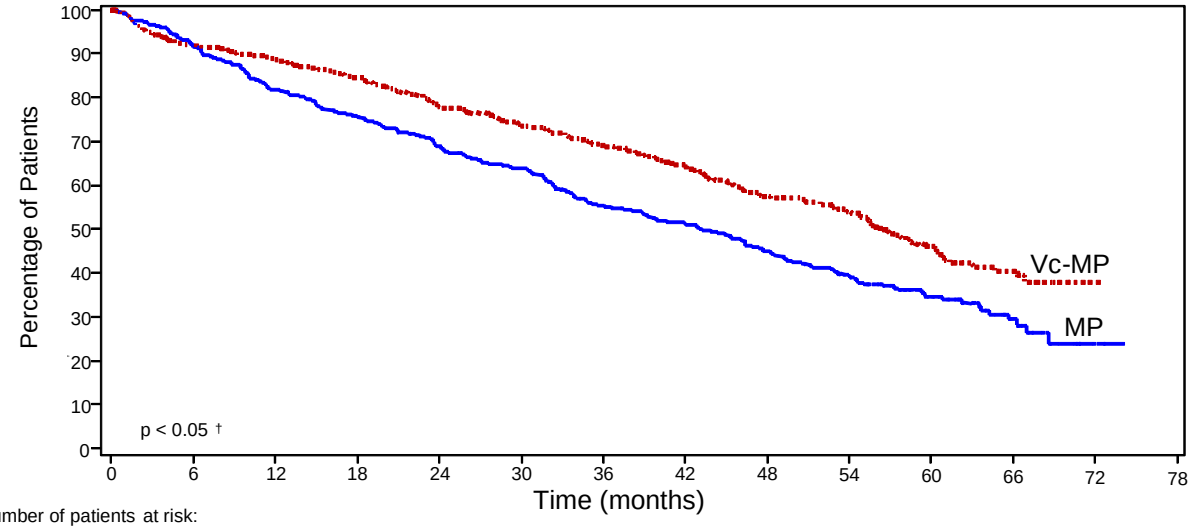
Number of patients at risk:

Vc-MP (n*)	344	309	280	258	240	200	159	114	81	53	35	20	13
MP (n*)	338	298	264	218	200	160	128	90	61	41	20	6	3

* Patients remaining after the indicated timepoint
† p-value from log-rank test

Overall survival was statistically significantly longer on the VELCADE, melphalan and prednisone arm *(see Figure 2)*. (median follow-up 60.1 months)

Figure 2: Overall Survival VELCADE, Melphalan and Prednisone vs Melphalan and Prednisone



Number of patients at risk:

Vc-MP (n*):	344	300	288	270	246	232	216	199	176	158	78	34	1	0
MP (n*):	338	301	262	240	216	196	168	153	133	112	61	24	3	0

* Patients remaining after the indicated timepoint
† p-value from log-rank test

<u>Randomized, Clinical Study in Relapsed Multiple Myeloma of VELCADE vs Dexamethasone</u>

A prospective Phase 3, international, randomized (1:1), stratified, open-label clinical study (NCT00048230) enrolling 669 patients was designed to determine whether VELCADE resulted in improvement in time to progression (TTP) compared to high-dose dexamethasone in patients with progressive multiple myeloma following 1 to 3 prior therapies. Patients considered to be refractory to prior high-dose dexamethasone were excluded as were those with baseline Grade ≥2 peripheral neuropathy or platelet counts <50,000/µL. A total of 627 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had previously received (one previous line vs more than one line of therapy), time of progression relative to prior treatment (progression during or within six months of stopping

their most recent therapy vs relapse >6 months after receiving their most recent therapy), and screening beta$_2$-microglobulin levels (≤2.5 mg/L vs >2.5 mg/L).

Baseline patient and disease characteristics are summarized in *Table* 16.

Table 16: Summary of Baseline Patient and Disease Characteristics in the Relapsed Multiple Myeloma Study

Patient Characteristics	**VELCADE (N=333)**	**Dexamethasone (N=336)**
Median age in years (range)	62.0 (33, 84)	61.0 (27, 86)
Gender: Male/female	56%/44%	60%/40%
Race: Caucasian/black/other	90%/6%/4%	88%/7%/5%
Karnofsky performance status score ≤70	13%	17%
Hemoglobin <100 g/L	32%	28%
Platelet count <75 x 10^9/L	6%	4%
Disease Characteristics		
Type of myeloma (%): IgG/IgA/Light chain	60%/23%/12%	59%/24%/13%
Median beta$_2$-microglobulin (mg/L)	3.7	3.6
Median albumin (g/L)	39.0	39.0
Creatinine clearance ≤30 mL/min [n (%)]	17 (5%)	11 (3%)
Median Duration of Multiple Myeloma Since Diagnosis (Years)	3.5	3.1
Number of Prior Therapeutic Lines of Treatment		
Median	2	2
1 prior line	40%	35%
>1 prior line	60%	65%
Previous Therapy		
Any prior steroids, e.g., dexamethasone, VAD	98%	99%
Any prior anthracyclines, e.g., VAD, mitoxantrone	77%	76%
Any prior alkylating agents, e.g., MP, VBMCP	91%	92%
Any prior thalidomide therapy	48%	50%
Vinca alkaloids	74%	72%
Prior stem cell transplant/other high-dose therapy	67%	68%
Prior experimental or other types of therapy	3%	2%

Patients in the VELCADE treatment group were to receive 8, three week treatment cycles followed by 3, five week treatment cycles of VELCADE. Patients achieving a CR were treated for four cycles beyond first evidence of CR. Within each three week treatment cycle, VELCADE 1.3 mg/m^2/dose alone was administered by intravenous bolus twice weekly for two weeks on Days 1, 4, 8, and 11 followed by a ten day rest period (Days 12 to 21). Within each five week treatment cycle, VELCADE 1.3 mg/m^2/dose alone was administered by intravenous bolus once weekly for four weeks on Days 1, 8, 15, and 22 followed by a 13 day rest period (Days 23 to 35) *[see Dosage and Administration (4.4)]*.

Patients in the dexamethasone treatment group were to receive 4, five week treatment cycles followed by 5, four week treatment cycles. Within each five week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 followed by a 15 day rest period (Days 21 to 35). Within each four week treatment cycle, dexamethasone 40 mg/day PO was administered once daily on Days 1 to 4 followed by a 24 day rest period (Days 5 to 28). Patients with documented progressive disease on dexamethasone were offered VELCADE at a standard dose and schedule on a companion study. Following a preplanned interim analysis of time to progression, the dexamethasone arm was halted and all patients randomized to dexamethasone were offered VELCADE, regardless of disease status.

In the VELCADE arm, 34% of patients received at least one VELCADE dose in all eight of the three week cycles of therapy, and 13% received at least one dose in all 11 cycles. The average number of VELCADE doses during the study was 22, with a range of 1 to 44. In the dexamethasone arm, 40% of patients received at least one dose in all four of the five week treatment cycles of therapy, and 6% received at least one dose in all nine cycles.

The time to event analyses and response rates from the relapsed multiple myeloma study are presented in *Table* **17**. Response and progression were assessed using the European Group for Blood and Marrow Transplantation (EBMT) criteria. Complete response (CR) required <5% plasma cells in the marrow, 100% reduction in M-protein, and a negative immunofixation test (IF^-). Partial response (PR) requires ≥50% reduction in serum myeloma protein and ≥90% reduction of urine myeloma protein on at least two occasions for a minimum of at least six weeks along with stable bone disease and normal calcium. Near complete response (nCR) was defined as meeting all the criteria for complete response including 100% reduction in M-protein by protein electrophoresis; however, M-protein was still detectable by immunofixation (IF^+).

Table 17: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study						
Efficacy Endpoint	**All Patients**		**1 Prior Line of Therapy**		**>1 Prior Line of Therapy**	
	VELCADE	**Dex**	**VELCADE**	**Dex**	**VELCADE**	**Dex**
	(n=333)	**(n=336)**	**(n=132)**	**(n=119)**	**(n=200)**	**(n=217)**
Time to Progression Events n (%)	147 (44)	196 (58)	55 (42)	64 (54)	92 (46)	132 (61)
Median* (95% CI)	6.2 mo (4.9, 6.9)	3.5 mo (2.9, 4.2)	7.0 mo (6.2, 8.8)	5.6 mo (3.4, 6.3)	4.9 mo (4.2, 6.3)	2.9 mo (2.8, 3.5)
Hazard ratio† (95% CI)	0.55 (0.44, 0.69)		0.55 (0.38, 0.81)		0.54 (0.41, 0.72)	
p-value‡	<0.0001		0.0019		<0.0001	
Overall Survival Events (deaths) n (%)	51 (15)	84 (25)	12 (9)	24 (20)	39 (20)	60 (28)
Hazard ratio† (95% CI)	0.57 (0.40, 0.81)		0.39 (0.19, 0.81)		0.65 (0.43, 0.97)	
p-value‡, §	<0.05		<0.05		<0.05	
Response Rate Population¶ n=627	n=315	n=312	n=128	n=110	n=187	n=202
CR# n (%)	20 (6)	2 (<1)	8 (6)	2 (2)	12 (6)	0 (0)
PR# n(%)	101 (32)	54 (17)	49 (38)	27 (25)	52 (28)	27 (13)
nCR#, ♠ n(%)	21 (7)	3 (<1)	8 (6)	2 (2)	13 (7)	1 (<1)
CR + PR# n (%)	121 (38)	56 (18)	57 (45)	29 (26)	64 (34)	27 (13)
p-value ♥	<0.0001		0.0035		<0.0001	

* Kaplan-Meier estimate

† Hazard ratio is based on Cox proportional-hazard model with the treatment as single independent variable. A hazard ratio less than one indicates an advantage for VELCADE

‡ p-value based on the stratified log-rank test including randomization stratification factors

§ Precise p-value cannot be rendered

¶ Response population includes patients who had measurable disease at baseline and received at least one dose of study drug

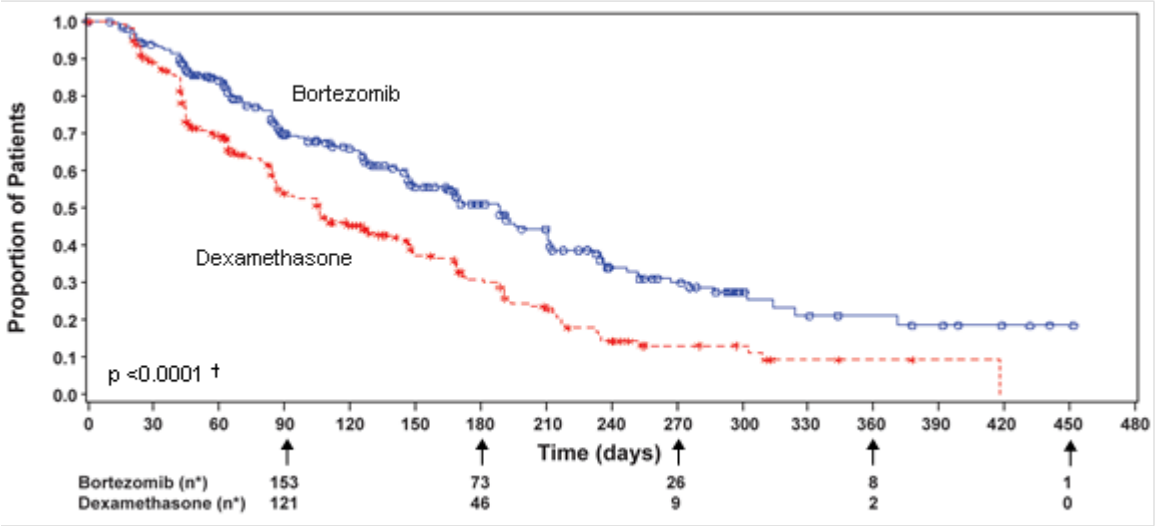
EBMT criteria; nCR meets all EBMT criteria for CR but has positive IF. Under EBMT criteria nCR is in the PR category

♠ In two patients, the IF was unknown

♥ p-value for Response Rate (CR + PR) from the Cochran-Mantel-Haenszel chi-square test adjusted for the stratification factors

TTP was statistically significantly longer on the VELCADE arm *(see Figure 3)*.

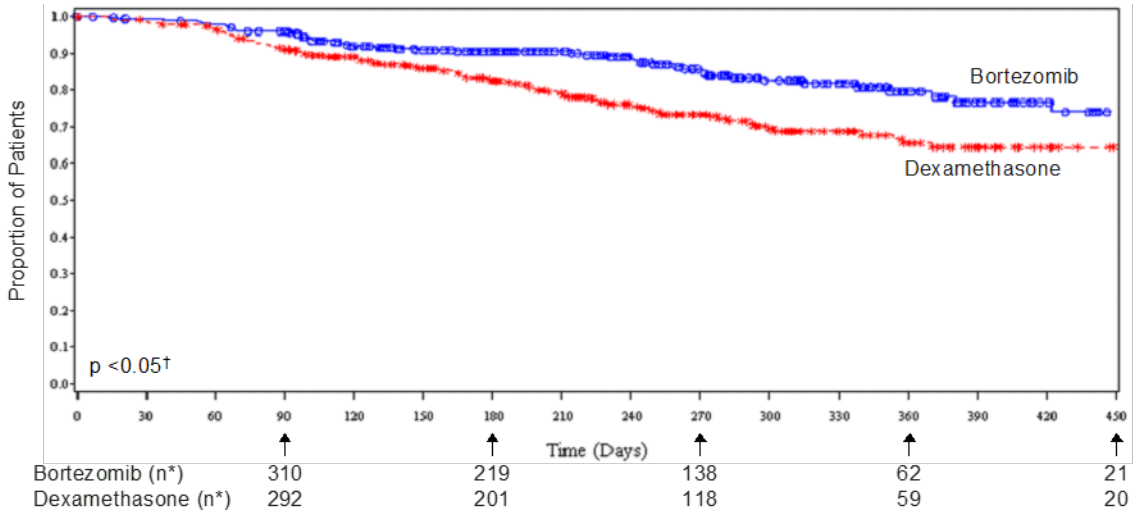
Figure 3: Time to Progression Bortezomib vs Dexamethasone (Relapsed Multiple Myeloma Study)



* Patients remaining after the indicated timepoint
† p-value from log-rank test

As shown in *Figure 4*, VELCADE had a significant survival advantage relative to dexamethasone (p <0.05). The median follow-up was 8.3 months.

Figure 4: Overall Survival Bortezomib vs Dexamethasone (Relapsed Multiple Myeloma Study)



* Patients remaining after the indicated timepoint
† p-value from log-rank test

For the 121 patients achieving a response (CR or PR) on the VELCADE arm, the median duration was 8.0 months (95% CI: 6.9, 11.5 months) compared to 5.6 months (95% CI: 4.8, 9.2 months) for the 56 responders on the dexamethasone arm. The response rate was significantly higher on the VELCADE arm regardless of beta$_2$-microglobulin levels at baseline.

Randomized, Open-Label Clinical Study of VELCADE Subcutaneous vs Intravenous in Relapsed Multiple Myeloma

An open-label, randomized, Phase 3 noninferiority study (NCT00722566) compared the efficacy and safety of the subcutaneous administration of VELCADE vs the intravenous administration. This study included 222 bortezomib naïve patients with relapsed multiple myeloma, who were randomized in a 2:1 ratio to receive 1.3 mg/m^2 of VELCADE by either the subcutaneous (n=148) or intravenous (n=74) route for eight cycles. Patients who did not obtain an optimal response (less than Complete Response (CR)) to therapy with VELCADE alone after four cycles were allowed to receive oral dexamethasone 20 mg daily on the day of and after

VELCADE administration (82 patients in subcutaneous treatment group and 39 patients in the intravenous treatment group). Patients with baseline Grade ≥2 peripheral neuropathy or neuropathic pain, or platelet counts <50,000/µL were excluded. A total of 218 patients were evaluable for response.

Stratification factors were based on the number of lines of prior therapy the patient had received (one previous line vs more than one line of therapy), and international staging system (ISS) stage (incorporating beta$_2$-microglobulin and albumin levels; Stages I, II, or III).

The baseline demographic and other characteristics of the two treatment groups are summarized as follows: the median age of the patient population was approximately 64 years of age (range: 38 to 88 years), primarily male (subcutaneous: 50%, intravenous: 64%); the primary type of myeloma is IgG (subcutaneous: 65% IgG, 26% IgA, 8% light chain; intravenous: 72% IgG, 19% IgA, 8% light chain), ISS staging I/II/III (%) was 27, 41, 32 for both subcutaneous and intravenous, Karnofsky performance status score was ≤70% in 22% of subcutaneous and 16% of intravenous, creatinine clearance was 67.5 mL/min in subcutaneous and 73 mL/min in intravenous, the median years from diagnosis was 2.68 and 2.93 in subcutaneous and intravenous respectively and the proportion of patients with more than one prior line of therapy was 38% in subcutaneous and 35% in intravenous.

This study met its primary (noninferiority) objective that single agent subcutaneous VELCADE retains at least 60% of the overall response rate after four cycles relative to single agent intravenous VELCADE. The results are provided in *Table* 18.

Table 18: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous vs Intravenous

	Subcutaneous VELCADE	**Intravenous VELCADE**
Intent to Treat Population	**(n=148)**	**(n=74)**
Primary Endpoint		
Response Rate at 4 Cycles		
ORR (CR + PR) n(%)	63 (43)	31 (42)
Ratio of Response Rates (95% CI)	1.01 (0.73, 1.40)	
CR n (%)	11 (7)	6 (8)
PR n (%)	52 (35)	25 (34)
nCR n (%)	9 (6)	4 (5)
Secondary Endpoints		
Response Rate at 8 Cycles		
ORR (CR + PR)	78 (53)	38 (51)
CR n (%)	17 (11)	9 (12)
PR n (%)	61 (41)	29 (39)
nCR n (%)	14 (9)	7 (9)
Median Time to Progression, months	10.4	9.4
Median Progression-Free Survival, months	10.2	8.0
1 Year Overall Survival (%)*	72.6	76.7

* Median duration of follow-up is 11.8 months

A Randomized, Phase 2 Dose-Response Study in Relapsed Multiple Myeloma

An open-label, multicenter study randomized 54 patients with multiple myeloma who had progressed or relapsed on or after front-line therapy to receive VELCADE 1 mg/m^2 or 1.3 mg/m^2 intravenous bolus twice weekly for two weeks on Days 1, 4, 8, and 11 followed by a ten day rest period (Days 12 to 21). The median duration of time between diagnosis of multiple myeloma and first dose of VELCADE on this trial was two years, and patients had received a median of one prior line of treatment (median of three prior therapies). A single complete response was seen at each dose. The overall response rates (CR + PR) were 30% (8/27) at 1 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

A Phase 2 Open-Label Extension Study in Relapsed Multiple Myeloma

Patients from the two Phase 2 studies, who in the investigators' opinion would experience additional clinical benefit, continued to receive VELCADE beyond 8 cycles on an extension study. Sixty-three (63) patients from the Phase 2 multiple myeloma studies were enrolled and received a median of seven additional cycles of VELCADE therapy for a total median of 14 cycles (range: 7 to 32). The overall median dosing intensity was the same in both the parent protocol and extension study. Sixty-seven percent (67%) of patients initiated the extension study at the same or higher dose intensity at which they completed the parent protocol, and 89% of patients maintained the standard three week dosing schedule during the extension study. No new cumulative or new long-term toxicities were observed with prolonged VELCADE treatment *[see Adverse Reactions (8.1)]*.

A Single-Arm Trial of Retreatment in Relapsed Multiple Myeloma

A single-arm, open-label trial (NCT00431769) was conducted to determine the efficacy and safety of retreatment with VELCADE. One hundred and thirty patients (≥18 years of age) with multiple myeloma who previously had at least partial response on a VELCADE-containing regimen (median of two prior lines of therapy [range: 1 to 7]) were retreated upon progression with VELCADE administered intravenously. Patients were excluded from trial participation if they had peripheral neuropathy or neuropathic pain of Grade ≥2. At least six months after prior VELCADE therapy, VELCADE was restarted at the last tolerated dose of 1.3 mg/m^2 (n=93) or ≤1 mg/m^2 (n=37) and given on Days 1, 4, 8 and 11 every three weeks for maximum of eight cycles either as single agent or in combination with dexamethasone in accordance with the standard of care. Dexamethasone was administered in combination with VELCADE to 83 patients in Cycle 1 with an additional 11 patients receiving dexamethasone during the course of VELCADE retreatment cycles.

The primary endpoint was best confirmed response to retreatment as assessed by European Group for Blood and Marrow Transplantation (EBMT) criteria. Fifty of the 130 patients achieved a best confirmed response of Partial Response or better for an overall response rate of 38.5% (95% CI: 30.1, 47.4). One patient achieved a Complete Response and 49 achieved Partial Response. In the 50 responding patients, the median duration of response was 6.5 months and the range was 0.6 to 19.3 months.

15.2 Mantle Cell Lymphoma

A Randomized, Open-Label Clinical Study in Patients with Previously Untreated Mantle Cell Lymphoma

A randomized, open-label, Phase 3 study (NCT00722137) was conducted in 487 adult patients with previously untreated mantle cell lymphoma (Stage II, III or IV) who were ineligible or not considered for bone marrow transplantation to determine whether VELCADE administered in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP) resulted in improvement in progression-free survival (PFS) when compared to the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). This clinical study utilized independent pathology confirmation and independent radiologic response assessment.

Patients in the VcR-CAP treatment arm received VELCADE (1.3 mg/m^2) administered intravenously on Days 1, 4, 8, and 11 (rest period Days 12 to 21); rituximab (375 mg/m^2) on Day 1; cyclophosphamide (750 mg/m^2) on Day 1; doxorubicin (50 mg/m^2) on Day 1; and prednisone (100 mg/m^2) on Day 1 through Day 5 of the 21 day treatment cycle. For patients with a response first documented at Cycle 6, two additional treatment cycles were allowed.

Median patient age was 66 years, 74% were male, 66% were Caucasian and 32% were Asian. Sixty-nine percent of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for MCL, 54% of patients had an International Prognostic Index (IPI) score of three (high-intermediate) or higher and 76% had Stage IV disease.

The majority of the patients in both groups received six or more cycles of treatment, 84% in the VcR-CAP group and 83% in the R-CHOP group. Median number of cycles received by patients in both treatment arms was six with 17% of patients in the R-CHOP group and 14% of subjects in the VcR-CAP group receiving up to two additional cycles.

The efficacy results for PFS, CR and ORR with a median follow-up of 40 months are presented in *Table* 19. The response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC). Final overall survival results at a median follow-up of 78.5 months are also presented in *Table* 19 and *Figure 6*. The combination of VcR-CAP resulted in statistically significant prolongation of PFS compared with R-CHOP *(see Table 18, Figure 5)*.

Table 19: Summary of Efficacy Analyses in the Previously Untreated Mantle Cell Lymphoma Study		
Efficacy Endpoint **n: Intent to Treat patients**	**VcR-CAP** **(n=243)**	**R-CHOP** **(n=244)**
Progression-Free Survival (by independent radiographic assessment)		
Events n (%)	133 (55)	165 (68)
Median* (months) (95% CI)	25 (20, 32)	14 (12, 17)
Hazard ratio[†] (95% CI)	0.63 (0.50, 0.79)	
p-value[‡]	<0.001	
Complete Response Rate (CR)[§]		
n (%) (95% CI)	108 (44) (38, 51)	82 (34) (28, 40)
Overall Response Rate (CR + Cru + PR)[¶]		
n (%)	214 (88)	208 (85)
(95% CI)	(83, 92)	(80, 89)
Overall Survival		
Events n (%)	103 (42)	138 (57)
Median* (months) (95% CI)	91 (71, NE)	56 (47, 69)
Hazard Ratio[†] (95% CI)	0.66 (0.51, 0.85)	

Note: All results are based on the analysis performed at a median follow-up duration of 40 months except for the overall survival analysis, which was performed at a median follow-up of 78.5 months.

CI = Confidence Interval; IPI = International Prognostic Index; LDH = Lactate dehydrogenase

* Based on Kaplan-Meier product limit estimates.

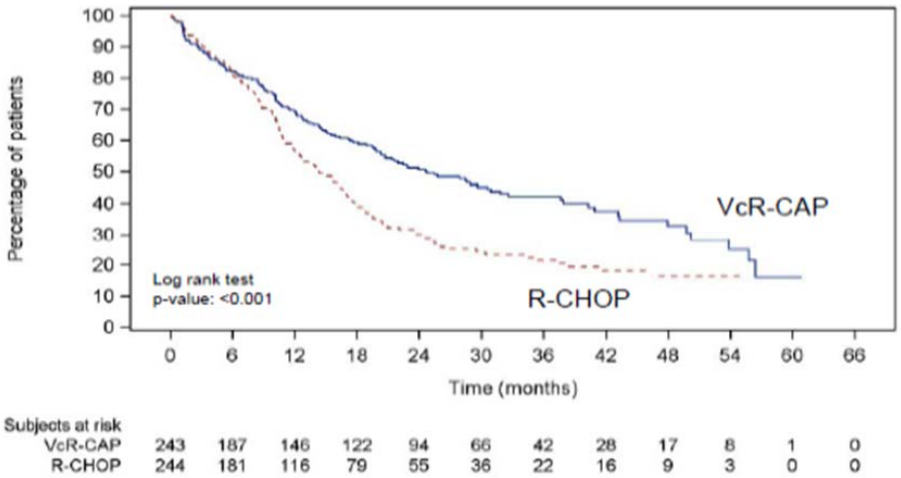
[†] Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio <1 indicates an advantage for VcR-CAP.

[‡] Based on Log rank test stratified with IPI risk and stage of disease.

[§] Includes CR by independent radiographic assessment, bone marrow, and LDH using ITT population.

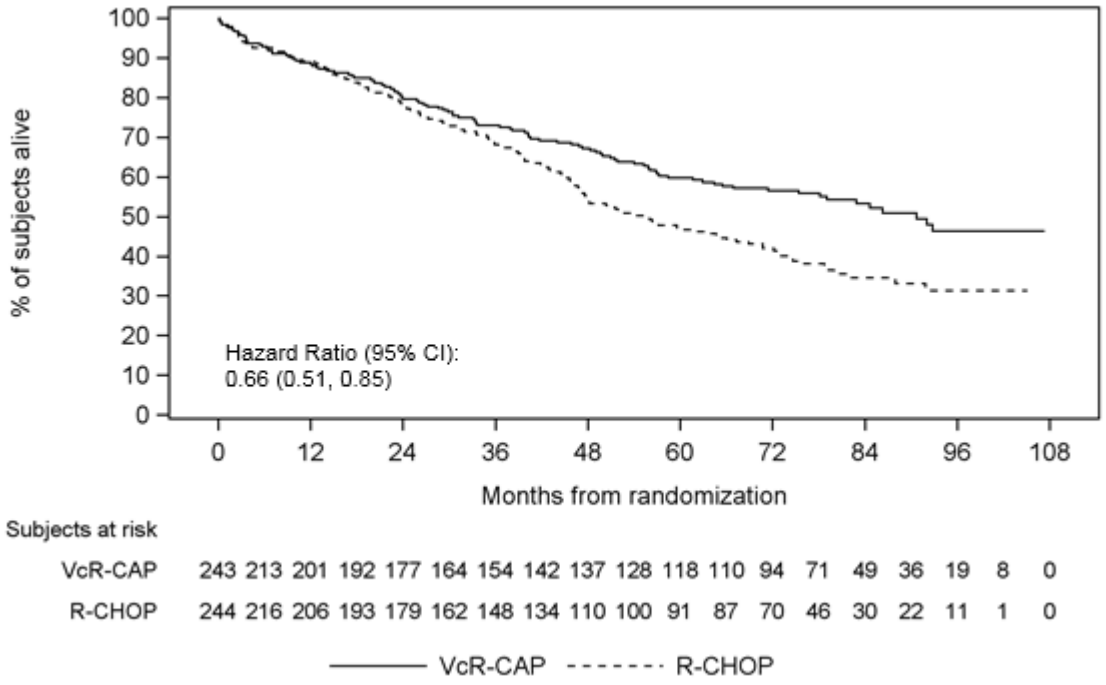
[¶] Includes CR + Cru + PR by independent radiographic assessment, regardless of the verification by bone marrow and LDH, using ITT population.

Figure 5: Progression-Free Survival VcR-CAP vs R-CHOP (previously Untreated Mantle Cell Lymphoma Study)



Key: R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP = VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Figure 6: Overall Survival VcR-CAP vs R-CHOP (previously Untreated Mantle Cell Lymphoma Study)



Key: R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone;
VcR-CAP = VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone.

A Phase 2 Single-Arm Clinical Study in Relapsed Mantle Cell Lymphoma after Prior Therapy

The safety and efficacy of VELCADE in relapsed or refractory mantle cell lymphoma were evaluated in an open-label, single-arm, multicenter study (NCT00063713) of 155 patients with progressive disease who had received at least one prior therapy. The median age of the patients was 65 years (42, 89), 81% were male, and 92% were Caucasian. Of the total, 75% had one or more extra-nodal sites of disease, and 77% were Stage 4. In 91% of the patients, prior therapy included all of the following: an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. A total of thirty-seven percent (37%) of patients were refractory to their last prior therapy. An intravenous bolus injection of VELCADE 1.3 mg/m^2/dose was administered twice weekly for two weeks on Days 1, 4, 8, and 11 followed by a ten day rest period (Days 12 to 21) for a maximum of 17 treatment cycles. Patients achieving a CR or CRu were treated for four cycles beyond first evidence of CR or CRu. The study employed dose modifications for toxicity *[see Dosage and Administration (4.3, 4.4)]*.
Responses to VELCADE are shown in *Table* 20. Response rates to VELCADE were determined according to the International Workshop Response Criteria (IWRC) based on independent radiologic review of CT scans. The median number of cycles administered across all patients was four; in responding patients the median number of cycles was eight. The median time to response was 40 days (range: 31 to 204 days). The median duration of follow-up was more than 13 months.

Table 20: Response Outcomes in a Phase 2 Relapsed Mantle Cell Lymphoma Study		
Response Analyses (N=155)	**N (%)**	**95% CI**
Overall Response Rate (IWRC) (CR + CRu + PR)	48 (31)	(24, 39)
Complete Response (CR + CRu)	12 (8)	(4, 13)
CR	10 (6)	(3, 12)
CRu	2 (1)	(0, 5)
Partial Response (PR)	36 (23)	(17, 31)
Duration of Response	**Median**	**95% CI**

CR + CRu + PR (N=48)	9.3 months	(5.4, 13.8)
CR + CRu (N=12)	15.4 months	(13.4, 15.4)
PR (N=36)	6.1 months	(4.2, 9.3)

Clinical efficacy in previously untreated mantle cell lymphoma (MCL)

Study LYM-3002 was a Phase III, randomised, open-label study comparing the efficacy and safety of the combination of VELCADE, rituximab, cyclophosphamide, doxorubicin, and prednisone (VcR-CAP; n=243) to that of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP; n=244) in adult patients with previously untreated MCL (Stage II, III or IV). Patients in the VcR-CAP treatment arm received VELCADE (1.3 mg/m^2; on days 1, 4, 8, 11, rest period days 12-21), rituximab 375 mg/m^2 IV on day 1; cyclophosphamide 750 mg/m^2 IV on day 1; doxorubicin 50 mg/m^2 IV on day 1; and prednisone 100 mg/m^2 orally on day 1 through day 5 of the 21 day VELCADE treatment cycle. For patients with a response first documented at cycle 6, two additional treatment cycles were given.

The primary efficacy endpoint was progression-free survival based on Independent Review Committee (IRC) assessment. Secondary endpoints included, time to progression (TTP), time to next anti-lymphoma treatment (TNT), duration of treatment free interval (TFI), overall response rate (ORR) and complete response (CR/CRu) rate, overall survival (OS) and response duration.

The demographic and baseline disease characteristics were generally well balanced between the two treatment arms: median patient age was 66 years, 74% were male, 66% were Caucasian and 32% Asian, 69% of patients had a positive bone marrow aspirate and/or a positive bone marrow biopsy for MCL, 54% of patients had an International Prognostic Index (IPI) score of ≥ 3, and 76% had Stage IV disease. Treatment duration (median=17 weeks) and duration of follow-up (median=40 months) were comparable in both treatment arms. A median of 6 cycles was received by patients in both treatment arms with 14% of subjects in the VcR-CAP group and 17% of patients in the R-CHOP group receiving 2 additional cycles. The majority of the patients in both groups completed treatment, 80% in the VcR-CAP group and 82% in the R-CHOP group. Efficacy results are presented in Table 21:

Table 21: Efficacy results from study LYM-3002

Efficacy endpoint	**VcR-CAP**	**R-CHOP**	
n: ITT patients	**243**	**244**	
Progression free survival (IRC)[a]			
Events n (%)	**133 (54.7%)**	**165 (67.6%)**	**HR[b] (95% CI)=0.63 (0.50; 0.79)** **p-value[d] < 0.001**
Median[c](95% CI) (months)	**24.7 (19.8; 31.8)**	**14.4 (12; 16.9)**	
Response rate			
n: response-evaluable patients	**229**	**228**	
Overall complete response (CR+CRu)[f] n(%)	**122 (53.3%)**	**95 (41.7%)**	**OR[e] (95% CI)=1.688 (1.148; 2.481)** **p-value[g]=0.007**
Overall response (CR+CRu+PR)[h] n(%)	**211 (92.1%)**	**204 (89.5%)**	**OR[e] (95% CI)=1.428 (0.749; 2.722)** **p-value[g]=0.275**

[a] Based on Independent Review Committee (IRC) assessment (radiological data only).

[b] Hazard ratio estimate is based on a Cox's model stratified by IPI risk and stage of disease. A hazard ratio < 1 indicates an advantage for VcR-CAP.

[c] Based on Kaplan-Meier product limit estimates.

[d] Based on Log rank test stratified with IPI risk and stage of disease.

[e] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used, with IPI risk and stage of disease as stratification factors. An odds ratio (OR) > 1 indicates an advantage for VcR-CAP.

[f] Include all CR+CRu, by IRC, bone marrow and LDH.

[g] P-value from the Cochran Mantel-Haenszel chi-square test, with IPI and stage of disease as stratification factors.

[h] Include all radiological CR+CRu+PR by IRC regardless the verification by bone marrow and LDH.

CR=Complete Response; CRu=Complete Response unconfirmed; PR=Partial Response; CI=Confidence Interval, HR=Hazard Ratio; OR=Odds Ratio; ITT=Intent to Treat

Median PFS by investigator assessment was 30.7 months in the VcR-CAP group and 16.1 months in the R-CHOP group (Hazard Ratio [HR]=0.51; p < 0.001). A statistically significant benefit (p < 0.001) in favour of the VcR-CAP treatment group over the R-CHOP group was observed for TTP (median 30.5 versus 16.1 months), TNT (median 44.5 versus 24.8 months) and TFI (median 40.6 versus 20.5 months). The median duration of complete response was 42.1 months in the VcR-CAP group compared with 18 months in the R-CHOP group. The duration of overall response was 21.4 months longer in the VcR-CAP group (median 36.5 months versus 15.1 months in the R-CHOP group). The final analysis for OS was performed after a median follow-up of 82 months. Median OS was 90.7 months for the VcR-CAP group compared with 55.7 months for the R-CHOP group (HR=0.66; p=0.001). The observed final median difference in the OS between the 2 treatment groups was 35 months.

16 HOW SUPPLIED/STORAGE AND HANDLING

VELCADE® (bortezomib) for Injection is supplied as individually cartoned 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.

Velcade 3.5 mg is available in cartons containing 1 single-use vial

There have been fatal cases of inadvertent intrathecal administration of VELCADE. VELCADE is authorized for IV or subcutaneous use only.

DO NOT ADMINISTER VELCADE INTRATHECALLY

Unopened vials: Do not store above 30°C. Keep container in the outer carton.

Shelf-life of unopened vials: the expiry date is indicated on the printing materials.

Consider handling and disposal of VELCADE according to guidelines issued for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact.

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. The total storage time for the reconstituted medicinal product should not exceed 8 hours prior to administration.

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