DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-602/S-006

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

Attention: Renu Vaish, M.S.
Associate Director, Oncology Regulatory Affairs

Dear Ms. Vaish:

Please refer to your supplemental new drug application dated September 27, 2004, received September 28, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Velcade (bortezomib) for Injection 3.5mg.

We acknowledge receipt of your submissions dated November 16, 2004; February 2, 7, 11, 23, and 25; March 12, 17, 18, 23, and 24, 2005.

This supplemental new drug application provides for the use of Velcade (bortezomib) for Injection for treatment of multiple myeloma patients who have received as least one prior therapy.

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 submitted March 24, 2005.

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 21-029/S-006**." Approval of this submission by FDA is not required before the labeling is used.

We approved this NDA under the regulations at 21 CFR 314 Subpart H for accelerated approval of new drugs for serious or life-threatening illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 314.510.

1. Provide complete study reports on the following ongoing studies:

    a. Study 039: "An International, Multi-center, Randomized, Open-label Study of PS-341 Versus High Dose Dexamethasone in Patients with Relapsed or Refractory Multiple

Myeloma" (This study report will be submitted to the Agency in the second quarter of 2005.)

b. Study 029: "A Phase II Open-Label, Extension Study to Provide PS-341 to Patients Who Previously Participated in a PS-341 Clinical Study and Who may Benefit from Re-Treatment with or Continuation of PS-341 Therapy" (This study report will be submitted to the Agency in the first quarter of 2004.)

2. Initiate and complete a study in previously untreated multiple myeloma patients comparing VELCADE alone, high-dose dexamethasone alone and combination of VELCADE plus high-dose dexamethasone. (It is anticipated that this study will be initiated in the third quarter of 2005.)

3. Provide follow up information to characterize the frequency, severity, and reversibility of the peripheral neuropathy on study 025, 029, and the current VELCADE myeloma protocol study 039. (The data for studies 025 and 029 will be submitted to the Agency in the first quarter of 2004. The data for study 039 will be submitted to the Agency in the second quarter of 2005.)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

We remind you of your postmarketing study commitments in your submission dated May 20, 2003. These commitments are listed below.

1. 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.)
   Protocol Submission: Within 3 months of the date of this letter
   Study Start: Within 5 months of the date of this letter
   Final Report Submission: Within 12 months of the date of this letter

Clinical Pharmacology and Biopharmaceutics:

3. Conduct a study to characterize the pharmacokinetics (PK) of bortezomib as a single agent at 1.3 and 1.0 mg/m^2 twice weekly in at least 12 multiple myeloma patients at each dose level. Patients should have normal to mildly decreased creatinine clearance value (≥50 mL/min). The pharmacokinetics should be characterized both at Cycle 1 and at a subsequent cycle to address the time dependent changes in the PK of bortezomib as a single agent. (This protocol will be submitted to the Agency for review in the fourth quarter of 2003.)
   Protocol Submission: Within 6 months of the date of this letter
   Study Start: Within 9 months of the date of this letter
   Final Report Submission: Within 22 months of the date of this letter

4. 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: Within 6 months of the date of this letter
   Study Start: Within 9 months of the date of this letter
   Final Report Submission: Within 26 months of the date of this letter

5. Conduct a study to evaluate the PK and PK/Safety of bortezomib in patients with advanced malignancies and varying degrees of renal dysfunction. (The projected clinical completion time for this study is second quarter 2004. Therefore, it is anticipated that the Clinical Pharmacology report will be (b)(4) vailable in September 2004.)
   Protocol Submission: --------Study 5874
   Study Start: May 12, 2003
   Final Report Submission: Within 16 months of the date of this letter

8. Conduct a PK and PK/PD (pharmacokinetics/pharmacodynamics) study to examine the potential drug-drug interactions between bortezomib and a drug that is an of cytochrome P450 3A4 inhibitor (e.g., antifungal agents or antibiotics that are potent inhibitors of CYP 3A4). You should also collect the adverse reactions noted in the 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.)
   Protocol Submission: Within 6 months of the date of this letter
   Study Start: Within 10 months of the date of this letter
   Final Report Submission: Within 25 months of the date of this letter

Submit clinical protocols to your IND for this product. Submit nonclinical 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**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product(s). Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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, HFD-410
FDA
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 Sean Bradley, R.Ph., Regulatory Project Manager, at (301) 594-5770.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Package Insert Labeling

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

/s/

Richard Pazdur
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