DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-602

Millennium Pharmaceuticals, Inc.
75 Sidney Street
Cambridge, MA 02139

Attention: Tanya Lewis, M.S.
Senior Manager, Worldwide Regulatory Affairs

Dear Ms. Lewis:

Please refer to your new drug application (NDA) dated January 21, 2003 received January 21, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Velcade (bortezomib) for Injection 3.5 mg.

We acknowledge receipt of your submissions dated December 31, 2002; January 22 and 29; February 7, 26, and 27; March 5,17, 24, 26(2), 27, and 31; April 1, 4(2), 7, 8(2), 10(2), 16(3), 17, 18, 24(2), and 25; May 1, 6(2), and 12, 2003.

This new drug application provides for the use of Velcade (bortezomib) for Injection for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

We completed our review of this application, as amended, according to the regulations for accelerated approval. It is approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), and immediate container and carton labels submitted January 21, 2003. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and (an) unapproved new drug.

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 ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-602**." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study commitments specified in your submission dated May 12, 2003. These commitments, along with any completion dates agreed upon, are listed below.

Clinical:

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.)

Nonclinical Pharmacology/Toxicology:

Additional non-clinical studies are warranted given the undefined etiology of cardiovascular effects seen in multiple animal studies, as well as the occurrence of cardiovascular adverse events in patients.

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.)

5. Conduct an additional *in vitro* study in mammalian cells transfected with the normal PrP gene to determine if pharmacologically relevant concentrations of bortezomib result in the accumulation of normal, misfolded, or detergent insoluble and proteinase resistant forms of PrP protein in the cytosol, similar to results obtained with other proteasome inhibitors as reported by Ma and Lindquist, 2002. As appropriate, further investigations should be undertaken to understand the implications of any observed effects. (We understand that you cannot commit to a completion date at this time because you will not have complete control over the conduct of the study.)

Clinical Pharmacology and Biopharmaceutics:

6. 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.)

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.)

8. 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 made available in September 2004.)

9. Conduct a study to evaluate the inhibition potential of bortezomib for CYP 3A4 using human liver microsomes with optimal midazolam concentration. If bortezomib significantly inhibits CYP 3A4 in the *in vitro* study, you may need to conduct a clinical drug interaction study to evaluate the interaction between bortezomib and midazolam or other CYP 3A4 substrate. (The protocol for the study to evaluate the inhibition potential of bortezomib for CYP 3A4 using human liver microsomes will be submitted to the Agency for review in the third quarter of 2003. It is anticipated that the final report will be submitted to the Agency in the fourth quarter of 2003. The protocol for the *in vitro* study to evaluate the inhibition of CYP 3A4 by bortezomib will be submitted to the Agency for review in the third quarter of 2003. It is anticipated that the final study report will be submitted to the Agency in the fourth quarter of 2003.)

10. Evaluate the contribution of cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2 in the metabolism of bortezomib using *in vitro* systems (microsomes, hepatocytes, liver, tissues,

etc.). Based on the results of the study, additional drug-drug interaction studies may be required. (A protocol for this study will be submitted in the third quarter of 2003. It is anticipated that the final study report will be submitted in the fourth quarter of 2003.)

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.)

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing study commitments must be clearly designated "Subpart H Postmarketing Study Commitments."

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 Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

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

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the 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}

Robert Temple, M.D.
Office Director
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Temple

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