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Information.

FOR THE HEALTHCARE PROFESSIONAL

ANSWERS TO FREQUENTLY ASKED QUESTIONS ABOUT VELCADE®

Q&A

**VELCADE**®
(bortezomib) FOR INJECTION

ABOUT VELCADE® (bortezomib) FOR INJECTION

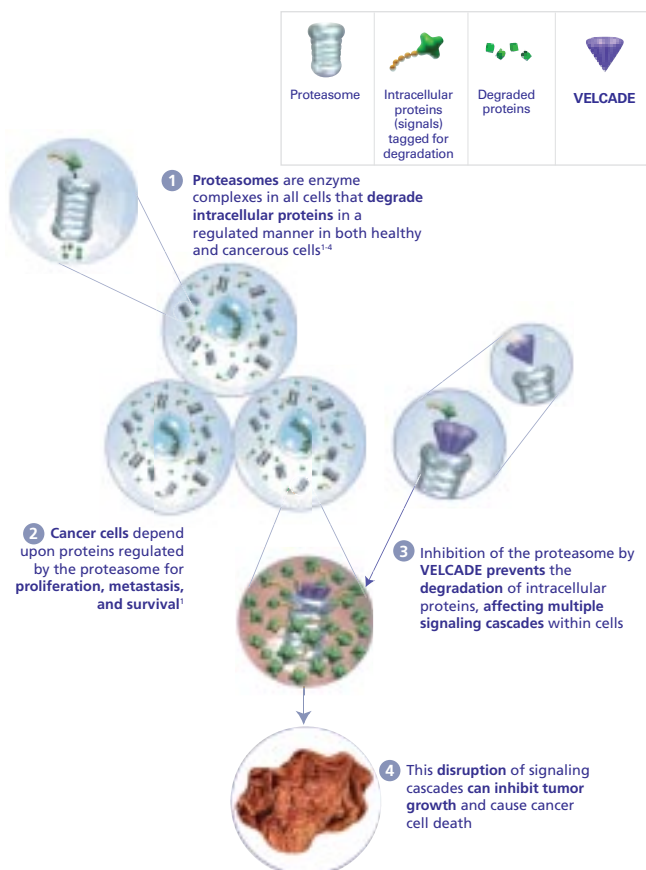
WHAT IS VELCADE?

VELCADE is a novel, first-in-class proteasome inhibitor that acts in a different manner than other chemotherapies.^{1,4}

VELCADE is indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy. The effectiveness of VELCADE is based on response rates. There are no controlled trials demonstrating a clinical benefit, such as improvement in survival.

The diagram below, based on nonclinical studies, illustrates the unique mechanism of action of VELCADE.^{1,4}

MECHANISM OF ACTION AS SHOWN IN (NONCLINICAL STUDIES)



CLINICAL TRIAL RESULTS WITH VELCADE®

HOW WAS THE EFFICACY OF VELCADE EVALUATED IN PATIENTS WITH MULTIPLE MYELOMA?

The efficacy of VELCADE was evaluated in an open-label, single-arm, multi-center Phase II clinical trial (SUMMIT) in 202 patients with multiple myeloma who had received at least 2 prior therapies (median = 6) and were progressing on their last therapy.

VELCADE was given as a 1.3 mg/m² IV push twice weekly for 2 weeks (administered on Days 1, 4, 8, and 11) followed by a 10-day rest period. Response rates were assessed by an Independent Review Committee based on two determinations 6 weeks apart. Of 202 patients, 188 were considered evaluable for response.

Complete Response (CR) determined by criteria defined by Bladé et al required 100% reduction in M protein on at least 2 determinations at least 6 weeks apart, a negative immunofixation test, < 5% plasma cells in the bone marrow, stable bone disease, and normal calcium. Partial Response (PR) required ≥50% reduction in M protein, ≥ 90% reduction in urine M protein on at least 2 determinations at least 6 weeks apart, stable bone disease, and normal calcium. Clinical remission by SWOG criteria was defined as ≥ 75% reduction in M protein on at least 2 determinations at least 6 weeks apart and/or ≥ 90% reduction in urine M protein, stable bone disease, and normal calcium.

In SUMMIT, VELCADE demonstrated an overall response rate (CR+PR) of 27.7% (95% CI = 21, 35). 17.6% (95% CI = 12, 24) of patients achieved a clinical remission as defined by the SWOG criteria.

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These response rates were independent of the number and type of previous therapies, including steroids, alkylators, anthracyclines, thalidomide, and stem cell transplant. In addition, the rate of response remained consistent regardless of the patient's gender, race, body surface area, performance status, myeloma type, $\beta 2$ microglobulin, or chromosome 13 deletion status.⁵ Predictors of decreased response were > 50% plasma cells in the bone marrow and abnormal cytogenetics; chromosome 13 deletion status was not an independent predictor of decreased response.

Patients maintained their response over time, with a median duration of response of 12 months (95% CI = 224 days, not estimable). The median overall survival of all patients enrolled in SUMMIT was 16 months (range <1 to 18+ months). Patients who experienced a CR or PR had decreased red blood cell transfusion requirements.

VELCADE® (bortezomib) for Injection activity was demonstrated at 1.0 mg/m² and 1.3 mg/m² doses in a separate, small, open-label, multicenter, dose-ranging study of patients with multiple myeloma who were progressing or relapsed on or after a median of 3 prior therapies.⁵ Major responses (CR + PR) were 30% (95% CI = 14, 50) and 38% (95% CI = 20, 59) at the 1.0 mg/m² and 1.3 mg/m² doses, respectively.

SIDE EFFECTS PROFILE FOR VELCADE®

In single-arm studies, it is often not possible to distinguish between drug-caused adverse events and those that reflect the patient's underlying disease. In 228 patients who were treated with VELCADE 1.3 mg/m²/dose in phase II studies, the most commonly reported adverse events were asthenic conditions (65%), nausea (64%), diarrhea (51%), decreased appetite including anorexia (43%), constipation (43%), thrombocytopenia (43%), peripheral neuropathy (37%), pyrexia (36%), vomiting (36%), and anemia (32%). Fourteen percent of patients experienced at least one episode of Grade 4 toxicity, with the most common toxicities being thrombocytopenia (3%) and neutropenia (3%).

A total of 113 (50%) of the 228 patients experienced Serious Adverse Events (SAEs) during the studies. The most commonly reported SAEs included pyrexia (7%), pneumonia (7%), diarrhea (6%), vomiting (5%), dehydration (5%), and nausea (4%).

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Treatment emergent adverse events ($\geq 25\%$ overall) are illustrated in the chart that follows.

Treatment emergent adverse events ($\geq 25\%$ overall) in Phase II clinical trials at 1.3 mg/m² dose (N=228)

Adverse Event	Overall	Grade 1/2*	Grade 3*	Grade 4*
Nausea	64%	58%	6%	0
Diarrhea	51%	43%	7%	<1%
Decreased appetite & anorexia	43%	41%	3%	0
Constipation	43%	41%	2%	0
Vomiting	36%	29%	7%	<1%
Thrombocytopenia	43%	13%	27%	3%
Anemia	32%	23%	9%	0
Asthenia (fatigue, malaise, weakness)	65%	46%	18%	<1%
Peripheral neuropathy	37%	23%	14%	0
Pyrexia	36%	32%	4%	0
Headache	28%	24%	4%	0
Insomnia	27%	26%	1%	0
Arthralgia	26%	21%	5%	0
Pain in limb	26%	19%	7%	0

In Phase II clinical trials, the most common adverse events leading to discontinuation of VELCADE[®] (bortezomib) for Injection were peripheral neuropathy (6%), gastrointestinal events (5%), thrombocytopenia (4%), and fatigue (2%). Eighteen percent of patients discontinued therapy due to drug-related adverse events.

* National Cancer Institute Common Toxicity Criteria (NCI, CTC, Version 2.0)⁶

PRESCRIBING CONSIDERATIONS

CONTRAINDICATIONS

VELCADE[®] is contraindicated in patients with hypersensitivity to bortezomib, boron, or mannitol.

WARNINGS

VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Pregnancy Category D

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE.

PRECAUTIONS

Peripheral Neuropathy: Treatment with VELCADE may be associated with a peripheral neuropathy that is predominantly sensory, although rare cases of mixed sensorimotor neuropathy have been reported. Patients with preexisting symptoms and/or signs of peripheral neuropathy may experience worsening during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as numbness, a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or neuropathic pain.

Hypotension: Treatment with VELCADE may be associated with orthostatic/postural hypotension 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.

Heart Failure: Acute development or exacerbation of congestive heart failure has been seen in patients with risk factors for or existing heart disease. Such patients should be closely monitored.

Laboratory Tests: Complete blood counts (CBCs) should be frequently monitored throughout treatment with VELCADE.

Tumor Lysis Syndrome: Tumor lysis syndrome may occur. Patients with high tumor burden prior to treatment should be monitored closely and appropriate precautions taken.

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Gastrointestinal Adverse Events: Nausea, diarrhea, constipation, and vomiting may occur during treatment with VELCADE® (bortezomib) for Injection.

Thrombocytopenia: Platelet counts should be frequently monitored prior to each dose of VELCADE. Thrombocytopenia was maximal at Day 11 and usually recovered by the next cycle and there was no evidence of cumulative thrombocytopenia. There have been reports of gastrointestinal and intracerebral hemorrhage in association with thrombocytopenia induced by VELCADE.

Patients with Hepatic or Renal Impairment
Patients with renal and hepatic impairment should be closely monitored for toxicities.

Animal Toxicity Findings

Toxicities observed with chronic administration in animals included severe anemia and thrombocytopenia; gastrointestinal, neurological and lymphoid system toxicities; and multifocal hemorrhage in the brain, eye and heart. At doses twice the recommended clinical dose, animals experienced profound hypotension and bradycardia resulting in myocardial damage and death.

DRUG INTERACTIONS

No formal drug interaction studies have been performed with VELCADE. *In vitro* studies indicate that bortezomib is a substrate for cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2. Patients who are concomitantly receiving VELCADE and drugs that are inhibitors or inducers of cytochrome P450 3A4 should be closely monitored for either toxicities or reduced efficacy. During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients receiving oral hypoglycemics. Close monitoring of blood glucose levels and adjustment of antidiabetic medications may be required.

HOW SUPPLIED/ DOSING/ADMINISTRATION

HOW IS VELCADE® SUPPLIED AND STORED?

VELCADE is supplied in 10-mL single-dose vials containing 3.5 mg bortezomib as a lyophilized white to off-white cake or powder without preservative. Each single-dose vial is intended for administration to one patient.



Store unopened vials at a controlled room temperature of 25°C (77°F) in the original package protected from light; excursions are permitted from 15°C to 30°C (59°F to 86°F).

HOW IS VELCADE RECONSTITUTED?

Reconstitute VELCADE with 3.5 mL of normal (0.9%) saline, Sodium Chloride Injection, USP. The concentration of reconstituted solution is 1 mg/mL. Reconstituted VELCADE should be administered within 8 hours of preparation. Reconstituted VELCADE



can be stored in the syringe for not more than 3 hours. Once reconstituted, VELCADE does not need to be protected from indoor lighting.

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**VELCADE**[®]
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ARE THERE ANY ADMINISTRATION PRECAUTIONS NECESSARY WITH VELCADE® (bortezomib) for Injection?

VELCADE is cytotoxic; therefore, caution should be used during handling and preparation. Proper aseptic technique should be used, and gloves and other protective clothing should be worn to prevent skin contact. VELCADE should be reconstituted under a hood.

WHAT ARE THE DOSING GUIDELINES FOR VELCADE?

VELCADE is administered as a 3- to 5-second IV push followed by a standard saline flush. One cycle consists of 2 doses given twice weekly for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12–21). At least a 72-hour rest period between doses is required.

Standard dosing regimen

Day 1	Day 4	Day 8	Day 11	10-DAY REST PERIOD	REPEAT CYCLE
VELCADE 1.3 mg/m ²	VELCADE 1.3 mg/m ²	VELCADE 1.3 mg/m ²	VELCADE 1.3 mg/m ²		

HOW IS THE NUMBER OF CYCLES OF VELCADE DETERMINED?

In the SUMMIT trial, patients with a confirmed complete response received 2 additional cycles of VELCADE treatment beyond confirmation of response. Patients who experienced a clinical benefit were allowed to continue beyond 8 cycles on an extension study.

HOW IS VELCADE® ADMINISTERED?

VELCADE may be injected directly into a peripheral line by IV push or injected into an infusion port. No central line is required.⁵To ensure a full dose, flush the line with normal saline. In clinical trials, extravasation of VELCADE was not associated with tissue damage. Local skin irritation was reported in 5% of patients.



Direct injection into a peripheral line by IV push



Injection into an infusion port

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ARE INFUSION-RELATED REACTIONS COMMON?

Infusion reactions and infusion-site reactions were rarely reported with VELCADE in Phase II clinical trials.

WHAT PREADMINISTRATION PROCEDURES SHOULD BE PERFORMED WITH EACH CYCLE OF VELCADE® (bortezomib) for Injection?

The following preadministration procedures are recommended with each cycle of VELCADE treatment:

Procedure/Test	Day 1	Day 4	Day 8	Day 11
Assess for symptom management (e.g., diarrhea, vomiting, fever, etc)	X	X	X	X
Monitor for symptoms of peripheral neuropathy, such as burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, or pain	X	X	X	X
Examine for signs of dyspnea and peripheral edema	X	X	X	X
Vital signs (blood pressure, respiration rate, temperature, pulse)	X	X	X	X
Clinical laboratory tests				
Hematology (CBC and platelet count)	X	X	X	X
Electrolytes	X	—	X	—
Clinical chemistries	X	—	X	—
Total protein/albumin	X	—	X	—
Weight (recalculate dose if weight change 8% or greater)	X	X	X	X

Please share “Information for Patients” from full Prescribing Information with all VELCADE recipients.

IS THE ADMINISTRATION OF VELCADE® DIFFERENT IN PATIENTS WITH RENAL IMPAIRMENT?

There are no pharmacokinetic data in patients with impaired hepatic function or renal insufficiency. Creatinine clearance in SUMMIT patients ranged from 14 to 220 mL/min. Patients with creatinine clearance values < 14 mL/min and those receiving hemodialysis should be closely monitored for toxicities during treatment with VELCADE.

HOW IS AN OVERDOSE OF VELCADE MANAGED?

No cases of overdose with VELCADE were reported during clinical trials. In the event of overdosage, the patient’s vital signs should be monitored and appropriate supportive care given to maintain blood pressure and body temperature. There is no known specific antidote for VELCADE overdose.

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SIDE EFFECTS MANAGEMENT

At the onset of Grade 3 non-hematological toxicities or Grade 4 hematological toxicities, therapy with VELCADE® (bortezomib) for Injection should be held. Once toxicity has resolved, VELCADE may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose). These guidelines are not to be used for the treatment of peripheral neuropathy; refer to the chart on page 16 for dose modification guidelines for neuropathic pain and/or peripheral sensory neuropathy related to VELCADE.

HOW IS ASTHENIA MANAGED?

Asthenic conditions (fatigue, malaise, or weakness) were reported in clinical trials with VELCADE. First onset of fatigue was reported most often during treatment Cycles 1 and 2. Most patients are able to continue therapy with VELCADE despite fatigue.

At the onset of Grade 3 non-hematological toxicities, including asthenic conditions, therapy with VELCADE should be held. Once toxicity has resolved, VELCADE may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose).

Management of asthenic conditions may include appropriate supportive care at the physician's discretion.

HOW IS THROMBOCYTOPENIA MANAGED?

Transient thrombocytopenia may occur with VELCADE treatment. Generally, platelet counts will drop during the dosing period (Days 1-11), with a return to baseline during the rest period (Days 12-21). There is no evidence of cumulative thrombocytopenia. There have been reports of gastrointestinal and intracerebral hemorrhage in association with thrombocytopenia induced by VELCADE.

VELCADE therapy should be held when the platelet count is <25,000/μl. Once toxicity has resolved, VELCADE may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose).

Platelet counts should be monitored prior to each dose of VELCADE. Observe patients for signs of thrombocytopenia during patient visits. Platelet transfusions may be utilized in cases of thrombocytopenia at the physician's discretion.

HOW IS PERIPHERAL NEUROPATHY ASSOCIATED WITH VELCADE MANAGED?

Treatment with VELCADE may be associated with a peripheral neuropathy that is predominantly sensory, although rare cases of mixed sensorimotor neuropathy have been reported. Patients with preexisting symptoms and/or signs of peripheral neuropathy may experience a worsening of the condition during treatment. Symptoms may improve or return to baseline in some patients upon discontinuation of VELCADE therapy. The complete time-course of this toxicity has not been fully characterized. Limited follow-up data regarding the outcome of peripheral neuropathy are available. Patients with pre-existing severe neuropathy should be treated with VELCADE only after careful risk/benefit assessment.

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Since peripheral neuropathy can be a dose-limiting side effect, patients should be frequently monitored for symptoms of neuropathy during VELCADE® (bortezomib) for Injection treatment, such as numbness, a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort or neuropathic pain. Early detection and appropriate dose/schedule modification may prevent the progression of neuropathy. Supportive care may be used at the physician's discretion.

Recommended dose modification for neuropathic pain and/or peripheral sensory neuropathy

Severity of peripheral neuropathy signs and symptoms	Modification of dose and regimen
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce VELCADE to 1.0 mg/m ²
Grade 2 with pain or Grade 3 (interfering with activities of living)	Withhold VELCADE therapy until toxicity resolves. When daily toxicity resolves reinstate with a reduced dose of VELCADE at 0.7 mg/m ² and change treatment schedule to once per week.
Grade 4 (permanent sensory loss that interferes with function)	Discontinue VELCADE

HOW ARE GASTROINTESTINAL EVENTS MANAGED?

Nausea, diarrhea, constipation, and vomiting may occur during treatment with VELCADE. The majority of gastrointestinal events are generally mild to moderate. Patients should be advised to maintain hydration, and should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

At the onset of Grade 3 non-hematological toxicities, including gastrointestinal events, therapy with VELCADE® should be held. Once toxicity has resolved, VELCADE may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose).

Management of gastrointestinal events associated with VELCADE treatment may include the administration of antiemetics and antidiarrheals. If the patient becomes dehydrated, administration of fluids and electrolytes is recommended.

DOES HYPOTENSION OCCUR WITH VELCADE?

Orthostatic/postural hypotension may occur throughout therapy with VELCADE.

At the onset of Grade 3 non-hematological toxicities, including hypotension, therapy with VELCADE should be held. Once toxicity has resolved, VELCADE may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose).

Caution should be used when treating patients with a history of syncope, patients receiving medications known to be associated with hypotension, or patients who are dehydrated.

Patients should be advised to maintain hydration, as well as to seek medical advice, if they experience symptoms of dizziness, light-headedness, or fainting spells. They should also be cautious when operating machinery, including automobiles.

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Management of hypotension related to VELCADE® (bortezomib) for Injection therapy may include the adjustment of antihypertensive medications, rehydration, and/or the administration of mineralocorticoids.

HOW IS NEUTROPENIA MANAGED?

Neutropenia may occur with VELCADE. The incidence of Grade 4 neutropenia was rare in clinical trials and febrile neutropenia was reported at < 1%.

At the onset of Grade 4 hematological toxicities, including neutropenia, therapy with VELCADE should be held. Once toxicity has resolved, VELCADE may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose).

The complete blood count (CBC) should be frequently monitored. Use of growth factors is at the physician's discretion.

REIMBURSEMENT/ SUPPORT

DOES VELCADE® OFFER A PATIENT ASSISTANCE PROGRAM?

The program is called the VELCADE Reimbursement Assistance Program. The program consists of coding and billing assistance, reimbursement information and coverage assistance, denials and appeals assistance and a patient assistance program.

The program is easily accessed through 1-866-VELCADE and is handled by Reimbursement Specialists. All registration can occur through the telephone and facsimile. Prospective and retrospective assistance is available.

WHERE CAN I GO FOR FURTHER SUPPORT OR INFORMATION ON VELCADE?

The VELCADE information line is staffed by professionals to answer all of your questions. Call toll-free: 1-866-VELCADE, 9 AM to 8 PM Eastern Time.

References: 1. Adams J, et al. Proteasome inhibitors: a novel class of potent and effective antitumor agents. *Cancer Res.* 1999;59:2615-2622. 2. Adams J, et al. Proteasome inhibition: a new strategy in cancer treatment. *Invest New Drugs.* 2000;18:109-121. 3. Glickman MH, et al. The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction. *Physiol Rev.* 2002;82:373-428. 4. Hideshima T, et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. *Cancer Res.* 2001;61(7):3071-3076. 5. Data on file, Millennium Pharmaceuticals, Inc. 6. National Cancer Institute Cancer Therapy Evaluation Program. Common Toxicity Criteria, Version 2.0, June 1, 1999.

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For more information call:

1.866.VELCADE

(1-866-835-2233)

9 AM to 8 PM Eastern Time

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Cambridge, MA 02139



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Printed in U.S.A.

V0063R1

04/04