DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-602/S-015

Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

Attention: Tanya Lewis, MS
Sr. Director, Regulatory Affairs

Dear Ms. Lewis:

Please refer to your supplemental new drug application dated December 20, 2007, received December 20, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Velcade® (bortezomib) for Injection, single use vial, 3.5 mg.

We acknowledge receipt of your submissions dated January 15, January 30, March 14, March 19, March 21, April 4, April 16, April 23, April 24, April 29, May 12, May 22, May 28, and June 19, 2008(electronic).

This supplemental new drug application provides for the use of Velcade® (bortezomib) for Injection, single use vial, 3.5 mg to treat patients with multiple myeloma.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-602/S-015**." Approval of this submission by FDA is not required before the labeling is used.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt and verification, we will transmit that version to the National Library of Medicine for public dissemination.

We have received your submission dated June 8, 2006, regarding the following postmarketing commitment:

4. Conduct additional investigations of the cardiovascular effects of bortezomib at acutely toxic doses that explore bortezomib induced lethality at 12–14 hours post-dose. Studies should be conducted in a species that most closely models the human response. An investigational study in cynomolgus monkeys would be appropriate, with a focus on potential interventions that could both explore mechanisms of cardiovascular effects and possible clinically relevant interventional therapies. Study protocols may be submitted to the Division for review prior to the conduct of the study. (This study will be completed in the second quarter of 2004.)

We have received your submissions dated March 30, 2007 and June 04, 2007, reporting on the following postmarketing commitments:

11. Conduct PK and PK/PD (pharmacokinetics/pharmacodynamics) studies to examine the potential for drug-drug interactions between bortezomib and drugs that are inhibitors (e.g., ketoconazole), or inducers (e. g., rifampin) of cytochrome P450 3A4. You should also collect adverse reactions noted in this study and evaluate any relationship between plasma levels and adverse reactions. (The draft protocol for this study will be submitted to the Agency for review in the third quarter of 2003.)

We have reviewed your submissions and have concluded that the above commitments were fulfilled.

We remind you of your open postmarketing study commitment #7 agreed upon in your submission dated May 13, 2003:

7. As bortezomib is metabolized and eliminated by the liver, a pharmacokinetic and pharmacokinetic/safety (PK and PK/Safety) study should be conducted in patients with hepatic impairment to provide dosing recommendations for this patient population. (A draft protocol will be submitted to the Agency for review in the fourth quarter of 2003. It is anticipated that this study will take approximately 12 months from initial patient enrollment to completion. A final Clinical Pharmacology report will be made available to the Agency within 3 months of clinical study completion.)

   Protocol Submission: November 13, 2003
   Study Start: February 13, 2004
   Final Report Submission: July 13, 2005

Submit clinical protocols to your IND for this product. Submit non-clinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Kim J. Robertson, Consumer Safety Officer, at (301) 796-1441.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, M.D.
Deputy Division Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure (label)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Farrell

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