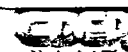
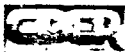


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-602

CHEMISTRY REVIEW(S)



NDA 21-602

VELCADE™ (bortezomib) for Injection

Millennium Pharmaceuticals, Inc.

**Chengyi Liang, Ph.D.
Division of Oncological Drug Products**

HFD-150/810

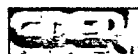
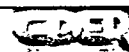
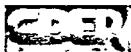


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Chemistry Review Data Sheet

1. NDA #: 21-602
2. CHEM. REVIEW#: 2
3. REVIEW DATE: May 6, 2003
4. REVIEWER: Chengyi Liang, Ph.D.

5. PREVIOUS DOCUMENTS

<u>Previous Documents</u>	<u>Document Date</u>
IND 	8-20-1998
NDA review 1	4-24-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Documnent Date</u>
Original	12-31-2002
Amendment 002	01-22-2003
Amendment 005	03-05-2003
Amendment 006	03-17-2003
Amendment BC	03-05-2003
Amendment BC	03-06-2003
Amendment 007	03-24-2003
Amendment 004	02-27-2003
Amendment 017	04-08-2003
Amendment 020	04-16-2003
Amendment 021	04-23-2003
Amendment BC	04-24-2003
Amendment BC	04-28-2003
Amendment BC	05-06-2003
Amendment BC	04-30-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Millennium Pharmaceuticals, Inc.
Address: 75 Sidney St.
 Cambridge, MA 02139

Representative: Melody A. Brown
 CMC director of Regulatory Affairs

Telephone: 617-551-4977

8. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary: VELCADE for Injection

- b. Nonproprietary Name/USAN: bortezomib
c. Code Name/#: PS-341
d. Chem. Type 1
e. Submission Priority P

9. LEGAL BASIS FOR SUBMISSION: Fulfilled PDUFA filing requirements

10. PHARMACOL. CATEGORY/INDICATION: Treatment of patients with relapsed and refractory multiple myeloma

11. DOSAGE FORM: for injection (lyophilized powder)

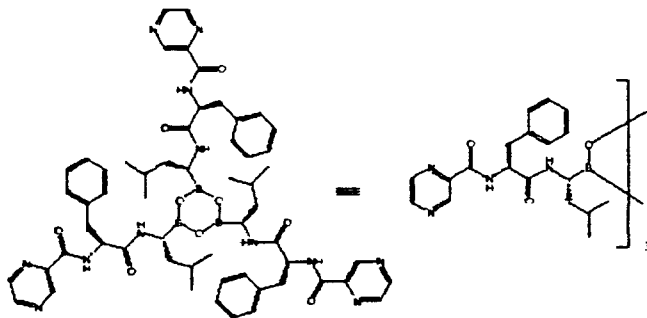
12. STRENGTHS/POTENCY: 3.5 mg/vial

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)
No

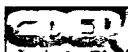
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



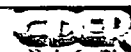
[(1R)-3-Methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]boronic acid

$C_{19}H_{25}BN_4O_4$, MW = 384.24

17. RELATED/SUPPORTING DOCUMENTS:



CHEMISTRY REVIEW

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
 	III	 	 	1	adequate	HFD-580, 3-14-2000	None
 	III	 	 	1	adequate	HFD-580, 3-1999	None
 	III	 	 	1	adequate	HFD-160, 12-31-2001	None

¹ Action codes for DMF Table:

1 - DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

B. Other Documents:

Document	Application Number	Description
CMC review 1	NDA 21-602	
IND	 	PS-341

18. STATUS:

Consults/CMC Related Reviews	Recommendation	Date	Reviewer
EES	Acceptable	May 8, 2003	Janine D Ambrogio
OPDRA	Acceptable	May 9, 2003	
Methods Validation	Package will be submitted		
EA	Categorical exclusion is acceptable	April 15, 2003	Chengyi Liang
Microbiology	Acceptable	April 30, 2003	Bryan Riley

The Chemistry Review for NDA 21-602

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended for approval based on the submitted CMC information and agreement in response to the FDA's comments to the applicant from chemistry review 1 dated 4/7/2003 and May 1, 2003. All deficiencies related to the drug substance and drug product have been addressed satisfactorily during the fast-track, priority review cycle.

B. Recommendation on Phase 4 (post marketing) Commitments, Agreements and/or Risk Management Steps, if Approvable

There are no phase 4 commitments.

II. Summary of Chemistry Assessments

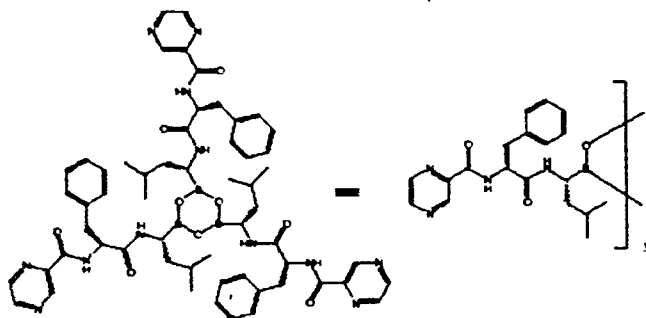
A. Description of the Drug Product(s) and Drug Substance(s)

Velcade (bortezomib) for Injection is an antineoplastic agent, which is available for intravenous injection as a sterile lyophilized powder in single-dose vials containing 3.5 mg bortezomib and 35 mg mannitol, USP.

The lyophilized drug product contains mannitol in a 10 fold excess by weight, and it is much more stable than the drug substance itself. This is most likely due to the formation of a more chemically stable mannitol ester form. The mannitol ester reverts to the drug substance upon dissolution prior to administration. The drug product can be stored at controlled room temperature. The DP lyophilized powder is reconstituted with 0.9% NaCl to the final concentration of 1 mg/ml prior to injection.

The drug substance, drug product, and the reconstituted drug product have three different molecular forms. PS-341 drug substance exists as the trimeric boroxine in the solid state. When exposed to water, the boroxine hydrolyzes to the monomeric boronic acid PS-341. The structure of the lyophilized PS-341 drug product has been determined to be the symmetrical mannitol ester. While reconstituted by 0.9% NaCl solution, the reconstituted PS-341 drug product consists of equilibrium between the mannitol ester and the PS-341 boronic acid. The inter-conversions between the various forms of the molecule have been taken into account during the pharmaceutical development of the PS-341 drug product.

The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-[[[(2S)-1-oxo-3-phenyl-2-[(pyrazinyl-carbonyl)-amino]propyl]amino]butyl]boronic acid, and it has the molecular formula $C_{19}H_{25}BN_4O_4$. The solubility of the drug substance



The drug substance is manufactured by _____ Two important starting materials containing chiral centers are purchased commercially but are well controlled. The drug substance is stored at -20°C due to decomposition at higher temperature and it is re-tested at 18 months.

B. Description of How the Drug Product is Intended to be Used

Bortezomib is a novel proteasome inhibitor. It can inhibit the chymotrypsin-like activity of 26S proteasome in mammalian cells. The inhibition of proteasome prevents the targeted proteolysis and affects multiple signaling cascades within the cell, ultimately resulting in cancer cell death.

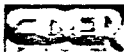
The recommended daily dose of Velcade is 1.45 mg to 2.0 mg/m².

C. Basis for Approvability Recommendation

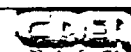
The information provided is adequate to support the approval of this NDA. There are no outstanding deficiencies remaining. Therefore, this application may be approved from a CMC perspective.

III. Administrative

A. Reviewer's Signature



CHEMISTRY REVIEW



NDA 21-602 Review # 2,

Velcade (bortezomib) for Injection

Page 8 of 33

Chengyi Liang, Ph.D., Review Chemist

Richard Lostritto, Ph.D.
Chemistry Team Leader

B. Endorsement Block

Chemist Name/Date: Chengyi Liang, Ph.D.

Chemistry Team Leader Name/Date: Richard Lostritto, Ph.D.

Project Manager Name/Date: Sean Bradley

C. CC Block

CC:

Orig. NDA 21-602

HFD-150 Division File

HFD-150/CLiang

HFD-150/RLostritto

HFD-150/SBradley

Chemistry Review Data Sheet

114 PAGE (S) WITHHELD

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

/s/

Chengyi Liang
5/12/03 04:36:57 PM
CHEMIST

Richard Lostritto
5/12/03 04:50:33 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**

ENVIRONMENTAL ASSESSMENT

**PLEASE SEE PAGE 84 OF
CHEMISTRY, MANUFACTURING
AND CONTROLS REVIEW**

2 PAGE (S) WITHHELD

Reason B4 CCI