October 8, 2014

Subject: FDA Approves VELCADE® (bortezomib)+R-CAP for Previously Untreated Mantle Cell Lymphoma (MCL)

Dear Healthcare Professional:

Millennium: The Takeda Oncology Company is pleased to announce that VELCADE in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) is now approved for patients with previously untreated MCL. VR-CAP is the first and only FDA-approved regimen for the treatment of patients with previously untreated MCL.

Phase 3 head-to-head trial comparing VR-CAP with R-CHOP

In a randomized, open-label, phase 3 study of VR-CAP vs rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (N=487):

- Replacing vincristine with VELCADE (bortezomib) delivered an 11-month progression-free survival (PFS) advantage (40-month median follow-up: 25 months vs 14 months; HR=0.63; 95% CI, 0.50-0.79; p<0.001)
- In addition, while overall response rates were similar between the 2 treatment groups (88% vs 85%, respectively), using VELCADE resulted in a higher rate of complete response (CR) vs R-CHOP (44% vs 34%, respectively)*
- Thrombocytopenia and neutropenia were transient and cyclical with VR-CAP. The cyclical pattern of platelet and neutrophil decreases and recovery remained consistent with other studies of VELCADE, with no evidence of cumulative thrombocytopenia or neutropenia in the treatment regimens studied
- The incidence of peripheral neuropathy was similar between the 2 treatment arms (30% with VR-CAP vs 27% with R-CHOP)

This study evaluated safety and efficacy in patients with previously untreated MCL (stage II, III, or IV) who were ineligible or not considered for bone marrow transplantation. The primary endpoint was PFS as assessed by an independent radiology review committee. Patients received six 21-day cycles of intravenous (IV) VELCADE (1.3 mg/m²) on days 1, 4, 8, and 11 (rest days 12 through 21); rituximab, cyclophosphamide, and doxorubicin on day 1; and prednisone on days 1 through 5. For patients with a response first documented at cycle 6, two additional treatment cycles were allowed. The 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 patients in the VR-CAP group receiving up to 2 additional cycles.

In the phase 3 study of VR-CAP vs R-CHOP, the most commonly reported ARs were neutropenia (87% vs 71%), thrombocytopenia (72% vs 17%), leukopenia (48% vs 36%), anemia (44% vs 29%), lymphopenia (28% vs 12%), peripheral neuropathy (30% vs 27%), diarrhea (25% vs 5%), nausea (23% vs 12%), and pyrexia (20% vs 10%).

A total of 38% of patients in the VR-CAP group experienced serious ARs vs 30% of patients in the R-CHOP group. The most commonly reported serious ARs included febrile neutropenia (11% vs 8%), pneumonia (8% vs 3%), neutropenia (5% vs 5%), and pyrexia (4% vs 2%), respectively.1 All of the ≥grade 3 bleeding events resolved without sequelae in the VR-CAP arm.

The incidence of bleeding events (≥grade 3) was similar between the VR-CAP and R-CHOP arms (1% and <1%, respectively). Febrile neutropenia was also observed (17% and 14%, respectively; all grades). Myeloid growth factor support was provided at a rate of 78% in the VR-CAP arm and 61% in the R-CHOP arm.

The incidence of herpes zoster reactivation was 4.6% in the VR-CAP arm and 0.8% in the R-CHOP arm. Antiviral prophylaxis was mandated by protocol amendment.

Discontinuations due to ARs were 8% with VR-CAP and 6% with R-CHOP. The most common AR leading to discontinuation in the VR-CAP arm was peripheral neuropathy (1%; 3 patients). The most common AR leading to discontinuation in the R-CHOP arm was febrile neutropenia (<1%; 2 patients).

Dosing guidelines for previously untreated mantle cell lymphoma

VR-CAP is administered for 6 three-week cycles each of 21 days in duration. VELCADE® (bortezomib) (1.3 mg/m²) is administered intravenously twice weekly on days 1, 4, 8, and 11 (rest days 12-21); rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), and doxorubicin (50 mg/m²) are on day 1 and prednisone (100 mg/m²) orally on days 1 through 5 of each 3-week cycle. For patients with a response first documented at cycle 6, two additional VR-CAP cycles are recommended. At least 72 hours should elapse between consecutive doses of VELCADE.

Dose modification guidelines for VR-CAP

Prior to the first day of each VR-CAP cycle (other than cycle 1): platelet count should be at least 100 × 10⁹/L and absolute neutrophil count should be at least 1.5 × 10⁹/L; hemoglobin should be at least 8 g/dL (at least 4.96 mmol/L); and nonhematologic toxicity should have recovered to grade 1 or baseline. Interrupt VELCADE treatment at the onset of grade 3 hematologic or nonhematologic toxicities. Please see full Prescribing Information for recommended dose modifications, including modifications for neuropathy and hepatic impairment.

Please see Important Safety Information continued on page 2 and accompanying full Prescribing Information, also available at VELCADE-hcp.com.
INDICATION: VELCADE (bortezomib) is indicated for the treatment of patients with mantle cell lymphoma.

IMPORTANT SAFETY INFORMATION FOR VELCADE® (bortezomib)

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.

WARNINGS AND PRECAUTIONS: VELCADE 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. Isolated 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 in combination with strong CYP3A4 inhibitors. Avoid concomitant use of strong CYP3A4 inducers.

ADDITIONAL ADVERSE REACTIONS

- **Relapsed mantle cell lymphoma**: In the phase 2 study of VELCADE in patients with relapsed mantle cell lymphoma who had received at least 1 prior therapy (N=155), the most commonly reported ARs were peripheral neuropathy NEC (54%), fatigue (52%), diarrhea NOS (39%), nausea (36%), constipation (34%), and vomiting and rash NOS (23% each).

*The response criteria used to assess efficacy were based on the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (IWRC).*

Please see accompanying full Prescribing Information, also available at VELCADE-hcp.com.

For additional information, call 1-866-VELCADE or contact your Millennium representative.

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