

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VELCADE safely and effectively. See full prescribing information for VELCADE.

VELCADE® (bortezomib) for injection, for subcutaneous or intravenous use

Initial U.S. Approval: 2003

-----RECENT MAJOR CHANGES-----

Warnings and Precautions (5.10)

6/2017

-----INDICATIONS AND USAGE-----

VELCADE is a proteasome inhibitor indicated for:

- treatment of patients with multiple myeloma (1.1)
- treatment of patients with mantle cell lymphoma (1.2)

-----DOSAGE AND ADMINISTRATION-----

- For subcutaneous or intravenous use only. Each route of administration has a different reconstituted concentration; Exercise caution when calculating the volume to be administered. (2.1, 2.10)
- The recommended starting dose of VELCADE is 1.3 mg/m² administered either as a 3 to 5 second bolus intravenous injection or subcutaneous injection. (2.2, 2.4, 2.6)
- Retreatment for multiple myeloma: May retreat starting at the last tolerated dose. (2.6)
- Hepatic Impairment: Use a lower starting dose for patients with moderate or severe hepatic impairment. (2.8)
- Dose must be individualized to prevent overdose (2.10)

-----DOSAGE FORMS AND STRENGTHS-----

- For injection: Single-use vial contains 3.5 mg of bortezomib as lyophilized powder for reconstitution and withdrawal of the appropriate individual patient dose. (3)

-----CONTRAINDICATIONS-----

- Patients with hypersensitivity (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. (4)
- Contraindicated for intrathecal administration. (4)

-----WARNINGS AND PRECAUTIONS-----

- Peripheral Neuropathy: Manage with dose modification or discontinuation. (2.7) Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment. (2.7, 5.1)

- Hypotension: Use caution when treating patients taking anti-hypertensives, with a history of syncope, or with dehydration. (5.2)
- Cardiac Toxicity: Worsening of and development of cardiac failure has occurred. Closely monitor patients with existing heart disease or risk factors for heart disease. (5.3)
- Pulmonary Toxicity: Acute respiratory syndromes have occurred. Monitor closely for new or worsening symptoms. (5.4)
- Posterior Reversible Encephalopathy Syndrome: Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected. (5.5)
- Gastrointestinal Toxicity: Nausea, diarrhea, constipation, and vomiting may require use of antiemetic and antidiarrheal medications or fluid replacement. (5.6)
- Thrombocytopenia or Neutropenia: Monitor complete blood counts regularly throughout treatment. (5.7)
- Tumor Lysis Syndrome: Closely monitor patients with high tumor burden (5.8)
- Hepatic Toxicity: Monitor hepatic enzymes during treatment. (5.9)
- Embryo-fetal Toxicity: VELCADE can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to avoid pregnancy. (5.10)

-----ADVERSE REACTIONS-----

Most commonly reported adverse reactions (incidence \geq 20%) in clinical studies include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Millennium Pharmaceuticals at 1-866 VELCADE or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Co-administration with strong CYP3A4 inhibitors can increase VELCADE exposure. Closely monitor patients receiving VELCADE in combination with strong CYP3A4 inhibitors. (7.1)
- Co-administration with strong CYP3A4 inducers can decrease VELCADE exposure. Avoid concomitant use of strong CYP3A4 inducers. (7.3)

-----USE IN SPECIFIC POPULATIONS-----

- Patients with diabetes may require close monitoring of blood glucose and adjustment of anti-diabetic medication. (8.8)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 6/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

VELCADE® (bortezomib) is indicated for the treatment of patients with multiple myeloma.

1.2 Mantle Cell Lymphoma

VELCADE is indicated for the treatment of patients with mantle cell lymphoma.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Guidelines

VELCADE is for intravenous or subcutaneous use only. VELCADE should not be administered by any other route.

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/m². VELCADE may be administered intravenously at a concentration of 1 mg/mL, or subcutaneously at a concentration of 2.5 mg/mL [see *Dosage and Administration (2.10)*].

VELCADE retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with VELCADE and who have relapsed at least 6 months after completing prior VELCADE treatment. Treatment may be started at the last tolerated dose [see *Dosage and Administration (2.6)*].

When administered intravenously, VELCADE is administered as a 3 to 5 second bolus intravenous injection.

2.2 Dosage in Previously Untreated Multiple Myeloma

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

2.3 Dose Modification Guidelines for VELCADE When Given in Combination with Melphalan and Prednisone

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

- Platelet count should be at least $70 \times 10^9/L$ and the absolute neutrophil count (ANC) should be at least $1.0 \times 10^9/L$
- Non-hematological 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 $30 \times 10^9/L$ or ANC is not above $0.75 \times 10^9/L$ 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 1 dose level (from 1.3 mg/m^2 to 1 mg/m^2 , or from 1 mg/m^2 to 0.7 mg/m^2) |
| Grade 3 or higher non-hematological 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 (2.7)*].

2.4 Dosage in Previously Untreated Mantle Cell Lymphoma

VELCADE (1.3 mg/m^2) is administered intravenously in combination with intravenous rituximab, cyclophosphamide, doxorubicin and oral prednisone (VcR-CAP) for six 3-week treatment cycles as shown in Table 3. VELCADE is administered first followed by rituximab. VELCADE is administered twice weekly for two weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period on Days 12-21. For patients with a response first documented at cycle 6, two additional VcR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of VELCADE.

Table 3: Dosage Regimen for Patients with Previously Untreated Mantle Cell Lymphoma

| Twice Weekly VELCADE (Six 3-Week Cycles) ^a | | | | | | | | |
|--|----------|----------|----------|----------|----------|----------|-----------|----------------|
| Week | 1 | | | | 2 | | 3 | |
| VELCADE (1.3 mg/m ²) | Day 1 | -- | -- | Day 4 | -- | Day 8 | Day 11 | rest period |
| Rituximab (375 mg/m ²) Cyclophosphamide (750 mg/m ²) Doxorubicin (50 mg/m ²) | Day 1 | -- | -- | | | -- | -- | rest period |
| Prednisone (100 mg/m ²) | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | -- | -- | rest period |

^a Dosing may continue for 2 more cycles (for a total of 8 cycles) if response is first seen at cycle 6.

2.5 Dose Modification Guidelines for VELCADE When Given in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone

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

- Platelet count should be at least $100 \times 10^9/L$ and absolute neutrophil count (ANC) should be at least $1.5 \times 10^9/L$
- Hemoglobin should be at least 8 g/dL (at least 4.96 mmol/L)
- Non-hematologic toxicity should have recovered to Grade 1 or baseline

Interrupt VELCADE treatment at the onset of any Grade 3 hematologic or non-hematological toxicities, excluding neuropathy [see Table 5 and Warnings and Precautions (5)]. For dose adjustments, see Table 4 below.

Table 4: Dose Modifications on Days 4, 8, and 11 during Cycles of Combination VELCADE, Rituximab, Cyclophosphamide, Doxorubicin and Prednisone Therapy

| Toxicity | Dose modification or delay |
|--|---|
| Hematological toxicity | |
| <ul style="list-style-type: none"> • Grade 3 or higher neutropenia, or a platelet count not at or above $25 \times 10^9/L$ | <p>Withhold VELCADE therapy for up to 2 weeks until the patient has an ANC at or above $0.75 \times 10^9/L$ and a platelet count at or above $25 \times 10^9/L$.</p> <ul style="list-style-type: none"> • If, after VELCADE has been withheld, the toxicity does not resolve, discontinue VELCADE. • If toxicity resolves such that the patient has an ANC at or above $0.75 \times 10^9/L$ and a platelet count at or above $25 \times 10^9/L$, VELCADE dose should be reduced by 1 dose level (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²) |
| Grade 3 or higher non-hematological toxicities | <p>Withhold VELCADE therapy until symptoms of the toxicity have resolved to Grade 2 or better. Then, VELCADE may be reinitiated with one dose level reduction (from 1.3 mg/m² to 1 mg/m², or from 1 mg/m² to 0.7 mg/m²).</p> <p>For VELCADE-related neuropathic pain and/or peripheral neuropathy, hold or modify VELCADE as outlined in Table 5.</p> |

For information concerning rituximab, cyclophosphamide, doxorubicin and prednisone, see manufacturer's prescribing information.

2.6 Dosage and Dose Modifications for Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

VELCADE (1.3 mg/m²/dose) is administered twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21). For extended therapy of more than 8 cycles, VELCADE may be administered on the standard schedule or, for relapsed multiple myeloma, on a maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35) [see *Clinical Studies (14)*]. At least 72 hours should elapse between consecutive doses of VELCADE.

Patients with multiple myeloma who have previously responded to treatment with VELCADE (either alone or in combination) and who have relapsed at least 6 months after their prior VELCADE therapy may be started on VELCADE at the last tolerated dose. Retreated patients are administered VELCADE twice weekly (Days 1, 4, 8, and 11) every three weeks for a maximum of 8 cycles. At least 72 hours should elapse between consecutive doses of VELCADE. VELCADE may be administered either as a single agent or in combination with dexamethasone [see *Clinical Studies (14.1)*].

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 (5)*]. Once the symptoms of the toxicity have resolved, VELCADE therapy may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1 mg/m²/dose; 1 mg/m²/dose reduced to 0.7 mg/m²/dose).

For dose modifications guidelines for peripheral neuropathy see section 2.7.

2.7 Dose Modifications for 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 5.

Table 5: 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 |
| 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 Terminology Criteria CTCAE v4.0

**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

2.8 Dosage in Patients with Hepatic Impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended VELCADE dose. Patients with moderate or severe hepatic impairment should be started on VELCADE at a reduced dose of 0.7 mg/m² per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² may be considered based on patient tolerance (see Table 6) [see *Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].

Table 6: Recommended Starting Dose Modification for VELCADE in Patients with Hepatic Impairment

| | Bilirubin Level | SGOT (AST) Levels | Modification of Starting Dose |
|----------|--------------------------------|--------------------------|--|
| Mild | Less than or equal to 1.0x ULN | More than ULN | None |
| | More than 1.0x–1.5x ULN | Any | None |
| Moderate | More than 1.5x–3x ULN | Any | Reduce VELCADE to 0.7 mg/m ² in the first cycle. Consider dose escalation to 1.0 mg/m ² or further dose reduction to 0.5 mg/m ² in subsequent cycles based on patient tolerability. |
| Severe | More than 3x ULN | Any | |

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;

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

2.9 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 *Dosage and Administration (2.10)*].

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 *Dosage and Administration (2.10)*]. Alternatively, the intravenous route of administration should be considered [see *Dosage and Administration (2.10)*].

VELCADE is an antineoplastic. Procedures for proper handling and disposal should be considered [see *How Supplied/Storage and Handling (16)*].

2.10 Reconstitution/Preparation for Intravenous and Subcutaneous Administration

Proper aseptic technique should be used. 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, caution should be used when calculating the volume to be administered** [see *Dosage and Administration (2.9)*].

For each 3.5 mg single-use vial of bortezomib reconstitute with the following volume of 0.9% sodium chloride based on route of administration (Table 7):

Table 7: 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]**

$$\frac{\text{VELCADE dose (mg/m}^2\text{)} \times \text{patient BSA (m}^2\text{)}}{1 \text{ mg/mL}} = \text{Total VELCADE volume (mL) to be administered}$$

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

$$\frac{\text{VELCADE dose (mg/m}^2\text{)} \times \text{patient BSA (m}^2\text{)}}{2.5 \text{ mg/mL}} = \text{Total VELCADE volume (mL) to be administered}$$

Stickers that indicate the route of administration are provided with each VELCADE vial. These stickers should be placed directly on the syringe of VELCADE once VELCADE is prepared to help alert practitioners of the correct route of administration for VELCADE.

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.

VELCADE contains no antimicrobial preservative. Reconstituted VELCADE should be administered within 8 hours of preparation. When reconstituted as directed, VELCADE may be stored at 25°C (77°F). The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to 8 hours in a syringe; however, total storage time for the reconstituted material must not exceed 8 hours when exposed to normal indoor lighting.

3 DOSAGE FORMS AND STRENGTHS

For injection: Each single-use 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 (2.10)*].

4 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 (6.1)*].

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

5 WARNINGS AND PRECAUTIONS

5.1 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 \geq 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 versus 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. 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 (2.7)*]. In the VELCADE versus dexamethasone phase 3 relapsed multiple myeloma study, improvement in or resolution of peripheral neuropathy was reported in 48% of patients with \geq 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 \geq Grade 3 peripheral neuropathy in the phase 2 multiple myeloma studies [*see Adverse Reactions (6.1)*]. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

5.2 Hypotension

The incidence of hypotension (postural, orthostatic, and hypotension NOS) was 8%. These events are observed throughout therapy. Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medications, hydration, and administration of mineralocorticoids and/or sympathomimetics [*see Adverse Reactions (6.1)*].

5.3 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. Patients with risk factors for, or existing heart disease should be closely monitored. In the relapsed multiple myeloma study of VELCADE versus 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 $\leq 1\%$ for each individual reaction in the VELCADE group. In the dexamethasone group the incidence was $\leq 1\%$ 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.

5.4 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 ($2\text{g}/\text{m}^2$ 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.

5.5 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.

5.6 Gastrointestinal Toxicity

VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting [see *Adverse Reactions (6.1)*] 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.

5.7 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 2 and 4 and Dosage and Administration (2.6)*]. 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 versus 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 8. The incidence of bleeding (\geq Grade 3) was 2% on the VELCADE arm and was $<$ 1% in the dexamethasone arm.

Table 8: Severity of Thrombocytopenia Related to Pretreatment Platelet Count in the Relapsed Multiple Myeloma Study of VELCADE versus Dexamethasone

| Pretreatment Platelet Count* | Number of Patients (N=331)** | Number (%) of Patients with Platelet Count $<$ 10,000/μL | Number (%) of Patients with Platelet Count 10,000-25,000/μL |
|--|-------------------------------------|--|---|
| \geq 75,000/ μ L | 309 | 8 (3%) | 36 (12%) |
| \geq 50,000/ μ L- $<$ 75,000/ μ L | 14 | 2 (14%) | 11 (79%) |
| \geq 10,000/ μ L- $<$ 50,000/ μ L | 7 | 1 (14%) | 5 (71%) |

* A baseline platelet count of 50,000/ μ L was required for study eligibility

** Data were missing at baseline for 1 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 (\geq Grade 4) was 32% versus 1% for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) arm as shown in Table 12. The incidence of bleeding events (\geq Grade 3) was 1% in the VcR-CAP arm (3 patients) and was $<$ 1% in the R-CHOP arm (1 patient).

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 (\geq Grade 4) was 70% in the VcR-CAP arm and was 52% in the R-CHOP arm. The incidence of febrile neutropenia (\geq 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.

5.8 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.

5.9 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 re-challenge information in these patients.

5.10 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 post-implantation loss and a decreased number of live fetuses [see *Use in Specific Populations (8.1)*].

Females of reproductive potential should avoid becoming pregnant while being treated with VELCADE. Advise females and males of reproductive potential that they must use contraception during treatment with VELCADE and for 2 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 (8.1, 8.3) and Nonclinical Toxicology (13.1)*].

6 ADVERSE REACTIONS

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

- Peripheral Neuropathy [see *Warnings and Precautions (5.1)*]
- Hypotension [see *Warnings and Precautions (5.2)*]
- Cardiac Toxicity [see *Warnings and Precautions (5.3)*]
- Pulmonary Toxicity [see *Warnings and Precautions (5.4)*]
- Posterior Reversible Encephalopathy Syndrome (PRES) [see *Warnings and Precautions (5.5)*]
- Gastrointestinal Toxicity [see *Warnings and Precautions (5.6)*]
- Thrombocytopenia/Neutropenia [see *Warnings and Precautions (5.7)*]
- Tumor Lysis Syndrome [see *Warnings and Precautions (5.8)*]
- Hepatic Toxicity [see *Warnings and Precautions (5.9)*]

6.1 Clinical Trials Safety 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 9 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 9: 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**

| System Organ Class Preferred Term | VELCADE, Melphalan and Prednisone (n=340) | | | Melphalan and Prednisone (n=337) | | |
|---|---|-----------------------|---------|-------------------------------------|-----------------------|---------|
| | Total n (%) | Toxicity Grade, n (%) | | Total n (%) | Toxicity Grade, n (%) | |
| | | 3 | ≥ 4 | | 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 ^a | 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 |

^a Represents High Level Term Peripheral Neuropathies NEC

Relapsed Multiple Myeloma Randomized Study of VELCADE versus 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/m² twice weekly for 2 out of 3 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 (9 months) with a median duration of 6 cycles (4.1 months). For inclusion in the trial, patients must have had measurable disease and 1 to 3 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 (14.1)*].

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 versus 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: 1 case each of cardiogenic shock, respiratory insufficiency, congestive heart failure and cardiac arrest. Four deaths were considered dexamethasone-related: 2 cases of sepsis, 1 case of bacterial meningitis, and 1 case of sudden death at home.

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

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

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

| Preferred Term | VELCADE N=331 | | | Dexamethasone N=332 | | |
|--------------------------------------|------------------|----------|---------|------------------------|----------|---------|
| | All | Grade 3 | Grade 4 | All | Grade 3 | Grade 4 |
| 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 ^a | 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 |

| Preferred Term | VELCADE N=331 | | | Dexamethasone N=332 | | |
|------------------------|------------------|---------|---------|------------------------|---------|---------|
| | 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 |

^a 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 23 months, including time on VELCADE in the prior VELCADE study [see *Clinical Studies (14.1)*].

Safety Experience from the Phase 3 Open-Label Study of VELCADE Subcutaneous versus 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/m². This was a randomized, comparative study of VELCADE subcutaneous versus intravenous in 222 patients with relapsed multiple myeloma. The safety data described below and in Table 11 reflect exposure to either VELCADE subcutaneous (n=147) or VELCADE intravenous (n=74) [see *Clinical Studies (14.1)*].

Table 11: Most Commonly Reported Adverse Reactions (≥ 10%), with Grade 3 and ≥ 4 Intensity in the Relapsed Multiple Myeloma Study (N=221) of VELCADE Subcutaneous versus Intravenous

| System Organ Class Preferred Term | Total n (%) | Subcutaneous (N=147) | | Total n (%) | Intravenous (N=74) | |
|---|----------------|-------------------------|-------|----------------|-----------------------|-------|
| | | Toxicity Grade, n (%) | ≥ 4 | | Toxicity Grade, n (%) | ≥ 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 ^a | 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 1 dose of study medication

^a 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 versus 9% intravenous), peripheral neuropathies (6% subcutaneous versus 15% intravenous),

neutropenia (13% subcutaneous versus 18% intravenous), and thrombocytopenia (8% subcutaneous versus 16% intravenous).

A local reaction was reported in 6% of patients in the subcutaneous group, mostly redness. Only 2 (1%) patients were reported as having severe reactions, 1 case of pruritus and 1 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 6 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 versus 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 1 (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 12 describes safety data from 240 patients with previously untreated mantle cell lymphoma who received VELCADE (1.3 mg/m²) administered intravenously in combination with rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), and prednisone (100 mg/m²) (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% versus R-CHOP 5%).

Table 12: Most Commonly Reported Adverse Reactions (≥ 5%) with Grades 3 and ≥ 4 Intensity in the Previously Untreated Mantle Cell Lymphoma Study

| System Organ Class Preferred Term | VcR-CAP n=240 | | | R-CHOP n=242 | | |
|---|------------------|------------------------------|-------------------------------|-----------------|------------------------------|-------------------------------|
| | 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) |

| System Organ Class Preferred Term | VcR-CAP n=240 | | | R-CHOP n=242 | | |
|---|------------------|------------------------------|-------------------------------|-----------------|------------------------------|-------------------------------|
| | All n (%) | Toxicity Grade 3 n (%) | Toxicity Grade ≥4 n (%) | All n (%) | Toxicity Grade 3 n (%) | Toxicity Grade ≥4 n (%) |
| 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 ^a | 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.

^a 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 2 arms (3 patients in the VcR-CAP arm and 1 patient 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%; 3 patients). The most commonly reported adverse reaction leading to discontinuation in the R-CHOP group was febrile neutropenia (< 1%; 2 patients).

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/m²/dose twice weekly for 2 weeks followed by a 10-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 versus 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.

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 1 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/m² Dose (N=1163)

| Preferred Term | All Patients N=1163 | | Multiple Myeloma N=1008 | | Mantle Cell Lymphoma N=155 | |
|--------------------------------------|------------------------|-----------|----------------------------|-----------|-------------------------------|-----------|
| | 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 ^a | 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) |

| Preferred Term | All Patients N=1163 | | Multiple Myeloma N=1008 | | Mantle Cell Lymphoma N=155 | |
|--------------------------|------------------------|---------|----------------------------|---------|-------------------------------|---------|
| | All | ≥ Grade | All | ≥ Grade | All | ≥ Grade |
| | | 3 | | 3 | | 3 |
| 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) |

^a 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 10-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 (5.7)*]. 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 versus 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 10-day rest period during each treatment cycle. Overall, neutropenia occurred in 15% of patients and

was Grade 3 in 8% of patients and \geq 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 \geq 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 \geq Grade 4 in $< 1\%$ of patients. Asthenia was reported as Grade 3 in 2% and \geq 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 ($> 38^{\circ}\text{C}$) was reported as an adverse reaction for 21% of patients. The reaction was Grade 3 in 1% and \geq 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 \geq 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 6-11%) than in the control groups (3-4%). Herpes simplex was seen in 1-3% in subjects treated with VELCADE and 1-3% 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%).

Retreatment in Relapsed Multiple Myeloma

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 \geq Grade 3 thrombocytopenia was 24%. Peripheral neuropathy occurred in 28% of patients, with the incidence of \geq 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

6.2 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

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)

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)

7 DRUG INTERACTIONS

Bortezomib is a substrate of cytochrome P450 enzyme 3A4, 2C19 and 1A2.

7.1 CYP3A4 inhibitors

Co-administration of ketoconazole, a strong CYP3A4 inhibitor, increased the exposure of bortezomib by 35% in 12 patients. Monitor patients for signs of bortezomib toxicity and consider a bortezomib dose reduction if bortezomib must be given in combination with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

7.2 CYP2C19 inhibitors

Co-administration of omeprazole, a strong inhibitor of CYP2C19, had no effect on the exposure of bortezomib in 17 patients.

7.3 CYP3A4 inducers

Co-administration of rifampin, a strong CYP3A4 inducer, is expected to decrease the exposure of bortezomib by at least 45%. Because the drug interaction study (n=6) was not designed to exert the maximum effect of rifampin on bortezomib PK, decreases greater than 45% may occur.

Efficacy may be reduced when VELCADE is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving VELCADE.

St. John's Wort (*Hypericum perforatum*) may decrease bortezomib exposure unpredictably and should be avoided.

7.4 Dexamethasone

Co-administration of dexamethasone, a weak CYP3A4 inducer, had no effect on the exposure of bortezomib in 7 patients.

7.5 Melphalan-Prednisone

Co-administration of melphalan-prednisone increased the exposure of bortezomib by 17% in 21 patients. However, this increase is unlikely to be clinically relevant.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action [*see Clinical Pharmacology (12.1)*] 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/m² in the rat and 0.05 mg/kg; 0.6 mg/m² in the rabbit) when administered during organogenesis. These dosages are approximately 0.5 times the clinical dose of 1.3 mg/m² 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/m² based on body surface area). Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05 mg/kg (0.6 mg/m²) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight.

8.2 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 breast fed infant, 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 breastfed infants from VELCADE is unknown, advise nursing women not to breastfeed during treatment with VELCADE and for 2 months after treatment.

8.3 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 (8.1)*].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating VELCADE treatment.

Contraception

Advise patients of reproductive potential to use effective contraception during treatment with VELCADE and for at least 2 months after treatment.

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 (13.1)*].

8.4 Pediatric Use

The effectiveness of VELCADE in pediatric patients with relapsed pre-B acute lymphoblastic leukemia (ALL) has not been established.

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, non-randomized cooperative group trial. An effective reinduction multiagent chemotherapy regimen was administered in 3 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/m² 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 10 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 pre-specified 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.

8.5 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 versus 4.3 mo, and 8.0 mo versus 4.9 mo, respectively]. On the VELCADE arm, 40% (n=46) of evaluable patients aged ≥ 65 experienced response (CR+PR) versus 18% (n=21) on the dexamethasone arm. The incidence of Grade 3 and 4 events was 64%, 78% and 75% for VELCADE patients ≤ 50, 51-64 and ≥ 65 years old, respectively [see *Adverse Reactions (6.1)*; *Clinical Studies (14.1)*].

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.

8.6 Patients with Renal Impairment

The pharmacokinetics of VELCADE are not influenced by the degree of renal impairment. Therefore, dosing adjustments of VELCADE are not necessary for patients with renal insufficiency. Since dialysis may reduce VELCADE concentrations, VELCADE should be administered after the dialysis procedure [see *Clinical Pharmacology (12.3)*].

8.7 Patients with Hepatic Impairment

The exposure of bortezomib is increased in patients with moderate (bilirubin ≥ 1.5 – 3x ULN) and severe (bilirubin > 3 x ULN) hepatic impairment. Starting dose should be reduced in those patients [see *Dosage and Administration (2.8)*, *Clinical Pharmacology (12.3)*].

8.8 Patients with Diabetes

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

10 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

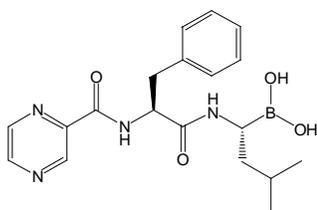
associated with the acute onset of symptomatic hypotension (5.2) and thrombocytopenia (5.7). In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given.

Studies in monkeys and dogs showed that intravenous bortezomib doses as low as 2 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 $3.0 \text{ mg}/\text{m}^2$ and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at 1 hour post-administration, with progression to death in 12 to 14 hours following drug administration.

11 DESCRIPTION

VELCADE[®] for Injection 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 $\text{C}_{19}\text{H}_{25}\text{BN}_4\text{O}_4$. 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-use 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.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

Following twice weekly administration of $1 \text{ mg}/\text{m}^2$ and $1.3 \text{ mg}/\text{m}^2$ bortezomib doses ($n=12$ per each dose level), the maximum inhibition of 20S proteasome activity (relative to baseline) in whole blood was observed 5 minutes after drug administration. Comparable maximum inhibition of 20S proteasome activity was observed between 1 and $1.3 \text{ mg}/\text{m}^2$ doses. Maximal inhibition ranged from 70% to 84% and from 73% to 83% for the $1 \text{ mg}/\text{m}^2$ and $1.3 \text{ mg}/\text{m}^2$ dose regimens, respectively.

12.3 Pharmacokinetics

Following intravenous administration of $1 \text{ mg}/\text{m}^2$ and $1.3 \text{ mg}/\text{m}^2$ doses to 24 patients with multiple myeloma ($n=12$, per each dose level), the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose

(Day 1) were 57 and 112 ng/mL, respectively. In subsequent doses, when administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m² dose and 89 to 120 ng/mL for the 1.3 mg/m² dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 193 hours after the 1 mg/m² dose and 76 to 108 hours after the 1.3 mg/m² dose. The mean total body clearances was 102 and 112 L/h following the first dose for doses of 1 mg/m² and 1.3 mg/m², respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m², respectively.

Following an intravenous bolus or subcutaneous injection of a 1.3 mg/m² dose to patients (n = 14 for intravenous, n = 17 for subcutaneous) with multiple myeloma, the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administration. The C_{max} after subcutaneous administration (20.4 ng/mL) was lower than intravenous (223 ng/mL). The AUC_{last} geometric mean ratio was 0.99 and 90% confidence intervals were 80.18% - 122.80%.

Distribution: The mean distribution volume of bortezomib ranged from approximately 498 to 1884 L/m² following single- or repeat-dose administration of 1 mg/m² or 1.3 mg/m² to patients with multiple myeloma. This suggests bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100 to 1000 ng/mL.

Metabolism: *In vitro* studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form 2 deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

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

Age: Analyses of data after the first dose of Cycle 1 (Day 1) in 39 multiple myeloma patients who had received intravenous doses of 1 mg/m² and 1.3 mg/m² showed that both dose-normalized AUC and C_{max} tend to be less in younger patients. Patients < 65 years of age (n=26) had about 25% lower mean dose-normalized AUC and C_{max} than those ≥ 65 years of age (n=13).

Gender: Mean dose-normalized AUC and C_{max} values were comparable between male (n=22) and female (n=17) patients after the first dose of Cycle 1 for the 1 and 1.3 mg/m² doses.

Race: The effect of race on exposure to bortezomib could not be assessed as most of the patients were Caucasian.

Hepatic Impairment: The effect of hepatic impairment (see Table 6 for definition of hepatic impairment) on the pharmacokinetics of bortezomib was assessed in 60 patients with cancer at bortezomib doses ranging from 0.5 to 1.3 mg/m². When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-normalized bortezomib AUC. However, the dose-normalized mean AUC values were increased by approximately 60% in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be monitored closely [see *Dosage and Administration (2.8) and Use in Specific Populations (8.7)*].

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 m², N=12), Mild (CrCl=40-59 mL/min/1.73 m², N=10), Moderate (CrCl=20-39 mL/min/1.73 m², N=9), and Severe (CrCl < 20 mL/min/1.73 m², 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/m² of bortezomib twice weekly. Exposure of bortezomib (dose-normalized AUC and C_{max}) was comparable among all the groups [see *Use in Specific Populations (8.6)*].

Pediatric: See *Use in Specific Populations (8.4)*.

Cytochrome P450: Bortezomib is a poor inhibitor of human liver microsomal cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC_{50} values of $> 30\mu M$ ($> 11.5\mu g/mL$). Bortezomib may inhibit 2C19 activity ($IC_{50} = 18\mu M$, $6.9\mu g/mL$) and increase exposure to drugs that are substrates for this enzyme. Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

13 NONCLINICAL TOXICOLOGY

13.1 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 6-month rat toxicity study, degenerative effects in the ovary were observed at doses $\geq 0.3\text{ mg/m}^2$ (one-fourth of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m^2 .

13.2 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 post dose. Doses $\geq 1.2\text{ mg/m}^2$ 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 2 weeks followed by 1-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.

14 CLINICAL STUDIES

14.1 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 682 patients 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 9 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 14. At a pre-specified 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, pre-specified 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 14: 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 ^a (months) | 20.7 | 15.0 |
| (95% CI) | (17.6, 24.7) | (14.1, 17.9) |
| Hazard ratio ^b | 0.54 | |
| (95% CI) | (0.42, 0.70) | |
| p-value ^c | 0.000002 | |
| Progression-free Survival | | |
| Events n (%) | 135 (39) | 190 (56) |
| Median ^a (months) | 18.3 | 14.0 |
| (95% CI) | (16.6, 21.7) | (11.1, 15.0) |
| Hazard ratio ^b | 0.61 | |
| (95% CI) | (0.49, 0.76) | |
| p-value ^c | 0.00001 | |
| Response Rate | | |
| CR ^d n (%) | 102 (30) | 12 (4) |
| PR ^d n (%) | 136 (40) | 103 (30) |
| nCR n (%) | 5 (1) | 0 |
| CR + PR ^d n (%) | 238 (69) | 115 (34) |
| p-value ^e | $<10^{-10}$ | |
| Overall Survival at median follow up of 36.7 months | | |
| Events (deaths) n (%) | 109 (32) | 148 (44) |
| Median ^a (months) | Not Reached | 43.1 |
| (95% CI) | (46.2, NR) | (34.8, NR) |
| Hazard ratio ^b | 0.65 | |
| (95% CI) | (0.51, 0.84) | |
| p-value ^c | 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.

^a Kaplan-Meier estimate

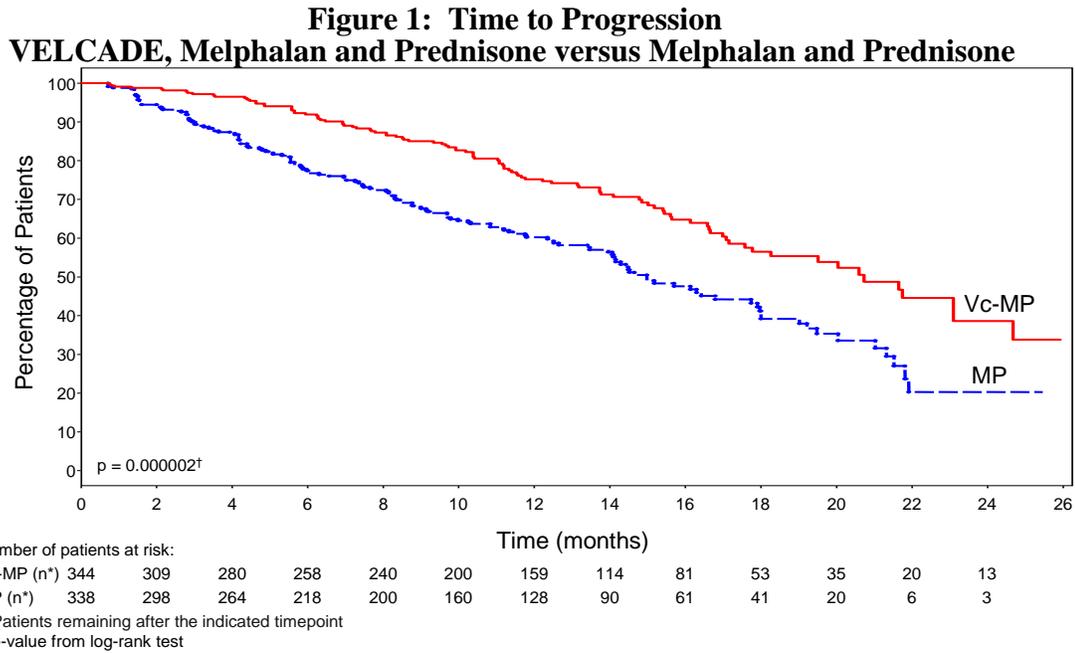
^b Hazard ratio estimate is based on a Cox proportional-hazard model adjusted for stratification factors: beta2-microglobulin, albumin, and region. A hazard ratio less than 1 indicates an advantage for VELCADE, melphalan and prednisone

^c p-value based on the stratified log-rank test adjusted for stratification factors: beta2-microglobulin, albumin, and region

^d EBMT criteria

^e 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)



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

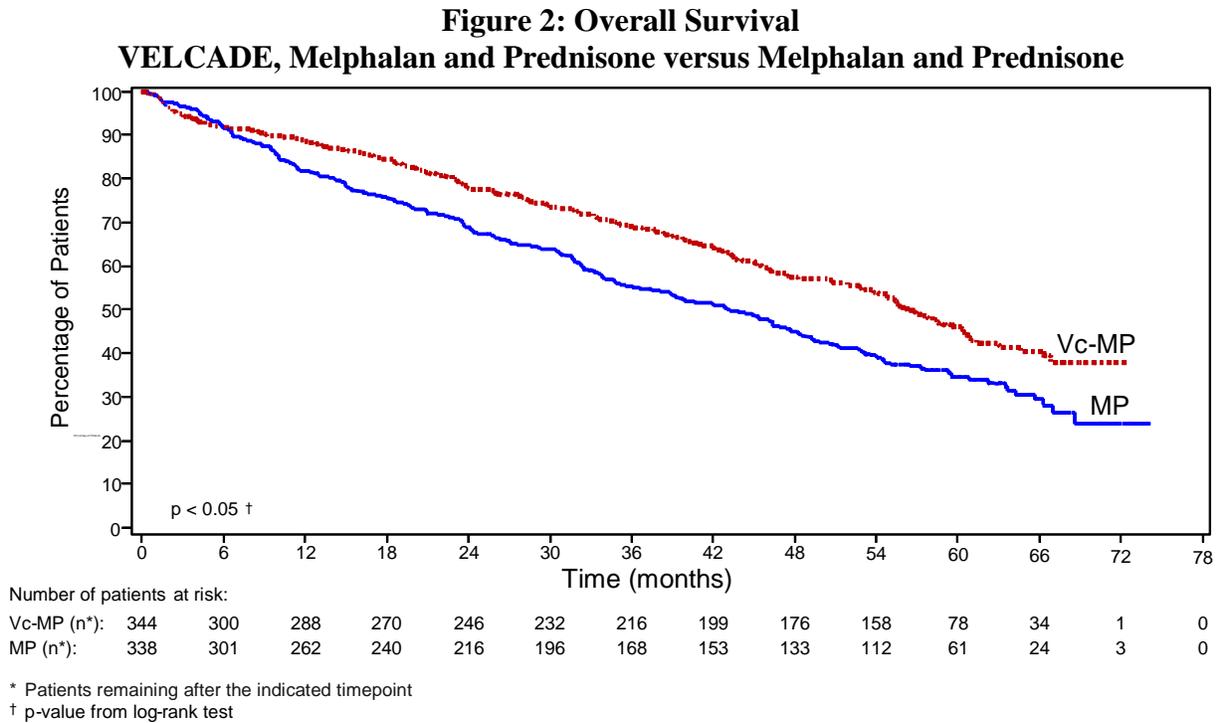


Table 17: Summary of Efficacy Analyses in the Relapsed Multiple Myeloma Study of VELCADE Subcutaneous versus Intravenous

| | 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 (%)^a | 72.6 | 76.7 |

^a 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/m² or 1.3 mg/m² intravenous bolus twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-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 2.0 years, and patients had received a median of 1 prior line of treatment (median of 3 prior therapies). A single complete response was seen at each dose. The overall response rates (CR + PR) were 30% (8/27) at 1 mg/m² and 38% (10/26) at 1.3 mg/m².

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 7 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 3-week dosing schedule during the extension study. No new cumulative or new long-term toxicities were observed with prolonged VELCADE treatment [see *Adverse Reactions (6.1)*].

A Single-Arm Trial of Retreatment in Relapsed Multiple Myeloma

A single arm, open-label trial 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 2 prior lines of therapy [range 1-7]) 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 6 months after prior VELCADE therapy, VELCADE was restarted at the last tolerated dose of 1.3 mg/m² (n=93) or ≤ 1.0 mg/m²

(n=37) and given on days 1, 4, 8 and 11 every 3 weeks for maximum of 8 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.

14.2 Mantle Cell Lymphoma

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

A randomized, open-label, Phase 3 study 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/m²) administered intravenously on days 1, 4, 8, and 11 (rest period days 12-21); rituximab (375 mg/m²) on Day 1; cyclophosphamide (750 mg/m²) on Day 1; doxorubicin (50 mg/m²) on Day 1; and prednisone (100 mg/m²) 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. 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 (high-intermediate) or higher and 76% had Stage IV disease.

The majority of the patients in both groups received 6 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 6 with 17% of patients in the R-CHOP group and 14% of subjects in the VcR-CAP group receiving up to 2 additional cycles.

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

Table 18: 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 ^a (months) | 25 | 14 |
| (95% CI) | (20, 32) | (12, 17) |
| Hazard ratio ^b | 0.63 | |
| (95% CI) | (0.50, 0.79) | |
| p-value ^c | <0.001 | |
| Complete Response Rate (CR)^d | | |
| n (%) | 108 (44) | 82 (34) |
| (95% CI) | (38, 51) | (28, 40) |
| Overall Response Rate (CR+CRu+PR)^e | | |
| n (%) | 214 (88) | 208 (85) |
| (95% CI) | (83, 92) | (80, 89) |

^a Based on Kaplan-Meier product limit estimates.

^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.

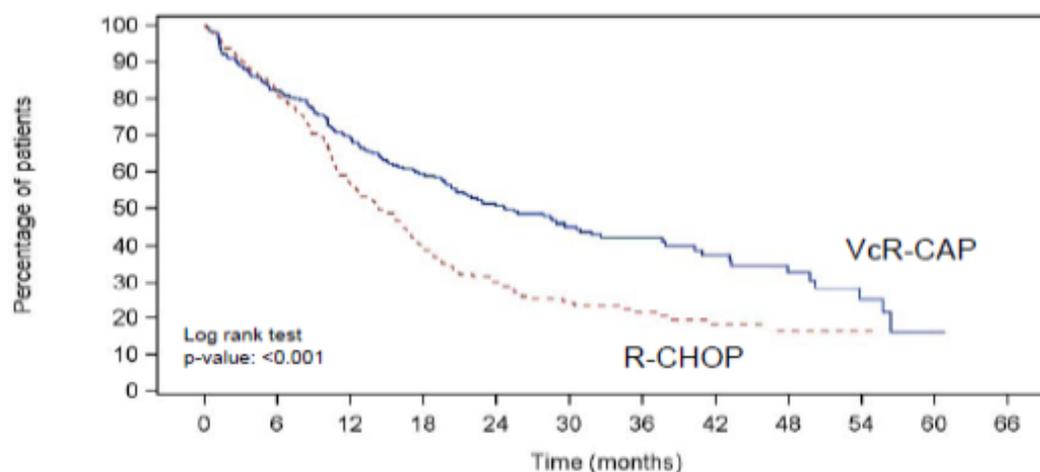
^c Based on Log rank test stratified with IPI risk and stage of disease.

^d Includes CR by independent radiographic assessment, bone marrow, and LDH using ITT population.

^e Includes CR+ CRu+PR by independent radiographic assessment, regardless of the verification by bone marrow and LDH, using ITT population.

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

**Figure 5: Progression Free Survival
VcR-CAP versus R-CHOP (previously untreated mantle cell lymphoma study)**



| Subjects at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 | 66 |
|------------------|-----|-----|-----|-----|----|----|----|----|----|----|----|----|
| VcR-CAP | 243 | 187 | 146 | 122 | 94 | 66 | 42 | 28 | 17 | 8 | 1 | 0 |
| R-CHOP | 244 | 181 | 116 | 79 | 55 | 36 | 22 | 16 | 9 | 3 | 0 | 0 |

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 of 155 patients with progressive disease who had received at least 1 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/m²/dose was administered twice weekly for 2 weeks on Days 1, 4, 8, and 11 followed by a 10-day rest period (Days 12 to 21) for a maximum of 17 treatment cycles. Patients achieving a CR or CRu were treated for 4 cycles beyond first evidence of CR or CRu. The study employed dose modifications for toxicity [see *Dosage and Administration* (2.6, 2.7)].

Responses to VELCADE are shown in Table 19. 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 4; in responding patients the median number of cycles was 8. 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 19: 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) |

15 REFERENCES

1. “OSHA Hazardous Drugs” (refer to antineoplastic weblinks including OSHA Technical Manual). *OSHA*. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

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.

NDC 63020-049-01
3.5 mg single-use vial

Unopened vials may be stored at controlled room temperature 25°C (77°F); excursions permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Retain in original package to protect from light.

Follow guidelines for handling and disposal for cytotoxic drugs, including the use of gloves and other protective clothing to prevent skin contact¹.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to treatment with VELCADE:

Ability to Drive or Operate Machinery or Impairment of Mental Ability: VELCADE may cause fatigue, dizziness, syncope, orthostatic/postural hypotension. Advise patients not to drive or operate machinery if they experience any of these symptoms.

Dehydration/Hypotension: Patients receiving VELCADE therapy may experience vomiting and/or diarrhea. Advise patients how to avoid dehydration. Instruct patients to seek medical advice if they experience symptoms of dizziness, light headedness or fainting spells, or muscle cramps.

Embryo-fetal Toxicity: Advise females of the potential risk to the fetus and to avoid pregnancy during treatment with VELCADE. Advise patients to use effective contraceptive measures to prevent pregnancy during treatment with VELCADE and for 2 months following treatment. Instruct patients to report pregnancy to their physicians immediately if they or their female partner becomes pregnant during treatment or within 2 months following treatment [*see Warnings and Precautions (5.10)*].

Lactation: Advise patients to avoid breastfeeding while receiving VELCADE and for 2 months after treatment [*see Use in Specific Populations (8.2)*].

Concomitant Medications: Advise patients to speak with their physicians about any other medication they are currently taking.

Diabetic Patients: Advise patients to check their blood sugar frequently if using an oral antidiabetic medication and to notify their physicians of any changes in blood sugar level.

Peripheral Neuropathy and Nervous System: Advise patients to contact their physicians if they experience new or worsening symptoms of peripheral neuropathy such as tingling, numbness, pain, a burning feeling in the feet or hands, or weakness in the arms or legs. Advise patients to contact their physicians if they experience symptoms possibly indicative of PRES [*see Warnings and Precautions (5.5)*] or PML, such as convulsion, persistent headache, reduced eyesight, blurred vision, confusion, lethargy, altered ability to think, or difficulty walking.

Cardiac: Advise patients to contact their physicians if they experience swelling of the feet, ankles, or legs or other heart-related problems [*see Warnings and Precautions (5.3)*].

Respiratory: Advise patients to contact their physicians if they experience shortness of breath, cough, or other lung problems [*see Warnings and Precautions (5.4)*].

Hepatic: Advise patients to contact their physicians if they experience jaundice or right upper quadrant abdominal pain [*see Warnings and Precautions (5.9)*].

Dermal: Advise patients to contact their physicians if they experience rash, severe injection site reactions [*see Dosage and Administration (2.9)*], or skin pain. Discuss with patients the option for antiviral prophylaxis for herpes virus infection [*see Clinical Trials Safety Experience (6.1)*].

Other: Instruct patients to contact their physicians if they develop an increase in blood pressure, bleeding, fever, constipation, or decreased appetite.

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