Millennium: The Takeda Oncology Company 40 Landsdowne Street, Cambridge, Massachusetts 02139 USA phone 617.679.7000 fax 617.374.7788 www.millennium.com

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Dear Healthcare Professional:

Millennium: The Takeda Oncology Company, is pleased to inform you about important updates to the full Prescribing Information for VELCADE® (bortezomib) for Injection. The new label includes updated survival data at a median 36.7 months follow-up in patients with previously untreated multiple myeloma. In addition, the new label includes dose adjustments for patients with moderate to severe hepatic impairment.

VELCADE is indicated for the treatment of patients with multiple myeloma. VELCADE also is indicated for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

The following sections have been updated:

Clinical Trial Section 14.1 Randomized, Open-Label Clinical Study in Patients with Previously Untreated Multiple Myeloma now includes the following new text: *A later pre-specified analysis of overall survival (with median follow-up of 36.7 months) continued to show a statistically significant survival benefit for the VELCADE, Melphalan and Prednisone treatment arm despite subsequent therapies including VELCADE-based regimens.*
In addition, table 9 has been revised to include the updated overall survival data as shown below.

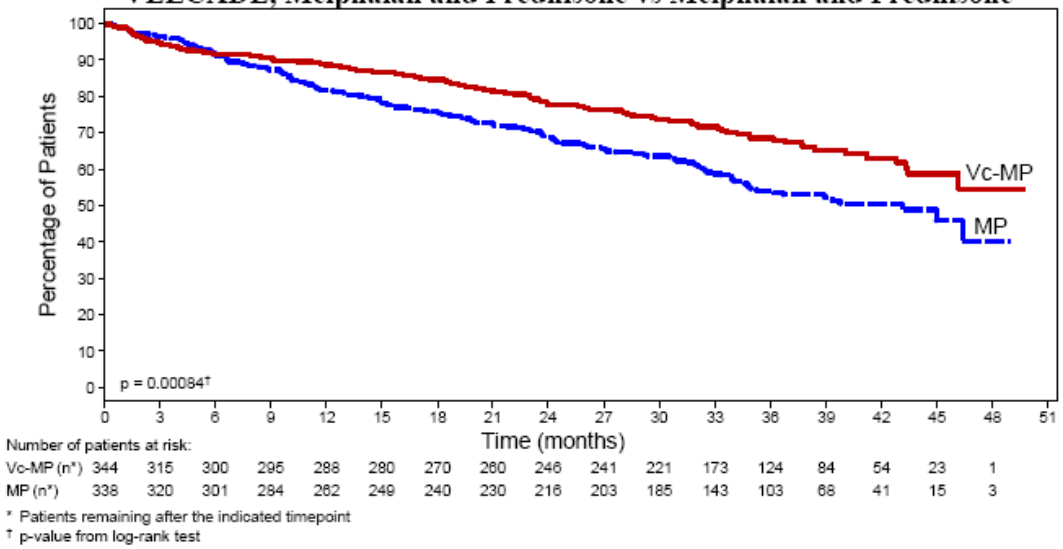
Table 9: Summary of Efficacy Analyses in the Previously Untreated Multiple Myeloma Study.

Efficacy Endpoint	VELCADE, Melphalan and Prednisone n=344	Melphalan and Prednisone n=338
Overall Survival		
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	

Figure 2 has also been updated with a revised Kaplan-Meier curve.

Overall survival was statistically significantly longer on the VELCADE, Melphalan and Prednisone arm (see Figure 2). (median follow up 36.7 months)

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



Section 2.5 Dosage in Patients with Hepatic Impairment has been added.
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/m^2 per injection during the first cycle, and a subsequent dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 may be considered based on patient tolerance (see Table 4).

Table 4: Recommended Starting Dose Modification for VELCADE in Patients with Hepatic Impairment

	Bilirubin Level	SGOT (AST) Levels	Modification of Starting Dose
Mild	≤ 1.0x ULN	> ULN	None
	> 1.0x–1.5x ULN	Any	None
Moderate	> 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	> 3x ULN	Any	

Abbreviations: SGOT = serum glutamic oxaloacetic transaminase;
AST = aspartate aminotransferase; ULN = upper limit of the normal range.

5.11 Patients with Hepatic Impairment now reads: *Bortezomib is metabolized by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with VELCADE at reduced starting doses and closely monitored for toxicities.*

8.7 Patients with Hepatic Impairment now reads: *The exposure of bortezomib is increased in patients with moderate and severe hepatic impairment. Starting dose should be reduced in those patients.*

12.3 Pharmacokinetics: Hepatic Impairment has been updated to read: *The effect of hepatic impairment on the pharmacokinetics of bortezomib was assessed in 51 cancer patients at bortezomib doses ranging from 0.5 to 1.3 mg/m^2. When compared to patients with normal hepatic function, mild hepatic impairment did not alter dose-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.*

Please see the enclosed new VELCADE full Prescribing Information. The full Prescribing Information can also be accessed at www.VELCADE.com or through your local VELCADE oncology sales representative.

IMPORTANT SAFETY INFORMATION FOR VELCADE

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

WARNINGS AND PRECAUTIONS:
VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic therapy. Complete blood counts (CBC) should be monitored frequently during treatment with VELCADE.

Pregnancy Category D: Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE.

Peripheral Neuropathy: VELCADE treatment causes a peripheral neuropathy that is predominantly sensory. However, cases of severe sensory and motor peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening peripheral neuropathy (including ≥Grade 3) during treatment with VELCADE. Patients should be monitored for symptoms of neuropathy, such as a burning sensation, hyperesthesia, hypoesthesia, paresthesia, discomfort, neuropathic pain or weakness. Patients experiencing new or worsening peripheral neuropathy may require change in the dose and schedule of VELCADE. The long-term outcome of peripheral neuropathy has not been studied in mantle cell lymphoma.

Hypotension: Hypotension (postural, orthostatic, and hypotension NOS) has been 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.

Cardiac Disorders: Acute development or exacerbation of congestive heart failure and new onset of decreased left ventricular ejection fraction have been reported, including reports in patients with no risk factors for decreased left ventricular ejection fraction. Patients with risk factors for, or who have existing heart disease should be closely monitored. There have been isolated cases of QT-interval prolongation in clinical studies; causality has not been established.

Pulmonary Disorders: There have been reports of acute diffuse infiltrative pulmonary disease of unknown etiology such as pneumonitis, interstitial pneumonia, lung infiltration and Acute Respiratory Distress Syndrome (ARDS) in patients receiving VELCADE. Some of these events have been fatal. There have been reports of pulmonary hypertension associated with VELCADE administration in the absence of left heart failure or significant pulmonary disease.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): There have been reports of RPLS in patients receiving VELCADE. RPLS is a rare, reversible, neurological disorder which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances.

Gastrointestinal Adverse Events: VELCADE treatment can cause nausea, diarrhea, constipation, and vomiting sometimes requiring use of antiemetic and antidiarrheal medications. Ileus can occur. Fluid and electrolyte replacement should be administered to prevent dehydration.

Thrombocytopenia/Neutropenia: VELCADE is associated with thrombocytopenia and neutropenia. Platelet counts should be monitored prior to each dose of VELCADE. Patients experiencing thrombocytopenia may require change in the dose and schedule of VELCADE. There have been reports of gastrointestinal and intracerebral hemorrhage in association with VELCADE. Transfusions may be considered.

Tumor Lysis Syndrome: Because VELCADE is a cytotoxic agent and can rapidly kill malignant cells, the complications of tumor lysis syndrome may occur.

Hepatic Events: Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions.

Patients with Hepatic Impairment: VELCADE exposure is increased in patients with moderate or severe hepatic impairment. These patients should be treated with VELCADE at reduced starting doses and closely monitored for toxicities.

ADVERSE EVENT DATA:

- **Previously Untreated MM:** In the phase 3 VELCADE with melphalan and prednisone study, 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%), vomiting (33% vs 16%), pyrexia (29% vs 19%), fatigue (29% vs 26%), lymphopenia (24% vs 17%), anorexia (23% vs 10%), asthenia (21% vs 18%), cough (21% vs 13%), insomnia (20% vs 13%), and edema peripheral (20% vs 10%).
- **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%), anemia (29%), edema (23%), headache, paresthesia and dysesthesia (each 22%), dyspnea (21%), and cough and insomnia (each 20%). Twenty percent (20%) of patients experienced at least 1 episode of ≥Grade 4 toxicity, most commonly thrombocytopenia (5%) and neutropenia (3%).

  In the integrated analysis, 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%).

DRUG INTERACTIONS: 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.

USE IN SPECIFIC POPULATIONS:

Nursing Mothers: It is not known whether bortezomib is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from VELCADE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of VELCADE in children has not been established.

Patients with Renal Impairment: Dosing adjustments of VELCADE are not necessary for patients with renal insufficiency. In patients undergoing dialysis, VELCADE should be administered after the dialysis procedure.

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

For more information on VELCADE® (bortezomib) for Injection, including the Reimbursement Assistance Program, call toll-free, 1-866-VELCADE.

Yours sincerely,

Dixie-Lee Esseltine, MD, FRCPC
Vice President, Global Medical Affairs
Millennium: The Takeda Oncology Company