On behalf of Millennium: The Takeda Oncology Company, I respectfully request the NCCN Multiple Myeloma Guidelines Panel to review the enclosed data on the use of VELCADE® (bortezomib) as maintenance therapy in patients with previously untreated multiple myeloma.

**Specific Changes:**
Inclusion of new data from studies employing bortezomib-based maintenance in the Myeloma Therapy section (MYEL-D, 1 of 2) of the NCCN Clinical Practice Guidelines (NCCN Guidelines™) in Multiple Myeloma (version V2.2013), specifically inclusion of:

- Bortezomib + thalidomide for maintenance therapy
- Bortezomib + prednisone for maintenance therapy.

In addition, inclusion of these new data and associated references are warranted within the narrative section of the Guidelines, specifically on pages MS-23–24 of version V2.2013, where the current data on bortezomib as maintenance therapy are included.

**FDA Clearance:** The FDA has approved VELCADE for the treatment of multiple myeloma. The US Prescribing Information describes a standard schedule and a maintenance schedule, albeit a different schedule than the studies described in this document. Data from the studies referenced below are not included in the US Prescribing Information for VELCADE.

**Rationale:** Data on post-transplant maintenance therapy with bortezomib-thalidomide (VT), thalidomide alone, or alfa-2b-interferon were published on August 23, 2012 in Blood, and updated data were presented at the 2012 Annual Meeting of the American Society of Hematology (ASH), from the Spanish GEM05MENOS65 phase III randomized trial. Results showed that:

- At the updated presentation, maintenance with VT increased the post-transplant complete response (CR) rate by 21%, compared with thalidomide or alfa-2b-interferon maintenance, which each increased the CR rate by 15%
- After a median follow-up of 34.9 months, PFS from start of maintenance was significantly longer with VT vs thalidomide vs alfa-2b-interferon (p=0.0009); there was no significant difference in overall survival (OS) (p=0.47)
- Rates of grade 3–4 thrombocytopenia were 10% vs 2% with VT vs thalidomide (p=0.01)
- In the VT, thalidomide, and alfa-2b-interferon arms, rates of grade 3 peripheral neuropathy (PN) were 15%, 14%, and 0, respectively.

Final data from the Spanish GEM2005MAS65 phase III randomized trial in transplant-ineligible patients were published on September 27, 2012 in Blood, including findings from the second randomization post-bortezomib-based induction, at which 178 patients were assigned to maintenance with VT or bortezomib-prednisone (VP). Results showed that:

- After a median of 38 months from the start of maintenance with VT or VP, the overall CR rate increased from 24% post-induction to 42% (VT: 46%, VP: 39%; difference not significant)
Depth of response improved in 33 (19%) patients (VT: 19, VP: 14), including 10 improvements from near-CR (nCR) to CR, and 17 from partial response (PR) to nCR (n=7) or CR (n=10).

After a median follow-up of 46 months from initial randomization to induction therapy, median PFS among all patients receiving maintenance was 35 months (VT: 39 months, VP: 32 months; p=0.1), and the 5-year OS rate was 58% (VT: 69%, VP: 50%; p=0.1).

PFS was significantly longer in patients who achieved CR vs nCR vs PR (median 54 months vs 39 months vs 24 months, respectively; hazard ratio [HR]=1.73, p<0.0001), and this translated into a significantly higher 5-year OS rate (78% vs 59% vs 54%, respectively; HR=1.5, p<0.0001).

1 patient in the VT arm had grade 3–4 neutropenia.

Rates of non-hematologic grade 3–4 adverse events with VT vs VP were 17% vs 5% (p=0.009), including 9% vs 3% grade 3–4 PN.

The following enclosures are submitted in support of the above proposed changes:

- Mateos M-V et al. Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial. Blood 2012;120(13):2581–8
- VELCADE (bortezomib) for Injection. United States prescribing information, Rev 15, issued October 2012.

Yours sincerely

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