VELCADE® (bortezomib) is indicated for the treatment of patients with multiple myeloma. VELCADE is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol. VELCADE is contraindicated for intrathecal administration.

Please see Important Safety Information within the Safety tab and accompanying full Prescribing Information, also available at VELCADEHCP.com.
ABOUT VELCADE® (bortezomib)

DESCRIPTION

▼ VELCADE is an antineoplastic agent
▼ VELCADE is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells
▼ Procedures for proper handling and disposal should be considered. Please see the Storage and Disposal tab

HOW SUPPLIED

▼ VELCADE is supplied as individually cartoned 10-mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder
▼ Each carton of VELCADE contains a glass vial with a royal blue cap in a transparent blister pack

STORAGE AND HANDLING

▼ Store unopened vials of VELCADE at controlled room temperature 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F). Retain vials in original package to protect from light
▼ Consider handling and disposal of VELCADE according to guidelines issued for cytotoxic drugs, including using gloves and other protective clothing to prevent skin contact

Please see Important Safety Information for VELCADE within the Safety tab.
VELCADE® (bortezomib) is an antineoplastic agent and should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Procedures for proper handling and disposal should be considered.

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

The volume of 0.9% sodium chloride used to reconstitute VELCADE for subcutaneous administration is less than the volume used for intravenous (IV) administration.

For subcutaneous reconstitution, add 1.4 mL of sterile 0.9% sodium chloride solution to the powder contained in the vial of VELCADE.

This reconstitution will result in a final concentration of 2.5 mg/mL VELCADE.

The reconstituted product should be a clear and colorless solution free of particulate matter.

Apply stickers to the vial and syringe that identify the intended route of administration.

VELCADE contains no antimicrobial preservative. Therefore, reconstituted VELCADE should be administered within 8 hours of preparation (see Storage and Disposal tab for storage guidelines).

The reconstituted concentration of VELCADE for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration for IV administration (1 mg/mL). Use caution when calculating the volume to be administered.

The recommended starting dose for both routes is 1.3 mg/m².

Please see Dose Modification tab for dosing with hematologic toxicities, nonhematologic toxicities, peripheral neuropathy (PN), and moderate to severe hepatic impairment.

Please see Important Safety Information for VELCADE within the Safety tab.
VELCADE® (bortezomib) is an antineoplastic agent and should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Procedures for proper handling and disposal should be considered.

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

The volume of 0.9% sodium chloride used to reconstitute VELCADE for IV administration is greater than the volume used for subcutaneous administration.

- For IV reconstitution, add 3.5 mL of sterile 0.9% sodium chloride solution to the powder contained in the vial of VELCADE.
- This reconstitution will result in a final concentration of 1 mg/mL VELCADE.
- The reconstituted product should be a clear and colorless solution free of particulate matter.

Apply stickers to the vial and syringe that identify the intended route of administration.

VELCADE contains no antimicrobial preservative. Therefore, reconstituted VELCADE should be administered within 8 hours of preparation (see Storage and Disposal tab for storage guidelines).

The reconstituted concentration of VELCADE for IV administration (1 mg/mL) is less than the reconstituted concentration for subcutaneous administration (2.5 mg/mL). Use caution when calculating the volume to be administered. The recommended starting dose for both routes is 1.3 mg/m².

Please see Dose Modification tab for dosing with hematologic toxicities, nonhematologic toxicities, peripheral neuropathy, and moderate to severe hepatic impairment.

Please see Important Safety Information for VELCADE within the Safety tab.
The recommended starting dose of VELCADE® (bortezomib) is 1.3 mg/m² for both subcutaneous and IV administrations.

Please see Dose Modification tab for dosing with hematologic and nonhematologic toxicities, peripheral neuropathy, and moderate to severe hepatic impairment.

The amount (in mg) of VELCADE to be administered is based on body surface area (BSA) calculations using a standard nomogram or according to institutional policy.

The drug quantity contained in one vial (3.5 mg) may exceed the dose required. Use caution when calculating the dose to prevent overdose.

**OVERDOSAGE**

There is no specific antidote known for overdosage with VELCADE. 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 and thrombocytopenia.


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

**EXAMPLES OF BSA CALCULATIONS**

BSA should be calculated using a standard nomogram. For example:

\[
\text{BSA} = \sqrt{\frac{\text{Ht (in)} \times \text{Wt (lb)}}{3131}}
\]

OR

\[
\text{BSA} = \sqrt{\frac{\text{Ht (cm)} \times \text{Wt (kg)}}{3600}}
\]

Please see section 2 of the full Prescribing Information for reconstitution, dosage, and administration instructions.

Please see Important Safety Information for VELCADE within the Safety tab.
**DOSING SCHEDULE: PREVIOUSLY UNTREATED MULTIPLE MYELOMA (MM)**

**TWICE-WEEKLY THEN WEEKLY DOSING FOR A TOTAL OF 54 WEEKS**

**TWICE WEEKLY**

- **Vc**
- **Vc**
- **Vc**
- **Vc**
- **Rest 12-21**

**Day 1 4 8 11**

**MP† on days 1-4 every 6 weeks**

**3 WEEKS X 8**

**WEEKLY**

- **Vc**
- **Vc**
- **Rest 9-21**

**Day 1 8**

**MP on days 1-4 every 6 weeks**

**3 WEEKS X 10**

- ▼ Administer VELCADE® (bortezomib) (1.3 mg/m²) as a subcutaneous injection or a 3- to 5-second bolus IV injection in combination with oral MP (melphalan 9 mg/m² and prednisone 60 mg/m²).
- ▼ Prior to initiating any cycle of therapy with VELCADE in combination with MP:
  - Platelet count should be at least 70 × 10⁹/L and absolute neutrophil count (ANC) should be at least 1.0 × 10⁹/L.
  - Nonhematologic toxicities should have resolved to grade 1 or baseline.
- ▼ Dosing adjustments of VELCADE are not necessary for patients with renal insufficiency. In patients undergoing dialysis, VELCADE should be administered after the dialysis procedure.
- ▼ Please see Dose Modification tab for guidelines for hematologic toxicities, nonhematologic toxicities, peripheral neuropathy, and moderate to severe hepatic impairment.
- ▼ In the VISTA trial, discontinuations due to adverse events (AEs) were 15% for VELCADE combination and 14% for MP alone.
- ▼ At least 72 hours should elapse between each VELCADE dose.

*VELCADE.*  
†Melphalan+prednisone.

Please see Trial Designs tab for clinical trial information.  
Please see Important Safety Information for VELCADE within the Safety tab.
DOSING SCHEDULE: RELAPSED MULTIPLE MYELOMA AND MANTLE CELL LYMPHOMA (MCL)

INITIAL THERAPY FOLLOWED BY EXTENDED THERAPY

FOR INITIAL THERAPY
TWICE WEEKLY

FOR EXTENDED THERAPY
WEEKLY MAINTENANCE SCHEDULE

Administer VELCADE® (bortezomib) (1.3 mg/m²) as a subcutaneous injection or a 3- to 5-second bolus IV injection

In the APEX trial, responding patients received a median of 31 weeks of therapy (39 planned) using twice-weekly followed by weekly dosing.

In the APEX trial, discontinuations due to AEs were 25% for VELCADE and 18% for dexamethasone. In the subcutaneous vs IV trial, discontinuations due to AEs were 18% vs 23%, respectively.

In the PINNACLE trial of MCL, 26% of patients discontinued VELCADE due to treatment-related AEs.

At least 72 hours should elapse between each VELCADE dose.

Please see Dose Modification tab for dosing with hematologic toxicities, nonhematologic toxicities, peripheral neuropathy, and moderate to severe hepatic impairment.

Please see Trial Designs tab for clinical trial information.

Please see Important Safety Information for VELCADE within the Safety tab.

*VELCADE.
**DOSE MODIFICATION: HEMATOLOGIC AND NONHEMATOLOGIC TOXICITIES**

### PREVIOUSLY UNTREATED MM

**Toxicity***
- **Neutropenia/thrombocytopenia**
  If prolonged grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding, is observed in the previous cycle
- **Thrombocytopenia during a 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)
- **Grade 3 or higher nonhematologic toxicities**

**Dose Modification or Delay**

- **Consider reduction of the melphalan dose by 25% in the next cycle**
- **VELCADE dose should be withheld**
- **If several doses in consecutive cycles are withheld due to toxicity, VELCADE dose should be reduced by 1 dose level†**
- **VELCADE therapy should be withheld until symptoms of the toxicity have resolved to grade 1 or baseline**
- **Then VELCADE may be reinitiated with 1 dose-level reduction†**

**RELAPSED MM AND MCL**

**VELCADE therapy should be withheld at the onset of any grade 3 nonhematologic or grade 4 hematologic toxicities, excluding neuropathy**

Once the symptoms of the toxicity have resolved, VELCADE therapy may be reinitiated at a dose reduced by 25%†

†From 1.3 mg/m² to 1 mg/m² or from 1 mg/m² to 0.7 mg/m².

- The degree of renal impairment does not influence the pharmacokinetics of VELCADE; therefore, dosing adjustments of VELCADE are not necessary for patients with renal insufficiency
- In patients undergoing dialysis, VELCADE should be administered after the dialysis procedure

*Please see subsequent pages for dose as well as modification guidelines for neuropathic pain and/or peripheral neuropathy related to therapy with VELCADE, and moderate to severe hepatic impairment.

Please see Important Safety Information for VELCADE within the Safety tab.

FOR HEALTHCARE PROFESSIONALS ONLY

VELCADE® (bortezomib) FOR INJECTION
DOSE MODIFICATION: HEPATIC IMPAIRMENT

<table>
<thead>
<tr>
<th>PREVIOUSLY UNTREATED OR RELAPSED MM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilirubin and SGOT (AST) Levels</strong></td>
</tr>
<tr>
<td><strong>MILD</strong></td>
</tr>
<tr>
<td>Bilirubin level less than or equal to 1.0 × ULN* and SGOT† (AST‡) levels more than ULN or Bilirubin level more than 1.0–1.5 × ULN and any SGOT (AST) level</td>
</tr>
<tr>
<td><strong>MODERATE</strong></td>
</tr>
<tr>
<td>Bilirubin level more than 1.5–3 × ULN and any SGOT (AST) level</td>
</tr>
<tr>
<td><strong>SEVERE</strong></td>
</tr>
<tr>
<td>Bilirubin level more than 3 × ULN and any SGOT (AST) level</td>
</tr>
</tbody>
</table>

Please review all dosing guidelines for hematologic and nonhematologic toxicities, moderate to severe hepatic impairment, and peripheral neuropathy throughout the Dose Modification tab.

Please see Important Safety Information for VELCADE within the Safety tab.

*Upper limit of normal range.
†Serum glutamic oxaloacetic transaminase.
‡Aspartate aminotransferase.
DOSE MODIFICATION: PERIPHERAL NEUROPATHY

<table>
<thead>
<tr>
<th>Severity of PN Signs/Symptoms*</th>
<th>Dose Modification or Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRADE 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) without pain or loss of function</td>
<td>No action</td>
</tr>
<tr>
<td>GRADE 1 WITH PAIN OR GRADE 2 (moderate symptoms; limiting instrumental activities of daily living (ADL)†)</td>
<td>Reduce VELCADE® (bortezomib) to 1 mg/m²</td>
</tr>
<tr>
<td>GRADE 2 WITH PAIN OR GRADE 3 (severe symptoms; limiting self-care ADL‡)</td>
<td>Withhold VELCADE until toxicity resolves, when toxicity resolves, reinitiate with a reduced dose of 0.7 mg/m² once per week</td>
</tr>
<tr>
<td>GRADE 4 (life-threatening consequences; urgent intervention indicated)</td>
<td>Discontinue VELCADE</td>
</tr>
</tbody>
</table>

Please review all dosing guidelines for hematologic and nonhematologic toxicities, moderate to severe hepatic impairment, and peripheral neuropathy throughout the Dose Modification tab.

Please see Important Safety Information for VELCADE within the Safety tab.

*Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.
†Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc.
‡Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

▼ Early detection of peripheral neuropathy is important in facilitating patient management
▼ Treatment-emergent peripheral neuropathy is generally manageable and reversible with appropriate dose modification
— In VISTA, 79% of patients who received dose modification experienced improvement within a median of 1.9 months³
— In APEX, 64%⁶ of patients experienced resolution or improvement within a median of 3.6 months¹⁰
▼ Treatment with VELCADE may cause peripheral neuropathy that is predominantly sensory. However, cases of severe sensory and motor peripheral neuropathy have been reported
▼ Patients with preexisting symptoms or signs of peripheral neuropathy may experience worsening peripheral neuropathy. Patients with preexisting severe neuropathy should be treated with VELCADE only after careful risk-benefit assessment
▼ Patients experiencing new or worsening peripheral neuropathy during therapy with VELCADE may benefit from dose modification or discontinuation. Please see full Prescribing Information for dose modification guidelines

³Peripheral neuropathy grade ≥2 (n=91).¹⁰

FOR HEALTHCARE PROFESSIONALS ONLY

VELCADE® (bortezomib) FOR INJECTION

DOSE MODIFICATION
SUBCUTANEOUS ADMINISTRATION

- Before VELCADE® (bortezomib) administration, visually inspect the solution for particulate matter and discoloration. If any discoloration or particulate matter is observed, do not use the reconstituted product. File a product complaint by calling 1-866-VELCADE.

- Verify that the dose in the syringe is correct.

INJECTION SITE REACTIONS

- In a clinical trial of VELCADE, a local reaction was reported in 6% of patients in the subcutaneous group as an adverse event.
  - Two patients (1%) were reported having severe reactions: 1 case of pruritus and 1 case of redness.
  - Local reactions rarely led to dose modifications, and all events resolved in a median of 6 days.

- If local injection site reactions occur following administration of VELCADE subcutaneously, a less concentrated solution of VELCADE (1 mg/mL instead of 2.5 mg/mL) may be administered. Alternatively, consider the IV route of administration.

Please see Adverse Events tab for safety experience in the subcutaneous vs IV clinical trial.

Please see Important Safety Information for VELCADE within the Safety Tab.

For Patient Assistance Information or Reimbursement Assistance, call 1-866-VELCADE (835-2233), Option 2, or visit VELCADEHCP.com
IV ADMINISTRATION

Before VELCADE® (bortezomib) administration, visually inspect the solution for particulate matter and discoloration. If any discoloration or particulate matter is observed, do not use the reconstituted product. File a product complaint by calling 1-866-VELCADE.

Verify that the dose in the syringe is correct.

INJECTION SITE REACTIONS

In 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.

VELCADE can be administered intravenously as a 3- to 5-second bolus IV injection.

Please see Important Safety Information for VELCADE within the Safety tab.

For Patient Assistance Information or Reimbursement Assistance, call 1-866-VELCADE (835-2233), Option 2, or visit VELCADEHCP.com.
STORAGE

UNOPENED VIALS

▼ Store unopened vials of VELCADE® (bortezomib) at controlled room temperature of 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F). Retain vials in original package to protect from light

▼ Unopened vials of VELCADE are stable until the date indicated on the package when stored in the original package protected from light

RECONSTITUTED VELCADE

▼ VELCADE contains no antimicrobial preservative. Administer reconstituted VELCADE 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

DISPOSAL

▼ Each vial of VELCADE is for only a single use. Dispose of any unused product or waste material in accordance with local requirements

▼ Consider handling and disposing of VELCADE according to guidelines issued for cytotoxic drugs, including using gloves and other protective clothing to prevent skin contact


Please see Important Safety Information for VELCADE within the Safety tab.

For Patient Assistance Information or Reimbursement Assistance, call 1-866-VELCADE (835-2233), Option 2, or visit VELCADEHCP.com
TRIAL DESIGNS

RELAPSED MULTIPLE MYELOMA: SUBCUTANEOUS VS IV
A 2:1 randomized, open-label, phase 3 non-inferiority study compared the efficacy and safety of VELCADE® (bortezomib) administered subcutaneously (n=148) with VELCADE administered intravenously (n=74) in patients with relapsed MM. The primary endpoint was ORR. Secondary endpoints included CR, nCR, TTP, PFS, 1-year survival, and safety assessments, including local injection site tolerability.

PREVIOUSLY UNTREATED MULTIPLE MYELOMA: VISTA
A randomized, open-label, international phase 3 trial (N=682) evaluating the efficacy and safety of VELCADE in combination with melphalan+prednisone (MP) vs MP in previously untreated MM. The primary endpoint was TTP. Secondary endpoints were CR, ORR, PFS, and OS. At a pre-specified interim analysis (median follow-up 16.3 months), VELCADE+MP resulted in significantly superior results for TTP, PFS, OS, and ORR. Further enrollment was halted and patients receiving MP were offered VELCADE in addition.

RELAPSED MULTIPLE MYELOMA: APEX
A randomized, open-label trial (N=669) evaluating the efficacy and safety of VELCADE vs dexamethasone in patients with previously treated MM. The primary endpoint was TTP. Secondary endpoints included OS, ORR, and safety. The APEX trial was terminated at a preplanned interim analysis of TTP. All dexamethasone patients were offered VELCADE.

MANTLE CELL LYMPHOMA: PINNACLE
A single-arm, multicenter, phase 2, open-label trial (N=155) evaluating the efficacy and safety of VELCADE in patients with MCL who had received at least 1 prior therapy. Primary endpoint was TTP and secondary endpoints were ORR, CR, duration of response, and OS. As an appropriate cohort of historical controls could not be found for comparison to the results of this study, the formal statistical comparisons of TTP and survival specified in the protocol could not be performed.

CR: complete response; nCR: near complete response; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TTP: time to progression; VGPR: very good partial response

Please see Important Safety Information for VELCADE within the Safety tab.
### MOST COMMONLY REPORTED (≥20%) ADVERSE EVENTS IN THE TRIAL OF SUBCUTANEOUS VS IV ADMINISTRATION (N=221)

<table>
<thead>
<tr>
<th></th>
<th>VELCADE® (bortezomib) Administered Subcutaneously (n=147), %</th>
<th>VELCADE Administered Intravenously (n=74), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Events</td>
<td>Grade 3 Events</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>38</td>
<td>5</td>
</tr>
<tr>
<td>Anemia</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>35</td>
<td>8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>29</td>
<td>15</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Neuralgia</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

Please see Trial Designs tab for clinical trial information.
Please see all safety experience throughout the Adverse Events tab.
Please see Important Safety Information for VELCADE within the Safety tab.

FOR HEALTHCARE PROFESSIONALS ONLY
ADVERSE EVENTS CONTINUED

RELAPSED MM: SUBCUTANEOUS VS IV

▼ The incidence of serious adverse events (SAEs) was similar for the subcutaneous and IV treatment groups (36% subcutaneous vs 35% IV). The most commonly reported SAEs in the subcutaneous treatment group were pneumonia (6%) and pyrexia (3%); in the IV treatment group, pneumonia (7%), diarrhea (4%), peripheral sensory neuropathy (3%), and renal failure (3%).

▼ Fewer dose reductions occurred in the subcutaneous treatment group due to drug-related AEs (31% subcutaneous vs 43% IV)

PREVIOUSLY UNTREATED MM

▼ In the phase 3 VELCADE with melphalan and prednisone study, the most commonly reported adverse events for VELCADE® (bortezomib)+MP vs MP were thrombocytopenia (52% vs 47%), neutropenia (49% vs 46%), nausea (48% vs 28%), peripheral neuropathy (47% vs 5%), diarrhea (46% vs 17%), anemia (43% vs 55%), constipation (37% vs 16%), neuralgia (36% vs 1%), leukopenia (33% vs 30%), vomiting (33% vs 16%)

▼ A total of 46% of patients in the VELCADE combination arm experienced SAEs vs 36% in the MP arm. The most commonly reported SAEs included pneumonia (11% vs 7%), diarrhea (5% vs <1%), vomiting (4% vs <1%), thrombocytopenia (4% vs 2%), pyrexia (4% vs 3%), dehydration (4% vs <1%), and nausea (3% vs <1%)

Please see Trial Designs tab for clinical trial information.

Please see all safety experience throughout the Adverse Events tab.

Please see Important Safety Information for VELCADE within the Safety tab.

RELAPSED MM AND MCL

▼ In the integrated analysis of 1163 patients in phase 2 and 3 studies, the most commonly reported adverse events were asthenic conditions (including fatigue, malaise, and weakness) (64%), nausea (55%), diarrhea (52%), constipation (41%), peripheral neuropathy NEC (including peripheral sensory neuropathy and peripheral neuropathy aggravated) (39%), thrombocytopenia and appetite decreased (including anorexia) (each 36%), pyrexia (34%), vomiting (33%)

▼ In the integrated analysis, a total of 50% of patients experienced SAEs. The most commonly reported SAEs included pneumonia (7%), pyrexia (6%), diarrhea (5%), vomiting (4%), and nausea, dehydration, dyspnea and thrombocytopenia (each 3%)
FREQUENTLY ASKED QUESTIONS

Q: The powder contained in the vial of VELCADE® (bortezomib) looks the same for subcutaneous and IV. Is it the same vial?
A: Yes, a vial of VELCADE can be used for either subcutaneous or IV administration. VELCADE is available in individual vials, each containing 3.5 mg of powdered product. However, the reconstitution of VELCADE for subcutaneous and IV injections differs. The reconstituted concentration of VELCADE for subcutaneous administration (2.5 mg/mL) is greater than the reconstituted concentration for IV administration (1 mg/mL). Stickers that indicate the route of administration are provided within the carton.

Q: What do I add to the 3.5-mg vial of VELCADE to reconstitute it for use as a subcutaneous administration?
A: For subcutaneous reconstitution, add 1.4 mL of sterile 0.9% sodium chloride solution to the powder contained in the vial of VELCADE.

Q: Not all of the reconstituted VELCADE was used. Can it be stored for future use?
A: Each vial of VELCADE is for only a single use. VELCADE contains no antimicrobial preservative. Administer reconstituted VELCADE 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.

Q: How far ahead of use can I reconstitute VELCADE for subcutaneous injection?
A: VELCADE contains no antimicrobial preservative. Administer reconstituted VELCADE within 8 hours preparation.

Q: How common are injection site reactions with subcutaneous administration of VELCADE?
A: In a clinical trial of VELCADE administered as a subcutaneous injection, a local reaction, mostly redness, was reported in 6% of patients as an adverse event. Only 2 patients (1%) were reported having severe reactions: 1 case of pruritus and 1 case of redness. Local reactions rarely led to dose modifications, and all events resolved in a median of 6 days.

Q: Is there any information on accidental overdosage of VELCADE?
A: In the event of an overdosage, monitor the patient’s vital signs and give appropriate supportive care. There is no specific antidote known for overdosage with VELCADE. 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 and thrombocytopenia.

Q: Is there any information on use in special populations, such as older patients?
A: No overall differences in safety or effectiveness were observed between patients 65 years or older and younger patients receiving VELCADE, but greater sensitivity of some older individuals cannot be ruled out.

Please see Important Safety Information for VELCADE within the Safety tab.
**INDICATIONS AND IMPORTANT SAFETY INFORMATION**

**INDICATIONS:** VELCADE® (bortezomib) is indicated for the treatment of patients with multiple myeloma. VELCADE is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy.

**CONTRAINDICATIONS:** VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol. VELCADE is contraindicated for intrathecal administration.

**WARNINGS AND PRECAUTIONS:** VELCADE is for subcutaneous or intravenous (IV) administration only. Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered. Complete blood counts should be monitored frequently during treatment with VELCADE.

- **Peripheral Neuropathy**, including severe cases, may occur. Patients should be monitored for symptoms and managed with dose modification or discontinuation. Patients with preexisting symptoms may experience worsening peripheral neuropathy (including ≥grade 3). Starting with VELCADE subcutaneously may be considered for patients who either have preexisting or are at high risk for peripheral neuropathy.

- **Hypotension** can occur. Caution should be used when treating patients receiving antihypertensives, those with a history of syncope, and those who are dehydrated.

- **Cardiac Disorders**, including acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction, have been reported. Isolated cases of QT-interval prolongation have been reported. Patients with risk factors for, or existing, heart disease should be closely monitored.

- **Pulmonary Disorders**, some fatal — including pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (ARDS) — have been reported. Pulmonary hypertension in the absence of left heart failure or significant pulmonary disease has also been reported.

- **Gastrointestinal Adverse Events**, including nausea, diarrhea, constipation, and vomiting, have occurred and may require use of antiemetic and antidiarrheal medications or fluid replacement.

- **Thrombocytopenia/Neutropenia** can occur — manage with dose and/or schedule modifications. Platelets should be monitored prior to each dose of VELCADE. There have been reports of gastrointestinal and intracerebral hemorrhage. Transfusions may be considered.

- **Patients with Hepatic Impairment:** Exposure to VELCADE is increased in patients with moderate or severe hepatic impairment. Start these patients at a lower dose of VELCADE and adjust after cycle 1, depending on tolerability.

Please see accompanying full Prescribing Information for VELCADE, also available at VELCADEHCP.com.
INDICATIONS AND IMPORTANT SAFETY INFORMATION CONTINUED

- **Patients with Diabetes:** Hypoglycemia and hyperglycemia have been reported with use of VELCADE. Patients may require close monitoring and adjustment of the antidiabetic medications.

- **Tumor Lysis Syndrome,** Reversible Posterior Leukoencephalopathy Syndrome (RPLS), and Acute Hepatic Failure have been reported.

- **Pregnancy and Nursing:** Women should avoid breastfeeding or becoming pregnant while on VELCADE.

**DRUG INTERACTIONS:** Closely monitor patients receiving VELCADE in combination with strong CYP3A4 inhibitors. Concomitant use of strong CYP3A4 inducers is not recommended.

**ADVERSE REACTIONS**

- **Previously Untreated Multiple Myeloma (MM):** In the phase 3 study of VELCADE administered IV with melphalan and prednisone (MP) vs MP alone, the most commonly reported adverse events were thrombocytopenia (52% vs 47%), neutropenia (49% vs 46%), nausea (48% vs 28%), peripheral neuropathy (47% vs 5%), diarrhea (46% vs 17%), anemia (43% vs 55%), constipation (37% vs 16%), neuralgia (36% vs 1%), leukopenia (33% vs 30%), and vomiting (33% vs 16%).

- **Relapsed MM and Mantle Cell Lymphoma (MCL):** In the integrated analysis of 1163 patients in phase 2 and 3 studies of VELCADE administered IV, the most commonly reported adverse events were asthenic conditions (including fatigue, malaise, and weakness) (64%), nausea (55%), diarrhea (52%), constipation (41%), peripheral neuropathy (including peripheral sensory neuropathy and peripheral neuropathy aggravated) (39%), thrombocytopenia and appetite decreased (including anorexia) (each 36%), pyrexia (34%), and vomiting (33%). A total of 50% of patients experienced serious adverse events (SAEs). The most commonly reported SAEs included pneumonia (7%); pyrexia (6%); diarrhea (5%); vomiting (4%); and nausea, dehydration, dyspnea, and thrombocytopenia (each 3%).

- **Relapsed MM Subcutaneous vs IV:** In the phase 3 study of VELCADE administered subcutaneously vs IV in relapsed MM, safety data were similar between the 2 treatment groups. The most commonly reported adverse events in this study were peripheral neuropathy (38% vs 53%), anemia (36% vs 35%), and thrombocytopenia (35% vs 36%). The incidence of SAEs was similar for the subcutaneous treatment group (36%) and the IV treatment group (35%). The most commonly reported SAEs were pneumonia (6%) and pyrexia (3%) in the subcutaneous treatment group and pneumonia (7%), diarrhea (4%), peripheral sensory neuropathy (3%), and renal failure (3%) in the IV treatment group.

Please see accompanying full Prescribing Information, also available at VELCADEHCP.com.
A vial of VELCADE® (bortezomib) can be used for either subcutaneous or IV administration, but reconstitution is different.

- The recommended starting dose of VELCADE is 1.3 mg/m² for both subcutaneous and IV administrations
- Because each route of administration has a different reconstituted concentration, use caution when calculating the volume to be administered
  - VELCADE is administered subcutaneously at a concentration of 2.5 mg/mL
  - VELCADE is administered intravenously at a concentration of 1 mg/mL as a 3- to 5-second bolus IV injection

Please see Important Safety Information for VELCADE on the Safety tab.
Please see accompanying full Prescribing Information, also available at VELCADEHCP.com.
Please see full Prescribing Information at
velcade.com/Files/PDFs/VELCADE_PRESCRIBING_INFORMATION.pdf