August 8, 2014

Subject: FDA Approves VELCADE® (bortezomib) Retreatment in Patients with Multiple Myeloma

Dear Healthcare Professional:

VELCADE (bortezomib) is the only FDA-approved agent to deliver an overall survival (OS) advantage in previously untreated and relapsed multiple myeloma. With over 10 years of clinical experience and 550,000 patients treated worldwide, the body of evidence for VELCADE continues to evolve with the addition of data supporting the benefit of retreatment in relapsed multiple myeloma.

Millennium: The Takeda Oncology Company is pleased to announce a label update that includes evidence and dosing guidelines supporting retreatment with VELCADE in relapsed multiple myeloma. VELCADE retreatment may be considered for patients with multiple myeloma who have previously responded to treatment with VELCADE and who have relapsed at least 6 months after completing prior VELCADE treatment. Retreatment may be started at the last tolerated dose.

This update is consistent with NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for the treatment of relapsed multiple myeloma, which includes:

If the relapse occurs at greater than 6 months after completion of the initial primary therapy, patients may be retreated with the same primary regimen.

RETRIEVE trial information

The updated information in the Prescribing Information is based on findings from the RETRIEVE clinical trial.

RETRIEVE, a single arm, open-label study, evaluated the efficacy and safety of retreatment with intravenous (IV) VELCADE (N=130). Patients with multiple myeloma who had previously achieved ≥PR on a VELCADE-containing regimen (median of 2 prior lines of therapy [range: 1-7]) and progressed ≥6 months after completing that regimen were retreated with IV VELCADE±dexamethasone. Patients received VELCADE on days 1, 4, 8, and 11 q 3 weeks for 24 weeks. The primary endpoint was best confirmed response to treatment as assessed by European Group for Blood and Marrow Transplantation criteria.

Patients retreated with VELCADE demonstrated a 38.5% ORR (95% CI, 30.1-47.4; 49/50 PR) and a duration of response of 6.5 months (range: 0.6 to 19.3 months). The safety profile demonstrated in the RETRIEVE trial was consistent with the well-characterized safety profile of IV VELCADE in relapsed multiple myeloma. Of note, no cumulative toxicities were observed with VELCADE retreatment.

The most common adverse drug reaction was thrombocytopenia, which occurred in 52% of patients (grade ≥3: 24%). Peripheral neuropathy was experienced by 28% of patients (grade ≥3: 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%). In total, 2 patients (2%) died and the cause of death was considered by the investigator to be related to study drug, including reports of sepsis and cerebrovascular accident.

Dosing guidelines for retreatment with VELCADE

Retreated patients may be started on VELCADE twice weekly (days 1, 4, 8, and 11) at the last tolerated dose every 3 weeks for a maximum of 8 cycles (24 weeks). 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.

INDICATIONS AND IMPORTANT SAFETY INFORMATION FOR VELCADE® (bortezomib)

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 (not including local reactions) to bortezomib, boron, or mannitol, including anaphylactic reactions. VELCADE is contraindicated for intrathecal administration. Fatal events have occurred with intrathecal administration of VELCADE.

Please see Important Safety Information continued on page 2 and accompanying full Prescribing Information, also available at VELCADE-hcp.com.
IMPORTANT SAFETY INFORMATION FOR VELCADE® (bortezomib) (continued)

WARNINGS AND PRECAUTIONS: VELCADE (bortezomib) is for subcutaneous or IV administration only. Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

▼ 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: Caution should be used when treating patients receiving antihypertensives, those with a history of syncope, and those who are dehydrated.

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

▼ Pulmonary toxicity: Acute respiratory distress syndrome (ARDS) and acute diffuse infiltrative pulmonary disease of unknown etiology have occurred (sometimes fatal). Pulmonary hypertension, in the absence of left heart failure or significant pulmonary disease, has been reported. In the event of new or worsening cardiopulmonary symptoms, consider interrupting VELCADE until a prompt and comprehensive diagnostic evaluation is conducted.

▼ Posterior reversible encephalopathy syndrome has occurred. Consider MRI imaging for onset of visual or neurological symptoms; discontinue VELCADE if suspected.

▼ Gastrointestinal toxicity, including nausea, diarrhea, constipation, and vomiting, has occurred and may require use of antiemetic and antidiarrheal medications or fluid replacement. Interrupt VELCADE for severe symptoms.

▼ Thrombocytopenia/Neutropenia: Manage with dose and/or schedule modifications. Complete blood counts should be monitored frequently during treatment. There have been reports of gastrointestinal and intracerebral hemorrhage. Transfusions may be considered.

▼ Tumor lysis syndrome: Closely monitor patients with high tumor burden and take appropriate precautions.

▼ Hepatic toxicity: Monitor hepatic enzymes during treatment. Upon occurrence, interrupt therapy with VELCADE to assess reversibility.

▼ Embryo-fetal risk: Women should avoid breast-feeding or becoming pregnant while on VELCADE.

▼ Patients with diabetes may require close monitoring and adjustment of the antidiabetic medications.

DRUG INTERACTIONS: Closely monitor patients receiving VELCADE (bortezomib) in combination with strong CYP3A4 inhibitors. Avoid concomitant use of strong CYP3A4 inducers.

ADVERSE REACTIONS

▼ Previously untreated multiple myeloma (MM): In the phase 3 study of VELCADE administered intravenously with melphalan and prednisone (MP) vs MP alone, the most commonly reported adverse reactions (ARs) were thrombocytopenia (48% vs 42%), neutropenia (47% vs 42%), peripheral neuropathy (46% vs 1%), nausea (39% vs 21%), diarrhea (35% vs 6%), neuralgia (34% vs <1%), anemia (32% vs 46%), and leukopenia (32% vs 28%).

▼ Relapsed MM and mantle cell lymphoma: In the integrated analysis of 1163 patients in phase 2 and 3 studies of VELCADE administered intravenously, the most commonly reported ARs were nausea (49%), diarrhea NOS (46%), fatigue (41%), peripheral neuropathy NEC (38%), and thrombocytopenia (32%). A total of 26% of patients experienced serious ARs. The most commonly reported serious ARs included diarrhea, vomiting, and pyrexia (each 3%); nausea, dehydration, and thrombocytopenia (each 2%); and pneumonia, dyspnea, peripheral neuropathies NEC, and herpes zoster (each 1%).

▼ Relapsed MM subcutaneous vs IV: In the phase 3 study of VELCADE administered subcutaneously vs intravenously in relapsed MM, safety data were similar between the two treatment groups. The most commonly reported ARs in the subcutaneous vs IV treatment groups were peripheral neuropathy (37% vs 50%) and thrombocytopenia (30% vs 34%). The incidence of serious ARs was similar in the subcutaneous treatment group (20%) and the IV treatment group (19%). The most commonly reported serious ARs were pneumonia and pyrexia (each 2%) in the subcutaneous treatment group and pneumonia, diarrhea, and peripheral sensory neuropathy (each 3%) in the IV treatment group.

Please see accompanying full Prescribing Information, also available at VELCADE-hcp.com.
Please see full Prescribing Information at
velcade.com/Files/PDFs/VELCADE_PREScribing_INFORMATION.pdf