Submitted by:
Deya Corzo, MD
Senior Medical Director, Global Medical Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139
Tel: (617) 551-3870
Email: Deya.Corzo@mpi.com
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NCCN Guidelines Panel: Multiple Myeloma

On behalf of Millennium Pharmaceuticals, Inc., I respectfully request the NCCN Multiple Myeloma Guidelines Panel to review the enclosed data on the use of VELCADE® (bortezomib) in patients with multiple myeloma.

Specific Changes: Inclusion of a specific footnote in the Myeloma Therapy section in the updated NCCN Clinical Practice Guidelines for Multiple Myeloma, indicating that bortezomib may be administered either as a bolus intravenous injection or by subcutaneous injection, with a Category 1 level of recommendation. We believe that these findings also warrant inclusion in the narrative section of the Guidelines.

FDA Clearance: FDA has approved VELCADE for the treatment of multiple myeloma; the recommended dose of VELCADE is 1.3 mg/m^2 administered as a 3 to 5 second bolus intravenous injection. FDA has not approved subcutaneous injection as an alternative route of administration. Please refer to the enclosed prescribing information for the full FDA-approved indications and safety information.

Rationale: Results from the Phase 3 MMY-3021 study of subcutaneous versus intravenous administration of VELCADE were recently presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) in Orlando, Florida, in December 2010.[1] Study results included the following:

- The primary objective was to demonstrate the non-inferiority of subcutaneous versus intravenous administration of VELCADE in patients with relapsed multiple myeloma following 1–3 prior lines of therapy, in terms of overall response rate after 4 cycles of therapy; this rate was 42% in both arms, clearly demonstrating the primary hypothesis.
- After 8 cycles of therapy, the overall response rate was 52%, including 25% very good partial response or better, in both arms; there were also no differences in duration of response, time to progression, and overall survival.
- Pharmacokinetic and pharmacodynamic studies demonstrated equivalent systemic exposure and comparable proteasome inhibition with subcutaneous and intravenous administration.
- Subcutaneous administration appeared associated with an improved safety profile, including significantly lower rates of peripheral neuropathy.

These findings are supported by data from an earlier phase 1 study (CAN-1004).[2]

The following enclosures are included for your review (copyright-paid where applicable):

- Moreau P, Pylypenko HV, Grosicki S, et al. A phase 3 prospective randomized international study (MMY-3021) comparing subcutaneous and intravenous administration of bortezomib in patients with relapsed multiple myeloma. Presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) in Orlando, FL; December 4–7, 2010. Oral presentation, abstract #312.

- Moreau P, Coiteux V, Hulin C, et al. Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma. *Haematologica*. 2008;93(12):1908-1911.
- VELCADE prescribing information.

Cited references:

1. Moreau P, Pylypenko HV, Grosicki S, et al. A phase 3 prospective randomized international study (MMY-3021) comparing subcutaneous and intravenous administration of bortezomib in patients with relapsed multiple myeloma. Presented at the 52nd Annual Meeting of the American Society of Hematology (ASH) in Orlando, FL; December 4–7, 2010. Oral presentation, abstract #312.
2. Moreau P, Coiteux V, Hulin C, et al. Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma. *Haematologica*. 2008;93(12):1908-1911.

Yours sincerely

Deya Corzo, MD
Senior Medical Director, Global Medical Affairs