OFFICE OF CLINICAL PHARMACOLOGY REVIEW

New Drug Application (SDN)	021602 (1278), Supplement-42 Efficacy
Submission Date (SDN)	03/25/2015
Compound	Bortezomib (Velcade ®)
Sponsor	Millennium Inc.
Indication(s)	Multiple Myeloma, Mantle Cell Lymphoma
Dosing Regimen	1.3 mg/m^2 administered twice weekly
Clinical Division	Division of Hematology Products
OCP Division	Division of Pharmacometrics
Primary Reviewer	Lian Ma, Ph.D.
Team Leader	Nitin Mehrotra, Ph.D.

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1.0 Executive Summary

Bortezomib (VELCADE®), a dipeptidyl boronic acid, is a selective inhibitor of the ubiquitin proteasome pathway. In the US, bortezomib for injection is currently approved for the treatment of adult patients with MM and is also indicated for the treatment of adult patients with mantle cell lymphoma. This current efficacy supplement is not seeking approval for a pediatric indication, but to support a proposed labeling change in the pediatric use section of US prescribing information for bortezomib and to request a pediatric exclusivity determination for the completion of studies described in the pediatric Written Request dated 13 November 2012.

The labeling updates with pediatric pharmacokinetic (PK) characteristics of bortezomib are based on a population PK analysis of data from the phase 2 Children's Oncology Group (COG) study AALL07P1 in pediatric patients with relapsed ALL and a phase 3 COG study AAML1031 in pediatric patients with de novo acute myelogenous leukemia (AML).

The PK of bortezomib after twice weekly repeated dosing in 104 pediatric patients with ALL or AML (42 patients 12-16 years of age and 62 patients 2-11 years of age) was described by a 3-compartment model with body surface area (BSA) identified as the only significant covariate affecting clearance. The results of this population PK analysis support the conclusion that total systemic exposures following BSA-scaled dosing in pediatric leukemia patients should be generally comparable to adult patients after IV administration of bortezomib at 1.3 mg/m^2 dose.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this sNDA to support revisions in section 8.4 of the label relating to pediatric pharmacokinetics. Pediatric Written Request dated 13 November 2012 is considered fulfilled.

As indicated above, the sponsor is not seeking an indication based on this efficacy supplement but have proposed labeling changes to the section 8.4, "pediatric use". Based on the pediatric labeling guidance (Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling 2013, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM341394.pdf): unless there is any safety concern (e.g. higher exposures in pediatrics), it is recommended that PK data should not be included in the label if the indication is not granted. Based on the discussions with the clinical division, the clinical pharmacology reviewers recommend providing a general statement regarding PK of bortezomib in pediatrics in the label without including detailed pediatric PK information.

For detailed labeling recommendations, please refer to Section 3.0.

1.2 Signatures

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1.3 Clinical Pharmacology Summary

Bortezomib (VELCADE®) is a proteasome inhibitor, currently approved for the treatment of patients with MM and also for the treatment of patients with mantle cell lymphoma. The recommended starting dose of VELCADE is 1.3 mg/m^2 twice weekly administered either as a 3 to 5 second bolus intravenous injection or subcutaneous injection.

A population PK analyses of bortezomib were conducted based on two COG studies AALL07P1 (N=51 patients) and AAML1031 (N=53 patients) in pediatric patients. The results of this analysis serve as the primary basis for describing the PK of bortezomib in the pediatric patient population and an assessment of the contribution of patient-specific factors (e.g., age, body size) to overall PK variability.

After twice-weekly, repeat-IV administration to pediatric patients (2-16 years) with ALL or AML, the PK of bortezomib was adequately described by a 3-compartment model. Body surface area was the only identified covariate on clearance, Mean and individual values of BSA-normalized clearances in both the 2-11 years and 12-16 years pediatric age groups were within the range of previously reported values in adult MM patients , thereby indicating that comparable systemic exposures of bortezomib should be achieved in pediatric leukemia patients and adult MM patients after IV administration of bortezomib at 1.3 mg/m^2 dose.

2.0 Question Based Review

2.1 What are the design features of the clinical studies used to support the pediatric labeling changes?

The PK or pharmacodynamics (PD) (whole blood 20S proteasome inhibition-time profiles) characteristics of bortezomib have been evaluated in 4 clinical studies in pediatric patients with advanced solid tumors or hematologic malignancies (leukemias or lymphomas). A summary of these 4 studies is shown in **Table 1**.

Table 1. Overview of clinical studies investigating bortezomib administration to pediatric patients with cancer

Study	Phase	VELCADE Dose(s) (mg/m^2)	Assessments	Number of Patients	
				Enrolled (N)	Assessed (n)
ADVL0015[a]	1	1.2, 1.6	Pharmacodynamics only	15	14
ADVL0317[a]	1	1.3, 1.7	PK1	12	5
AALL07P1[b]	2	1.3	PK2	140	51
AAML1031[b]	3	1.3	PK2	54	53

Source: CSRs for Study ADVL0015, Study ADVL0317, Study AALL07P1, Study AAML1031.

Abbreviations: COG=Children's Oncology Group; CSR=clinical study report; n=number of patients in the PK or pharmacodynamic subgroup; N=total number of patients in the study; PK1=pharmacokinetics after the first dose; PK2=pharmacokinetics after twice-weekly, repeat-dosing.

a VELCADE administered as a single agent.

b VELCADE administered as part of a multi-agent chemotherapy regimen.

The primary purpose of the two phase 1 studies (ADVL0317 in patients with refractory/recurrent leukemias; ADVL0015 in patients with advanced solid tumors) was to evaluate the safety of bortezomib in pediatric cancer patients when administered IV in a twice-weekly dosing schedule (Days 1, 4, 8, and 11, every 21 days) and to determine the pediatric single agent MTD. Additionally, these phase 1 studies also provided preliminary PK (ADVL0317 in 5 patients) or PD (ADVL0015 in 14 patients) information for bortezomib when administered as a single agent. In Study ADVL0317, all PK samples were collected after the first dose of bortezomib.

In study AALL07P1, bortezomib was added to a multi-agent standard chemotherapy backbone regimen in patients with relapsed ALL. Sparse PK sampling was conducted in consenting patients between the ages of 2 through 16 years following twice-weekly, repeat-dose, IV administration of bortezomib (on Day 8) to contribute to the pediatric population PK analysis. To ensure availability of data from an adequate number of patients (20 each in the two age groups of 2-11 and 12-16 years) for the population PK analysis, sparse PK sampling after repeat-dosing of bortezomib was also incorporated into another COG study, the phase 3 study AAML1031 in de novo AML patients.

Pharmacokinetic data from 104 patients across both studies AALL07P1 (N=51 patients) and AAML1031 (N=53 patients) contributed to the pediatric population PK analysis. The demographics of the 104 patients are summarized in **Table 2** and **Table 3**.

Table 2. Summary Statistics of Age, Body Surface Area, and Body Weight in the Population PK Analysis Population (Studies AAML1031 and AALL07P1)

Study	Variable	Mean	Std Dev	Q1	Median	Q3	Range	N
AAML1031	Age (yr)	11.4	3.934	9.0	12	15	3.7-16.8	53
	BSA (m^2)	1.402	0.4676	1.08	1.43	1.71	0.61-2.53	53
	Weight (kg)	49.59	26.82	28.9	44	64	13.9-139.7	53
AALL07P1	Age (yr)	8.451	4.076	5	8	12	2.2-16.5	51
	BSA (m^2)	1.199	0.4434	0.815	1.16	1.46	0.6-2.21	51
	Weight (kg)	40.62	23.83	20.6	35.1	50.65	14.3-100.2	51
All	Age (yr)	9.952	4.25	6	10.5	14	2.2-16.8	104
	BSA (m^2)	1.303	0.465	0.88	1.25	1.645	0.6-2.53	104
	Weight (kg)	45.19	25.67	25.3	39.35	60.58	13.9-139.7	104

Source: Population PK Report, Table 3.

Abbreviations: BSA=body surface area; N=total number of patients in the group; Q1=first quartile; Q3=third quartile; Std Dev=standard deviation.

Table 3. Summary Statistics of Categorical Demographic Variables in the Population PK Analysis Population (Studies AAML1031 and AALL07P1)

		AALL07P1		AAML1031		Overall	
Variable	**Category**	**N**	**%**	**N**	**%**	**N**	**%**
Study	AAML1031	-	-	53	100	53	51
	AALL07P1	51	100	-	-	51	49
Risk Group	Low risk	-	-	40	75.5	40	75.5
(AAML1031 only)	High risk	-	-	13	24.5	13	24.5
Treatment Plan Strata	Pre-B-ALL; ≤ 21 yrs; early[a]	20	39.2	-	-	20	39.2
(AALL07P1 only)	Pre-B-ALL; ≤ 21 yrs; late[b]	26	51	-	-	26	51
	T-cell ALL	4	7.8	-	-	4	7.8
	T-cell LL	1	2	-	-	1	2
Race	Unknown	5	9.8	3	5.7	8	7.7
	White	33	64.7	34	64.2	67	64.4
	Black or African American	9	17.6	10	18.9	19	18.3
	Asian	3	5.9	3	5.7	6	5.8
	American Indian or Alaskan Native	1	2	1	1.9	2	1.9
	Other	-	-	2	3.8	2	1.9
Gender	Female	20	39.2	24	45.3	44	42.3
	Male	31	60.8	29	54.7	60	57.7
Age Group	2-11 years	36	70.6	26	49.1	62	59.6
	12-16 years	15	29.4	27	50.9	42	40.4

Source: Population PK Report, Table 4.

Abbreviations: ALL=acute lymphoblastic leukemia; LL=lymphoblastic lymphoma; N=the total number of patients in the group.

a Early relapse occurred within 18 months of the initial diagnosis.

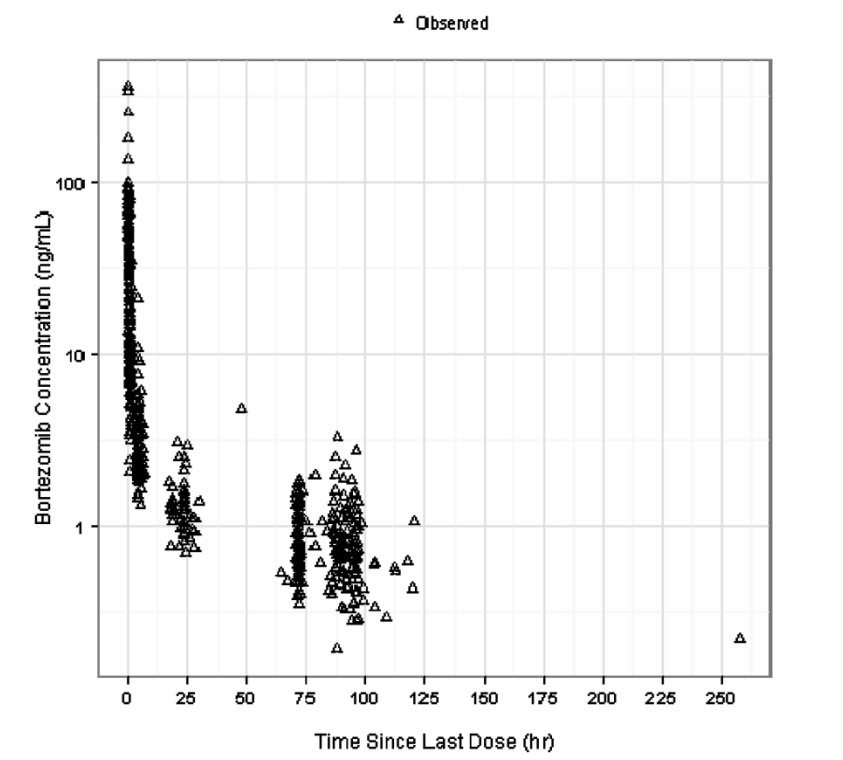
b Late relapse occurred 18-36 months from the initial diagnosis.

2.2 What are the pharmacokinetics characteristics in pediatric patients?

The sponsor developed a population PK model using sparse PK data collected in study AALL07P1 and study AAML1031. The results of this population PK analysis serve as the primary basis for describing the PK of bortezomib in the pediatric patient population and an assessment of the contribution of patient-specific factors (eg, age, body size) to overall PK variability.

After twice-weekly IV bolus administration, the bortezomib plasma concentration-time profile was assessed on Day 8. The observed concentration-time profile is shown in **Figure 1.** Plasma concentrations declined in a multi-exponential manner, indicating a multi-compartmental PK model.

Figure 1. Observed bortezomib concentration time profile since last dose (Studies AAML1031 and AALL07P1)



A 3-compartment PK model was selected as the base model based on objective function value, condition number and goodness-of-fit considerations (refer to sponsor's Population PK study report for more details). Body surface area was the only identified covariate on clearance over the pediatric age range of 2 through 16 years without additional considerations of patient age or gender.

Descriptive statistics of CL and Vss, and alpha, beta, and gamma (terminal/elimination) phase half-lives in the overall population and by age group (2-11 years: N=62; 12-16 years: N=42) are shown inTable 4. As bortezomib is administered using BSA-scaled dosing, CL and Vss of bortezomib are reported as BSA-normalized values.

Table 4. Descriptive statistics for bortezomib PK parameters by age group

Parameter	Age Group (years)	Geometric Mean	Median	Mean	Std Dev	CV%	Min	Max	N
CL (L/hr/m^2)	12-16	7.69	8.13	7.94	1.99	25	4.66	12.7	42
	2-11	7.85	7.87	8.11	2.01	25	3.52	12.7	62
	All (2-16)	7.79	8.00	8.04	1.99	25	3.52	12.7	104
V_{ss} (L/m^2)	12-16	599	594	609	114	19	400	849	42
	2-11	1040	1030	1090	312	29	625	1690	62
	All (2-16)	834	814	894	344	39	400	1690	104
Alpha Half-life (min)	12-16	5.21	5.22	5.55	2.00	36	2.31	11.5	42
	2-11	6.88	6.99	7.14	1.91	27	2.97	12.0	62
	All (2-16)	6.15	6.44	6.50	2.09	32	2.31	12.0	104
Beta Half-life (hr)	12-16	1.38	1.36	1.39	0.182	13	1.14	1.99	42
	2-11	1.72	1.77	1.74	0.260	15	1.21	2.34	62
	All (2-16)	1.58	1.55	1.60	0.289	18	1.14	2.34	104
Gamma Half-life (hr)	12-16	73.4	70.9	76.3	21.9	29	39.7	133	42
	2-11	123	122	131	47.4	36	49.3	293	62
	All (2-16)	100	100	109	47.4	44	39.7	293	104

Source: Population PK Report, Table 13 and Table 14.

Abbreviations: CL=clearance; CV=coefficient of variation; Max=maximum; Min=minimum; N=number; V_{ss}=volume of distribution at steady-state; Std Dev=standard deviation.

Geometric mean (%CV) clearance was 7.79 (25%) L/hr/m^2; Vss was 834 (39%) L/m^2; and half-lives for the alpha, beta, and gamma (terminal/elimination) disposition phases of the 3-compartment model were 6.15 (32%) minutes, 1.58 (18%) hours, and 100 (44%) hours, respectively. Descriptive statistics of the individual parameter values show that BSA normalized CL was similar across age groups in patients with ALL and AML.

Comparison of bortezomib PK in pediatric and adult patient populations

Bortezomib PK in adult patients with multiple myeloma (MM) following twice-weekly repeat-dose administration has been described previously in Study M34103-058(2) and is being used as the point of reference for comparison to the pediatric PK data discussed. After twice-weekly IV bolus administration of bortezomib, plasma bortezomib concentrations declined in a multi-phasic manner in both pediatric leukemia and adult MM patient populations, with similar mean elimination half-lives of 100 hours and 40 to 193 hours, respectively.

As bortezomib is administered at BSA-scaled doses, BSA-normalized CL is compared as it is relevant for the total systemic exposure (AUC) of bortezomib in individual patients. Estimates of BSA-normalized CL of bortezomib in adult and pediatric patient populations are presented in **Table 5**.

Table 5. BSA-normalized clearance of bortezomib in adult patients with multiple myeloma and pediatric patients with leukemia

	Adult (Study M34103-058)		Pediatric (Studies COG AALL07P1 and AAML1031)	
BSA-normalized CL	**1 mg/m^2**	**1.3 mg/m^2**	**2-11 years**	**12-16 years**
N	12	11	62	42
Mean (L/hr/m^2)	**12.9**	**14.9**	**8.11**	**7.94**
CV (%)	70	63	25	25
Range	**2.75-33.4**	**5.06-38.4**	**3.52-12.7**	**4.66-12.7**

No apparent differences were observed in BSA-normalized CL in pediatric vs. adult patient populations. Mean and individual values of BSA-normalized clearances in both the 2-11 years and 12-16 years pediatric age groups were within the range of previously reported values in adult MM patients although the variability in pediatric patients appears to be smaller than adults. These findings indicate that total systemic exposures of bortezomib following IV administration at 1.3 mg/m^2 doses to pediatric patients should be generally comparable to those achieved in adult MM patients.

Reviewer's Comments:
The sponsor's population PK analysis appears adequate for describing the PK of bortezomib in the pediatric patient population. However, this current submission is not seeking approval for a pediatric indication, but to support a proposed labeling change in the pediatric use section. Based on the pediatric labeling guidance (Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling 2013): unless there is any safety concern (e.g. higher exposures in pediatrics), PK data should not be included in the label if the indication is not granted. The reviewers therefore recommend providing a general statement regarding PK of bortezomib in pediatrics in the label without including detailed pediatric PK information.

3.0 Labeling Recommendations

Current Approved Labeling (04/2012)	Sponsor's Proposed Labeling	Reviewer's Recommendation
8 USE IN SPECIFIC POPULATIONS **8.4 Pediatric Use** The safety and effectiveness of VELCADE in children have not been established	**8 USE IN SPECIFIC POPULATIONS** (b) (4)	**8 USE IN SPECIFIC POPULATIONS** **8.4 Pediatric Use** [Defer to Clinical Review]

Current Approved Labeling (04/2012)	Sponsor's Proposed Labeling	Reviewer's Recommendation
	(b) (4)	The BSA-normalized clearance of bortezomib in pediatric patients was similar to that observed in adults.

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/s/

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08/26/2015

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08/26/2015