DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-602/S-008, S-009

Millennium Pharmaceuticals
40 Landsdowne Street
Cambridge, MA 02139

Attention:
Tanya Lewis, M.S.
Associate Director, Regulatory Affairs

Dear Ms. Lewis:

Please refer to your supplemental new drug applications dated November 11, 2005 (S008), received November 14, 2005, and March 22, 2006 (S009), received March 23, 2006 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 submission dated March 30, 2006.

These supplemental new drug applications provide safety information to strengthen and clarify the PRECAUTIONS section and the OVERDOSAGE section and include the addition of safety terms that are consistent and harmonized with the Core Data sheet for Velcade. We note that S008 was submitted as a Prior Approval supplement and S009 as a "Changes Being Effected" supplement.

We have completed our review of these applications, as amended. S009 is approved, effective on the date of this letter, for use as recommended in the attached agreed-upon labeling text. S008 has been superseded by S009 and will be retained in your file.

Please note the following additional revisions to the OVERDOSAGE section which were agreed upon and should be implemented at the next printing of the package insert.

> In humans, fatal outcomes followed the administration of more than twice the recommended therapeutic dose and were associated with the acute onset of symptomatic hypotension and thrombocytopenia.
>
> Studies in monkeys and dogs showed that IV bortezomib doses as low as 2 times the recommended clinical dose on a mg/m2 basis were associated with increases in heart rate, decreases in contractility, hypotension, and death. In the dog studies, a slight increase in the corrected QT interval was observed at doses resulting in mortality. In monkeys, doses of 3.0 mg/m2 and greater (approximately twice the recommended clinical dose) resulted in hypotension starting at 1 hour post-administration, with progression to death in 12 to 14 hours following drug administration.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert and/or submitted labeling 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 these submissions "**FPL for approved supplement NDA 21-602/S-009**." Approval of this submission by FDA is not required before the labeling is used.

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
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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 Tammie Brent-Steele, Regulatory Project Manager, at (301) 796-1409.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.
Acting Director
Division of Drug Oncology Products
Office of Oncology Drug Products
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/

Ann Farrell
5/31/2006 10:56:29 AM
Farrell for Justice