CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205004Orig1s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

TO: File for NDA 205004

FROM: Matthew D Thompson, PhD, MPH
Pharmacology-Toxicology Reviewer
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

THROUGH: Christopher M Sheth, PhD
Pharmacology-Toxicology Supervisor
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

DATE: 11/06/2017

SUBJECT: Excipients in Fresenius's Bortezomib for Injection

The Applicant, Fresenius Kabi USA, is seeking approval for Bortezomib for Injection under the 505(b)(2) pathway. For approval of its application, Fresenius is relying on FDA's finding of safety and effectiveness for Velcade (NDA 021602, Millennium Pharmaceuticals Inc).

Recommendation

Pharmacology/Toxicology continues to recommend approval based on the original assessment of nonclinical data submitted with the NDA. Pharmacology/Toxicology has no safety concerns with the excipients in the product.

Background

Fresenius's Bortezomib for Injection and Velcade have the following formulations:

	Velcade ®	Bortezomib for Injection	Function of Ingredients
Ingredients	**Amount**	**Amount**	
Bortezomib	3.5 mg/vial	3.5 mg/vial	Active pharmaceutical ingredient
Mannitol	35 mg/vial	N/A	(b) (4)
Boric Acid, NF	N/A	10.5 mg/vial	
Glycine, USP	N/A	25 mg/vial	
			(b) (4)
[redacted][1]			

[1] Water (b) (4) lyophilization process (b) (4) emoved during (b) (4) (b) (4)

(*Excerpted from Applicant's Submission*)

The Fresenius product contains the excipients boric acid and glycine, whereas Velcade contains the excipient mannitol.

Pharmacology/Toxicology Comments
The Applicant has not performed any toxicology studies in support of the NDA for Bortezomib for Injection.

An in vitro proteasome inhibition assay was used by the Applicant to compare the activity of Velcade and the Fresenius Bortezomib for Injection. Pharmacology/toxicology found the assay results to be comparable, concluding that the differences in excipients did not interfere with activity.

Regarding safety, the excipient glycine is a conditionally essential amino acid that is biosynthesized in the body. The amount of glycine administered in the Fresenius product would be approximately 16 mg for the twice weekly administration (2 weeks on/ 1 week off). This is negligible compared to the approximately 3 g of glycine that is biosynthesized in humans per day. Therefore, we do not consider glycine to pose a safety issue.

In evaluating the safety of boric acid, we ask several related questions: 1) what evidence exists that toxicities associated with various routes of boric acid exposure have been well-studied? 2) what evidence exists that systemic boric acid exposures and their associated toxicities have been well-studied? 3) based on this evidence, would additional studies add significantly to our knowledge of boric acid's safety profile?

We considered the following information in assessing the safety profile of boric acid as an excipient in Fresenius's product: 1) FDA's prior experience with boric acid as an excipient in approved drug products, including those with intravenous administration; 2) the permitted daily exposure for boron; and 3) the weight of toxicological evidence in the published literature, including extensive reviews by U.S. government agencies. Based on the totality of the evidence, we conclude that the level of the boric acid excipient in the Fresenius product does not pose a safety issue.

In assessing the safety of an excipient (such as boric acid), among other sources, we consider data, including human data, from other approved products, independent of the proposed application being classified as a 505(b)(1) NDA or a 505(b)(2) NDA. (See Page 2, Section III, the second paragraph under the following guidance document: Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients (May 2005).

> The Centers recognize that existing human data for some excipients can substitute for certain nonclinical safety data, and an excipient with

> documented prior human exposure under circumstances relevant to the proposed use may not require evaluation in the full battery of toxicology studies outlined in this guidance. For example, the Centers will continue to consider factors such as use in previously approved products or GRAS status as a direct food additive. Under some circumstances (e.g., similar route of administration, level of exposure, patient population, and duration of exposure) experience associated with the prior use may adequately qualify an excipient.

We also consider systemic exposure resulting from different routes of administration. As stated in the FDA Guidance for Industry: Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route (Oct. 2015, see page 3) "All routes of administration can result in systemic exposure". In the Guideline for Industry Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (Mar. 1995, see page 4), systemic exposure is described.

> The quantification of systemic exposure provides an assessment of the burden on the test species and assists in the interpretation of similarities and differences in toxicity across species, dose groups and sexes. The exposure might be represented by plasma (serum or blood) concentrations or the AUC's of parent compound and/or metabolite(s).

The intravenous route of administration is directly into the circulation and results in systemic exposure. Routes of exposure to boric acid, such as oral exposure, may result in systemic exposure, as documented in the published literature detailed below. As such, toxicities associated with systemic boric acid exposures resulting from routes of administration other than intravenous can be informative of toxicities occurring with exposures via the intravenous route.

Several sources have been identified, including reports by both the U.S. government and non-U.S. government regulatory/scientific sources representing both environmental and medical product regulatory perspectives, that characterize boric acid’s safety profile. Further, FDA has extensive experience in reviewing and approving drug products with boric acid as an excipient. As of October 2017, the inactive ingredient database describes eighteen boric acid-containing products administered by otic, intravenous, ophthalmic, oral, and topical routes. Considering that boric acid as an excipient is found in numerous drug products with different routes of administration, the weight of evidence supports the overall safety of boric acid and that for approval of Fresenius’s product additional testing on boric acid is not required at this time.

In 1992, FDA approved NDA 020166, a sodium thiosulfate injection product (250 mg/ml) that contained boric acid levels of (b) (4) mg/ml. Furthermore, documented prior human exposure under circumstances relevant to the proposed use of boric acid is found in an approved drug product (NDA 203923, Sodium Thiosulfate Injection Solution) at 2.8 mg/mL for IV injection. Sodium Thiosulfate is indicated for sequential use with sodium nitrite for the treatment of acute cyanide poisoning that is judged to be life-threatening. A second dose using one-half the original dose is recommended for a total amount of 210 mg boric acid per patient. Since the proposed dose for bortezomib is 1.3 mg/m^2, and assuming a patient body surface area of 1.73 m^2, a patient would receive 2.25 mg bortezomib per dose and approximately 6.7 mg of boric acid per dose. An exposure to 6.7 mg of boric acid is 30X lower than the amount in the FDA-approved drug, Sodium Thiosulfate (NDA 203923). Therefore, a patient being treated with Fresenius' Bortezomib for Injection would need to receive 20 doses of the drug to approximate the amount of boric acid a patient receives from one dose of Sodium Thiosulfate or 31 doses of the drug to approximate the amount of boric acid a patient receives from 2 doses of Sodium Thiosulfate. Twenty doses of bortezomib represent 15 weeks of treatment for the twice weekly administration (2 weeks on/ 1 week off) and 30 weeks of treatment for the weekly administration (2 weeks on/ 1 week off). Therefore, a patient receiving Fresenius's formulation of bortezomib must be treated for at least 15 weeks to be exposed to the amount of boric acid delivered in one dose administration of Sodium Thiosulfate Injection approved under NDA 203923.

Additional information on the safety risk of the boric acid level in the Fresenius product comes from determining a permitted daily exposure (PDE). A PDE is derived from the no-observed-effect level (NOEL) or the lowest-observed effect level (LOEL) in the most relevant animal study and is the maximum acceptable intake per day. Regulatory and/or scientific organizations outside of the United States have extensively reviewed the scientific literature, and using expert judgment, determined a PDE (or TDI) for boron. The European Medicines Agency published a background review for the excipient boric acid on September 10, 2017.[1] The EMA concluded that the PDE for boron compounds is 10 mg boron per day for patients >18 years of age. The World Health Organization (WHO) established a tolerable daily intake (TDI) for boron of 0.17 mg boron/kg/day that was rounded to 0.2 mg boron/kg/day (or 12 mg boron per day for a 60-kg individual).[2] As described later, U.S. government agencies have also conducted risk assessment for boron-containing boric acid using two additional approaches. If the Fresenius product

[1] European Medicines Agency. Boric acid and borate used as excipients. (September 10, 2017) (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001674.jsp&mid=)

[2] World Health Organization. Boron in drinking-water. (2009)

yields exposures below a PDE for boron, we would not consider Fresenius's product to carry a significant and unnecessary safety risk.

The mass of a molecule is used for safety determination, and therefore the mass ratio is more relevant than the molar ratio. The Fresenius product contains 3.5 mg/vial of bortezomib and 10.5 mg/vial of boric acid. The amount of boric acid-to-bortezomib in Bortezomib for Injection is 3:1 w/w (a molar ratio of approximately 18:1).

Our calculation of a PDE for boron is based on a NOAEL of 22 mg boron per kilogram per day, as reported in the ATSDR for boron.[3] The calculation of the PDE is based on the Q3C guidance[4]:

PDE = NOEL x Weight Adjustment/(F1 x F2 x F3 x F4 x F5)
PDE = NOAEL x 50 kg/(2.5x10x1x1x5) Note: NOAEL used in place of NOEL
PDE = 22 mg/kg/day X 50 kg /(125) = 8.8 mg boron/d
Where F1 = 2.5 (A factor to account for extrapolation between species, rabbit to human)
F2 = 10 (A factor of 10 to account for variability between individuals.)
F3 = 1 (A variable factor to account for toxicity studies of short-term exposure.)
F4 = 1 (A factor that may be applied in cases of severe toxicity)
F5 = 5 (A variable factor that may be applied if the NOEL was not established.)

As described above, a patient would typically receive 6.7 mg of boric acid per dose. The U.S. Environmental Protection Agency published an integrated risk information system chemical assessment summary for boron and compounds that specified the conversion factor for doses in mg boric acid to mg boron is calculated by multiplying the ratio of the formula weight of boron to the molecular weight of boric acid (10.81/61.84 = 0.1748).[5] Therefore, the boric acid exposure per dose of the Fresenius product (6.7 mg) is equivalent to 1.2 mg boron per dose. This boron level falls below our calculated PDE for boron compounds of 8.8 mg boron per day by a factor of 7X and below the EMA PDE for boron of 10 mg boron per day by a factor of 8X. A PDE approach adds support for the safety of boric acid levels in the Fresenius product; we conclude that it does not raise concerns for a significant and unnecessary safety risk.

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[3] Agency for Toxic Substances and Disease Registry (ATSDR), Public Health Service, U.S. Department of Health and Human Services. Toxicological Profile for Boron. (November 2010) (https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=453&tid=80)

[4] U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry Q3C Impurities: Residual Solvents. (December 1997)

[5] U.S. Environmental Protection Agency. Toxicological Review of Boron and Compounds. (June 2004) (www.epa.gov/iris)

In the Agency for Toxic Substances and Disease Registry (ATSDR), published by the Public Health Service of the U.S. Department of Health and Human Services in November 2010, the toxicological profile of boron was described.[6] The ATSDR toxicological profile "succinctly characterizes the toxicologic and adverse health effects information", which "identifies and reviews the key literature that describes a substance's toxicologic properties." Each profile includes "the examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects." The ATSDR notes the following regarding the absorption of boric acid: "Near-complete gastrointestinal absorption was indicated in humans as evidenced by the urinary recovery of 93.9% of the ingested dose of boric acid over a 96-hour collection period (Jansen et al. 1984a). Dourson et al. (1998) reviewed data from the literature to estimate oral absorption fractions of 81–92% for humans and 95% for animals (rats)." This finding in the ATSDR report allows us to use expert judgment to extrapolate findings for oral toxicity of boric acid to intravenous toxicity based on the level of systemic exposure that occurs with oral boric acid. The ATSDR report defines a minimal risk level (MRL) as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects over a specified duration of exposure. The ATSDR reported the oral MRL for boron is 0.2 mg per kilogram bodyweight per day derived for acute-duration oral exposure (1–14 days). The ATSDR also noted that "[a]cute-duration oral exposures of humans to high levels of boron (as boric acid) have resulted in little or no observable toxicity." For a 60-kg individual, the MRL would be 12 mg boron per day. The ATSDR also describes chronic-duration studies that were conducted in rats and dogs exposed to boric acid and the associated toxicity profiles.

The U.S. Environmental Protection Agency published an integrated risk information system chemical assessment summary for boron and compounds titled the "Toxicological Review of Boron and Compounds" in June of 2004. The purpose of the review was "to provide scientific support and rationale for the hazard and dose-response assessment . . . [pertaining to] chronic exposure to boron and compounds." The report notes that "Boron is well absorbed from the gastrointestinal tract in humans" and that "Studies in animals have shown that boron is readily absorbed following oral exposure…" These statements are consistent with findings from the ATSDR report and further add weight to the FDA's approach to consider the toxicological profile of

[6] Agency for Toxic Substances and Disease Registry (ATSDR), Public Health Service, U.S. Department of Health and Human Services. Toxicological Profile for Boron. (November 2010) (https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=453&tid=80)

intravenously (systemically) administered boric acid to be reasonably characterized by oral toxicity studies and other routes of exposure. The EPA report determined an oral reference dose (RfD). An RfD is “an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.” The RfD for boron exposure was determined to be 0.2 mg per kilogram bodyweight per day, consistent with the MRL.

The European Medicines Agency published a background review for the excipient boric acid in September 2017. The EMA is a European Union agency and member of ICH, responsible for the protection of public and animal health through the scientific evaluation and supervision of medicines. In the report on boric acid as an excipient, the EMA concluded that the PDE for boron compounds is 10 mg boron per day for patients >18 years of age. In the European Commission's Scientific Committee on Consumer Safety opinion, that the EMA report referenced, the oral and inhalational routes were assumed to have 100% (systemic) absorption.

In summary, we answer the several related questions: **1) what evidence exists that toxicities associated with various routes of boric acid exposure have been well-studied?** Extensive reviews have been conducted by U.S. government and non-U.S. government regulatory/scientific organizations with different perspectives on the safety risks associated with boric acid exposure. **2) what evidence exists that systemic boric acid exposures and their associated toxicities have been well-studied?** The extensive reviews we noted have repeatedly described that boric acid administered by routes other than intravenous result in systemic exposure. This allows us to use expert judgment that the toxicological risk profile associated intravenously (systemically) administered boric acid has been described through toxicity studies using other routes of administration. **3) Based on this evidence, would additional studies add significantly to our knowledge of boric acid’s safety profile?** In considering the substantive reviews by U.S. government agencies on a) the toxicological profile of boric acid; and b) the systemic exposures achieved with routes of administration other than intravenous, and considering the Agency’s prior experience with boric acid as an excipient in several approved products, including intravenously administered drug products, in our expert judgment and using the weight of evidence, we conclude that additional studies to study the toxic effects of boric acid are not deemed necessary given the levels of boric acid in the Fresenius product and likely boric acid exposures to patients.

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/s/

MATTHEW D THOMPSON
11/06/2017

CHRISTOPHER M SHETH
11/06/2017
I concur with the primary reviewer

MEMORANDUM

TO: File for NDA 205004

FROM: Pedro L. Del Valle, PhD
Pharmacology-Toxicology Reviewer
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

THROUGH: Christopher Sheth
Pharmacology-Toxicology Supervisor
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

DATE: October 23, 2015

SUBJECT: Recommend Approval of the NDA

The Applicant Fresenius Kabi USA submitted an NDA in accordance with Section 505(b)(2) to seek marketing clearance for Bortezomib for Injection on November 30, 2012. The Pharmacology and Toxicology team filed a review on April 5, 2013 which was amended on September 27, 2013 recommending approval for the proposed indications. Due to major deficiencies identified with respect to facility inspections, a Complete Response (CR) letter was issued by the FDA on October 3, 2013.

The Applicant resubmitted the application on October 3, 2014 to address the items identified in the CR Letter and this amendment did not contain nonclinical information for review. The Pharmacology and Toxicology team issued a Memo to the NDA file on March 13, 2015 recommending approval for the proposed indications. Due to major deficiencies identified with respect to facility inspections, a CR letter was issued by the FDA on April 2, 2015.

Subsequently, the Applicant resubmitted the application on May 22, 2015 to address the items identified in the CR Letter. This submission contains no new nonclinical pharmacology and toxicology information for review. The Pharmacology and Toxicology team continue recommending approval for the proposed indications based on the original assessment of nonclinical data submitted with the NDA.

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/s/

PEDRO L DEL VALLE
10/23/2015

CHRISTOPHER M SHETH
10/23/2015

Division of Hematology Oncology Toxicology Memorandum

NDA	205004 SDN 13
Submission Date:	10/13/2014
Drug Name:	Bortezomib Injection
Sponsor:	Fresenius Kabi USA, LLC.
Acting Team Leader:	Pedro L Del Valle, PhD

The original 505(b)(2) application was submitted on 11/30/12 for Bortezomib Injection, 100 mg/mL in single-dose vials. At that time, due to major deficiencies identified with respect to facility inspections, a Complete Response (CR) letter was issued by the FDA on 10/3/13.

The current submission is a minor amendment to address the items identified in the Complete Response Letter. This submission contains no new nonclinical pharmacology and toxicology information for review. NDA 205004 is recommended for approval from the standpoint of pharmacology and toxicology.

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/s/

PEDRO L DEL VALLE
03/13/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 205004
Supporting document/s:	3
Applicant's letter date:	December 3, 2012
CDER stamp date:	December 3, 2012
Product:	Bortezomib for Injection
Indication:	Multiple myeloma and Mantle cell lymphoma
Applicant:	Fresenius Kabi USA, LLC (FK USA)
Review Division:	Division of Hematology Oncology Toxicology
Reviewer:	Pedro L. Del Valle, PhD
Supervisor/Team Leader:	Haleh Saber, PhD
Division Director:	John Leighton, PhD, DABT
Project Manager:	Ebla Ali Ibrahim

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205004 are owned by FK USA or are data for which FK USA has obtained a written right of reference. Any information or data necessary for approval of NDA 205004 that FK USA does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205004.

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1 Executive Summary

1.1 Introduction

Velcade® (bortezomib) is an antineoplastic agent approved in 2003 (NDA 021,602) for the treatment of patients with multiple myeloma and in 2006 for relapsed mantle cell lymphoma. Bortezomib reversibly inhibits the chymotrypsin-like activity of the 26S proteasome in mammalian cells and thus the degradation of poly-ubiquitinated proteins intended for catalysis. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death.

The listed drug (LD), Velcade, is a lyophilized product approved for both intravenous (IV) and subcutaneous (SC) use. The Applicant, Fresenius Kabi USA, LLC (FK USA), has submitted this 505(b)(2) NDA for IV administration only. The to-be-marketed formulation is slightly different from Velcade®, (b) (4) boric acid and incorporating glycine to deliver the same amount of bortezomib (3.5 mg) in a lyophilized powder. The Bortezomib for Injection product from FK USA will be reconstituted with (b) (4) sodium chloride. Bortezomib for Injection is intended to be used for the same indications as the LD, i.e. for the treatment of patients with multiple myeloma and patients with mantle cell lymphoma who have received at least one prior therapy.

The Applicant FK USA included in this NDA a study comparing the in vitro proteasome inhibition of bortezomib drug substance, the proposed FK USA drug product Bortezomib for Injection and Velcade® using the proteasome inhibition assay by Lightcap et al ("Proteasome Inhibition Measurements: Clinical Application", Clinical Chemistry, 46:5, 673-683, 2000). Data provided evidence that the proposed FK USA drug product, Bortezomib for Injection, and Velcade® had similar in vitro proteasome inhibition activity and that the excipients in the formulation did not contribute to this inhibition. The Applicant submitted a summary of the pharmacology, PK/PD, and toxicology profile of Bortezomib for Injection supported by literature references.

1.2 Brief Discussion of Nonclinical Findings

FK USA relies upon the Agency's previous findings of safety and effectiveness for Velcade®. The Applicant has not performed any toxicology studies in support of the NDA approval for Bortezomib for Injection. FK USA conducted one in vitro study to evaluate the pharmacologic activity of their product, and compare the proteasome inhibition of Bortezomib for Injection product and Velcade®.

The proteasome inhibition assay included evaluation of the suitability of the assay, evaluation of responses from positive control, excipients and vehicle, and evaluation of the inhibitory activity of the bortezomib drug substance, Velcade® and FK USA's Bortezomib for Injection. Results provided evidence for the suitability of the assay, the

lack of contribution of excipients to the in vitro inhibitory activity, and the similar in vitro inhibition activity of the drugs tested.

The amount of boric acid in each vial of FK USA's Bortezomib for Injection is acceptable based on the amount present in an FDA approved I.V. product (Sodium Thiosulfate). The Applicant's proposed specifications for impurities in Bortezomib for injection are acceptable. The impurities (b) (4) are within the qualification threshold defined by the ICH Q3B(R2).

There are no pharmacology/toxicology concerns with this application.

1.3 Recommendations

1.3.1 Approvability

From the Pharmacology/Toxicology perspective, Bortezomib for Injection may be approved for the proposed indications.

There is sufficient information about the safety and efficacy of bortezomib including the Agency's prior evaluation of safety and efficacy of Velcade®. The Applicant has provided the bridge between their product and Velcade based on the comparative in vitro proteasome inhibition.

1.3.2 Additional Non Clinical Recommendations

None at this time.

1.3.3 Labeling

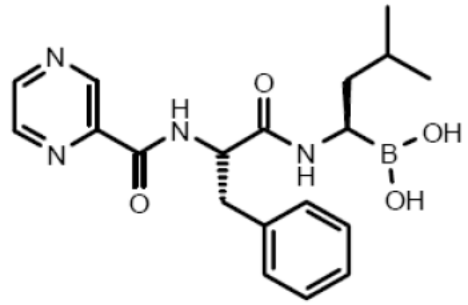
The nonclinical sections of the label will be comparable to the label of the listed drug.

2 Drug Information

2.1 Drug

CAS Registry Number:	179324-69-7
Generic Name:	Bortezomib
Code Name:	No provided
Chemical Name:	[(1*R*)-3-methyl-1-[[(2*S*)-1-oxo-3-phenyl-2-(pyrazinylcarbonyl)-amino]propyl] amino]butyl] boronic acid
Molecular Formula:	$C_{19}H_{25}BN_4O_4$
Molecular Weight:	384.24
Pharmacologic Class:	Proteasome Inhibitor

Structure or Biochemical Description



2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 021,602 (Velcade)

2.3 Drug Formulation

The drug product is provided as a sterile lyophilized monomeric boronic acid form of bortezomib powder contained in a 10-mL type 1 (b) (4) amber glass vial. Table 1 shows the composition of the drug product.

Table 1 Composition of FK USA Drug Product Bortezomib for Injection

(Excerpted from Applicant's submission)

Strength	3.5 mg/vial		
Packaging Configuration	(b) (4) a 10-cc vial (b) (4)		
Vial	10 cc,, 20 mm Finish, Type I (b) (4) Amber Glass vial		
Stopper	20 mm (b) (4)		
Seal	20 mm, Flip-off Aluminum crimp seal		
Bortezomib for Injection	**Content (per mL)**	**Function**	**Quality of ingredient**
Bortezomib	(b) (4) mg/mL	Active ingredient	Per API supplier specifications
(b) (4) (b) (4)	ng	(b) (4)	NF
Boric Acid, NF	ng		NF
Glycine, USP	ng		USP
(b) (4)			USP/EP
			NF
			USP
[1] Water (b) (4) during the lyophilization process			(b) (4) removed (b) (4)
(b) (4)			

The Certificates of Analysis issued in support of this NDA application were generated for lots R340-025, R340-024, C340-013 and R342-032 that were manufactured on 08/02/2010, 08/23/2010, 09/03/2010 and 05/30/2012, respectively. FK USA has subsequently derived new limits for impurities (b) (4) and total impurities based on the application of ICH Guidance documents for setting impurity limits. Lot R342-032 is a process qualification batch manufactured in May 2012 at the intermediate scale. Table 2 shows the specifications proposed for the impurities.

Table 2 Proposed Specifications for FK USA Product

(Excerpted from Applicant's submission)

Test	Acceptance Criteria	Test Method[1]
Description	Solid in an amber vial	Visual Examination
Identification:		
A HPLC	A. The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard Preparation*. (b) (4)	A. 10-08-03-6530
B. Ultraviolet (UV) Spectrum using Photoiodide Array Detector	B. (b) (4) in the *Standard Preparation* and the *Finished Product* *Assay* Preparation exhibit maxima at the same wavelength (b) (4) nm.	B. 10-08-03-6530
Reconstitution Time	Reconstitute each vial with 3.5 mL of 0.9% Sodium Chloride Injection, USP NMT (b) (4)	10-08-05-6005
Constituted Solution		
1. Completeness	1 The solid dissolves completely leaving no visible residue as undissolved matter	10-08-05-6005 USP<1>
2. Clarity	2. The constituted solution is not significantly less clear than an equal volume of Sterile Water for Injection contained in a similar vial and examined similarly.	
3. Particulate Matter	3. The constituted solution is essentially free from particles of foreign matter that can be observed on visual inspection.	
4. Visual Color	4. Colorless	10-08-05-6005
Water Content	NMT (b) (4)	10-08-03-6581 USP <921> Method 1c
Uniformity of Dosage Units	Meets USP requirements	USP<905>
(b) (4)		
Container/Closure Integrity[2]	The differential pressure of all sample vials being tested for each lot must be below the two bracketing Self Tests	10-08-00-6031 10-08-00-6032
Bortezomib Assay Label Claim 3.5 mg/vial	(b) (4) % of Label Claim	10-08-03-6530
Impurities[3]		
1. (b) (4)	1. NMT (b) (4) %	10-08-03-6530
2.	2. NMT %	
3. Any Other Individual Impurity	3. NMT %	
4. Total Impurities	4. NMT %	
(b) (4)		
Particulate Matter in Injections	1. For particles ≥ 10µm : NMT (b) (4) per container 2. For particles ≥ 25µm : NMT (b) (4) per container	USP<788>
Sterility[4]	Sterile	USP <71>
Bacterial Endotoxins	NMT (b) (4) EU/mg	USP <85>
(b) (4)		

[1] References to compendia signify current compendia. If a compendial monograph or test changes, FK USA will implement the changes and report them via annual report.

[2] CCIT is performed only at annual stability interval

2.4 Comments on Novel Excipients

FK USA developed an alternative formulation to the LD (b) (4) boric acid and incorporating glycine to have the same amount of bortezomib (3.5 mg) in a lyophilized powder. Table 3 presents the Applicant's justification for the proposed level of excipients based on the levels listed in the FDA Inactive Ingredient List.

Table 3 Excipients in FK USA Bortezomib for Injection Product

(Excerpted from Applicant's submission)

Excipient	Concentration in Reconstituted Solution	Safety Justification
Boric Acid, NF	(b) (4) %	FDA Inactive Ingredient Database: • 0.31% boric acid in FDA approved IV injection • 37.2% boric acid in FDA approved ophthalmic solution Calculated maximum daily dose: • From Bortezomib Maximum Daily Dose of 2.25 mg (1.3 mg/m^2 for an average body surface area of 1.73 m^2), a patient receives 6.7 mg of boric acid. Other information: • Boric acid is considered low toxicity material. It occurs naturally and is exempt from the requirement of a tolerance (maximum residue limit) by EPA. It is assigned Toxicity Category III which is the same category as sodium chloride. Its LD_{50} by IV in mouse is 1.2 g/kg. It's LD_{50} by oral in rat is 2.7 g/kg which is slightly lower than sodium chloride which is 3 g/kg.
Glycine, USP	(b) (4) %	FDA Inactive Ingredient Database: • 90% glycine in FDA approved IV injection Calculated maximum daily dose: • From Bortezomib Maximum Daily Dose of 2.25 mg (1.3 mg/m^2 for an average body surface area of 1.73 m^2), a patient receives 15.8 mg of glycine.
(b) (4)		

Boric acid is used in an approved drug product (NDA 203923, Sodium Thiosulfate Injection Solution) at 2.8 mg/mL in a dose of 50 mL with a recommended second dose using one-half the original dose for a total amount of 210 mg boric acid per subject. The amount of boric acid-to-bortezomib in Bortezomib for Injection is 3:1. Since the recommended dose for bortezomib is 2.25 mg/dose, each patient will receive approximately 6.7 mg of boric acid per dose which is 30X lower than the amount of

boric acid each subject may receive from administration of the drug Sodium Thiosulfate Injection. Glycine is an amino acid and can be used at the proposed level.

2.5 Comments on Impurities/Degradants of Concern

There are two FK USA-related product impurities and two API-related impurities. Table 4 shows the proposed limits for impurities in bortezomib drug substance and FK USA Bortezomib for Injection. The Applicant states that (b) (4) impurities are (b) (4) characterized their chemical structure using LCMS (LCMS Study PD11-NP/A-021). Our calculations below for an acceptable level of each impurity are based on the guidance documents for impurities, (b) (4) .

Table 4 Proposed Limits for Impurities

(Excerpted from Applicant's submission)

Impurity	Proposed Specification Limit	
	Bortezomib Drug Substance	Bortezomib for Injection
AOII	NMT (b) (4)%	NMT (b) (4)%
(b) (4)	NMT (b) (4)% NMT %[1]	NMT (b) (4)%[1] NMT %[1]
[2] API Process Impurities • (b) (4) •	NMT (b) (4)% NMT %	Not required[2] Not required[2]
Total Impurities	NMT (b) (4)%	NMT (b) (4)%
(b) (4)		

[2] These API process related impurities are controlled in the drug substance. They show no growth in the finished product during accelerated and long-term stability.

Table 5 Comparison of Impurity Levels of FK USA Bortezomib for Injection and Velcade®

		Impurities (%)					
FK USA		(b) (4) Limit NMT (b) (4)%		(b) (4) Limit NMT (b) (4)%		AOII Limit NMT (b) (4)%	
Lot Number		Initial	18 Months[1]	Initial	18 Months[1]	Initial	18 Months[1]
			↑ ↓		↑ ↓		↑ ↓
C340-013		(b) (4)					
R340-024							
R340-025							
Velcade	Test / Expiration date	(b) (4)					
8CZT000	0609 / 0211	(b) (4)					
7BZXSV00	1209 / 0110						

[1] Long term storage conditions 25±2 °C/60±5% RH; ↑: upright orientation, ↓: inverted orientation

The impurities [redacted] and AOII were found at higher levels compared to Velcade levels in the different lots of FK USA Bortezomib for Injection, Table 5.

The impurity [redacted] is controlled at NMT [redacted]% in the drug substance and the control limit of NMT [redacted]% is proposed for the finished product. Based on the recommended dose of [redacted] mg/m^2, the total daily intake of [redacted] from FK USA Bortezomib for Injection is calculated as:

[redacted] mg total dose
[redacted] total daily intake (TDI)

The impurity [redacted] is controlled at NMT [redacted]% in the drug substance and the control limit of NMT [redacted]% is proposed for the finished product. Based on the recommended dose of [redacted] mg/m^2, the total daily intake of [redacted] from FK USA Bortezomib for Injection is calculated as:

[redacted] mg total dose
[redacted] total daily intake (TDI)

[redacted] at NMT [redacted]% and [redacted]%, respectively, in Bortezomib for Injection drug product is acceptable based on ICH Q3B(R2) qualification threshold of 1.0% or 50 µg per day intake, for daily drug intake of less than 10 mg/day.

2.6 Proposed Clinical Population and Dosing Regimen

FK USA proposed dosing recommendations consistent with current Velcade® labeling (excluding SC administration) for treatment of multiple myeloma and mantle cell lymphoma. The recommended dose is 1.3 mg/m^2. Bortezomib for Injection may be administered intravenously at a concentration of 1 mg/mL administered as a 3 to 5 second bolus intravenous injection.

2.7 Regulatory Background

Bortezomib (Velcade®) is an antineoplastic agent approved in 2003 (NDA 021,602) for the treatment of patients with multiple myeloma and in 2006 for relapsed mantle cell lymphoma. The Applicant, FK USA, has developed an alternative formulation to the listed drug, Velcade®.

A pre-IND/pre-NDA meeting was held with APP Pharmaceuticals (FK USA) on April 6, 2010, to discuss their plans to submit a 505(b)(2) NDA for Bortezomib for Injection.

3 Studies Submitted

3.1 Studies Reviewed

In-vitro Proteasome Inhibition Study Comparing APP's Bortezomib for Injection with VELCADE®

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

None

4 Pharmacology

FK USA conducted an extensive literature search, Table 6, and included a review of the pharmacology of bortezomib. The Applicant conducted one in vitro study to evaluate and compare the proteasome inhibition of the proposed Bortezomib for injection product and Velcade®.

Table 6 Summary of Literature Search

(Excerpted from Applicant's submission)

Study Type	Additional Published Studies
Inhibition Binding Studies	Approximately 770 published studies available
Isoform Studies	16 published studies available
In Vitro System Effects	Approximately 400 published studies available
In Vivo System Effects	Approximately 300 published studies available
Binding Affinity of Impurities	None found

4.1 Primary Pharmacodynamics

Study title: In-vitro Proteasome Inhibition Study Comparing APP's Bortezomib for Injection with VELCADE®

Study No.: PD11-NB/F-016
Report Date: August 2, 2011
Study report location: eCTD 4.3
Conducting Laboratory: APP Pharmaceuticals (Skokie, IL)
GLP: No

Introduction

The 26S proteasome holoenzyme consists of 19S and 20S subunits displaying chymotryptic activity. The holoenzyme degrades ubiquitinated proteins playing an essential role in maintaining homeostasis within cells. Inhibition of the 26S proteasome

prevents the targeted proteolysis affecting multiple signaling cascades within the cell. Bortezomib inhibits the chymotryptic activity of the proteasome leading to inhibition of ubiquitinated protein hydrolysis and causing cytotoxicity to a variety of cancer cell types in vitro. The in vitro proteasome inhibition of bortezomib was used by the Applicant to compare the activity of Velcade® and FK USA's Bortezomib for Injection.

Key Study Findings

- Epoxomicin, used as a positive control, had an average inhibition of 98.7% and the normal saline solution (diluent) produced no significant signal.
- Excipients from Velcade® and FK USA's Bortezomib for injection did not interfere with the proteasome activity measured with the inhibition assay.
- Results and statistical analysis showed comparable results between the drug response curves of Bortezomib drug substance and Velcade®, and between the drug response curves of Bortezomib drug substance and APP's (FK USA) Bortezomib for Injection.

Rationale for the Inhibition Assay

Velcade® and Bortezomib for Injection contain different excipients. FK USA conducted an in vitro proteasome inhibition study with Velcade® and FK USA's Bortezomib for Injection to evaluate the effects of excipients on drug activity.

Figure 1 Plate Layout Showing Location of Samples in Plates of Proteasome Inhibition Assay

(Excerpted from Applicant's submission)

	1	2	3	4	5	6	7	8	9	10	11	12
A	Blank Sample	API	RLD	APP	API	RLD	APP	API	RLD	APP	Blank Sample	RLD Placebo
B	Positive Control	API	RLD	APP	API	RLD	APP	API	RLD	APP	Negative Control	APP Placebo
C	Negative Control	API	RLD	APP	API	RLD	APP	API	RLD	APP	Positive Control	Blank Sample
D	APP Placebo	API	RLD	APP	API	RLD	APP	API	RLD	APP	RLD Placebo	Negative Control
E	APP Placebo	API	RLD	APP	API	RLD	APP	API	RLD	APP	APP Placebo	APP Placebo
F	Negative Control	API	RLD	APP	API	RLD	APP	API	RLD	APP	Blank Sample	Negative Control
G	RLD Placebo	API	RLD	APP	API	RLD	APP	API	RLD	APP	RLD Placebo	RLD Placebo
H	Blank Sample	API	RLD	APP	API	RLD	APP	API	RLD	APP	Negative Control	Blank Sample

Blank Sample: Normal Saline was used in a blank sample for correcting fluorescence reading of the test drug samples.
Positive Control: Epoxomicin used for specificity test to confirm presence of chymotryptic subunit.
Negative Control: Buffer containing proteasome without any inhibitors used to demonstrate 100% activity for system suitability test. Also serve as a placebo sample of Bortezomib drug substance.
RLD Placebo: Excipient in Velcade® in normal saline, tested.
APP Placebo: Excipients in APP's Bortezomib for Injection in normal saline.
API: Bortezomib drug substance in normal saline tested in a serial dilution of 8 different concentrations, tested in triplicate.
RLD: Velcade® in normal saline tested in a serial dilution of 8 different concentrations, tested in triplicate.
APP: APP's Bortezomib for Injection in normal saline tested in a serial dilution of 8 different concentrations, tested in triplicate.

Methods:

Assay:	20S Proteasome Assay kit (b) (4)
Concentrations tested:	0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, and 5.0 ng/well
Inhibition range:	0 to 100%
Format:	96 well-plate/test
Number:	Three replicates/test, total 9 plates
Negative control:	Assay buffer containing proteasome with no inhibitors to establish maximum activity and suitability of the test
Positive control:	Epoxomicin to establish 100% inhibition activity (0% proteasome activity)
Test drug samples:	Bortezomib drug substance manufactured by (b) (4) Velcade® containing mannitol manufactured by Millennium Pharmaceuticals Bortezomib for Injection containing boric acid and glycine manufactured by APP Pharmaceuticals
Diluent and Blank sample:	Sodium Chloride, USP (0.9%) for injection manufactured by APP Pharmaceuticals
Excipients:	Mannitol manufactured by (b) (4) Boric acid manufactured by (b) (4) Glycine manufactured by (b) (4)
Working stock solutions of drug and excipients:	Three-500 ng/mL prepared from a previously HPLC-confirmed 500 mcg/mL stock solution
Quantitative analysis:	Stock solutions and dilutions confirmed using a validated quantitative HPLC method
Statistical analysis:	Dose-response profile parallelism to evaluate difference or equivalence among drugs Comparison with drug substance to evaluate effect of excipients

Proteasome Inhibition Assay

(Excerpted from Applicant's submission)

Purified proteasome from human erythrocytes, test solution, and buffer solution were mixed and incubated for 10 minutes at 30°C and a substrate was then added. The slope, indicating relative velocity of 20S proteasome subunit activity in the substrate cleavage kinetic, was calculated from "Relative Fluorescence Unit (RFU) versus Time" profile. The slope (RFU/min) of each test sample was plotted against the sample drug concentration.

Results

Concentrations of the serial dilutions ranged 1% to 18% coefficient of variation (CV), Table 7. Proteasome inhibition assay suitability was defined using proteasome activity measured in the absence of inhibitors (negative control), Table 8. Seven test plates passed the system suitability and two test plates failed to meet the system suitability requirement described in the proteasome test method. Results were widely distributed from 203.6 to 926.5 RFU/min and an average 38% coefficient of variation. Epoxomicin,

used as positive control, had an average inhibition of 98.7% and the normal saline solution (diluent) produced no significant signal, Table 8.

Table 7 Summary of Concentration Verification of Serial Dilutions

(Excerpted from Applicant's submission)

Theoretical Concentration (ng/mL)	Actual HPLC Test Results (ng/mL) of Spiking Solutions														
	Bortezomib Drug Substance					Velcade®					APP's Bortezomib for Injection				
	Set 1	Set 2	Set 3	Average	S.D.	Set 1	Set 2	Set 3	Average	S.D.	Set 1	Set 2	Set 3	Average	S.D.
500.0	(b) (4)			469.6	18.65	(b) (4)			475.0	13.75	(b) (4)			491.4	0.60
250.0				234.8	5.54				219.5	2.54				239.6	4.15
125.0				112.4	7.08				112.3	7.36				117.1	2.10
62.5				56.1	2.38				55.6	2.17				58.8	2.79
31.3				26.3	1.85				25.7	0.76				29.5	0.40
15.6				12.1	2.15				12.1	0.50				13.0	0.12
7.8				6.7	0.38				6.7	0.85				7.0	0.17

Note: The lowest concentration of 3.9 ng/mL in each serial dilution is outside the validated range of HPLC analysis; therefore, was not tested

Table 8 Summary of Proteasome Inhibition Assay of Different Controls

(Excerpted from Applicant's submission)

Sample	Proteasome Activity as Measured by the Linear Slope of Proteasome-Substrate Reaction Kinetics (RFU/min)								
	S1P2 (Plate 1)	S1P4 (Plate 2)	S2P1 (Plate 3)	S2P2 (Plate 4)	S2P3 (Plate 5)	S3P2 (Plate 6)	S3P3 (Plate 7)	Average	S.D.
Negative Control	(b) (4)							560.2	212.27
Positive Control								7.2	3.97
Blank Sample								2.3	2.81

Negative Control: Buffer solution containing proteasome without any inhibitors was used as a control sample to demonstrate proteasome activity for suitability test on proteasome used in the study. Tested at N = 6 in each test plate (Refer to Figure 1 for the plate layout).

Positive Control: Epoxomicin (selective chymotriptic inhibitor) was used for specificity test to confirm presence and inhibition of chymotryptic subunit which is a specific inhibition site of bortezomib within the 20S proteasome. Tested at N = 2 in each test plate (Refer to Figure 1 for the plate layout).

Blank Sample: A diluent (normal saline) containing substrate but no proteasome, used for correcting background fluorescence reading of test drug samples.

Excipients from Velcade® and FK USA's Bortezomib for Injection did not have any proteasome activity when measured with the inhibition assay, Table 9. The RFU/min in the presence of Velcade's excipients varied from 242.5 to 871.1 with an average 32.6% CV; the RFU/min in the presence of FK USA's Bortezomib for injection's excipients varied from 238.3 to 746.8 RFU/min with an average 30.5% CV. These values are within the RFU/min values obtained using the negative control (maximum proteasome activity) and within the same percent of variation.

Table 9 Summary of Proteasome Inhibition Assay of Excipients

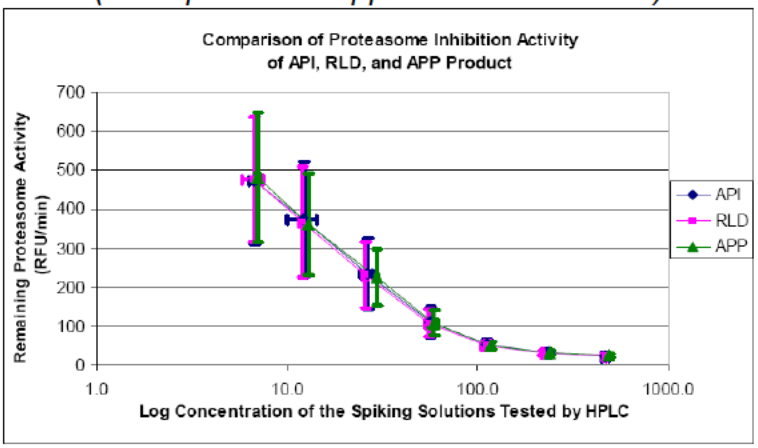
(Excerpted from Applicant's submission)

Plate Set	Placebo Sample	Proteasome Activity as Measured by the Linear Slope of Proteasome-Substrate Reaction Kinetics (RFU/min)						
		Well 1	Well 2	Well 3	Well 4	Well 5	Average	S.D.
S1P2 (Plate 1)	Velcade® Excipients	(b) (4)					273.9	33.49
	APP's Excipients						304.0	76.96
S1P4 (Plate 2)	Velcade® Excipients						642.2	136.44
	APP's Excipients						593.8	149.68
S2P1 (Plate 3)	Velcade® Excipients						355.4	71.11
	APP's Excipients						340.6	62.54
S2P2 (Plate 4)	Velcade® Excipients						485.4	98.27
	APP's Excipients						481.7	69.32
S2P3 (Plate 5)	Velcade® Excipients						620.5	52.75
	APP's Excipients						642.4	31.13
S3P2 (Plate 6)	Velcade® Excipients						733.5	74.22
	APP's Excipients						690.2	38.55
S3P3 (Plate 7)	Velcade® Excipients						522.2	22.40
	APP's Excipients						537.5	75.83
All Plate Average ± S.D.	Velcade® Excipients	519.0 ± 168.95						
	APP's Excipients	512.9 ± 156.17						

Proteasome inhibition was assessed using the active pharmaceutical ingredient (API) bortezomib, FK USA's Bortezomib for Injection and Velcade®. The three test articles showed similar concentration-response curves in a wide range of concentrations from minimum to full proteasome inhibition, Figure 2. Results from the seven plates for each drug tested are included in Section 5 Appendix/Attachments.

Figure 2 Comparison of Proteasome Inhibition Assay of FK USA's Bortezomib for Injection, Velcade® and Bortezomib Drug Substance

(Excerpted from Applicant's submission)



The similarity or equivalence in drug-response curves was tested using validated statistical software, StatLIA®, for the weighted regression and parallelism comparison. Data analysis showed a fit probability of ≥0.01 that met acceptance criteria for curve fitting and a Chi Square (χ^2) probability of ≥0.01 that met acceptance criteria for parallelism. These results indicate equivalence for the concentration-response curves

between the API and Velcade, and between the API and APP's (FK USA) Bortezomib for Injection.

5 Appendix/Attachments

Table 10 Summary of Proteasome Inhibition Test Results for the API, Velcade® and Bortezomib for Injection

(Excerpted from Applicant's submission)

Theoretical Drug Concentration in Spiking Solutions (ng/mL)	Proteasome Activity as Measured by the Linear Slope of Proteasome-Substrate Reaction Kinetics (RFU/min)								
	S1P2 (Plate 1)	S1P4 (Plate 2)	S2P1 (Plate 3)	S2P2 (Plate 4)	S2P3 (Plate 5)	S3P2 (Plate 6)	S3P3 (Plate 7)	Average	S.D.
3.91	(b) (4)							552.7	194.60
7.81								472.6	163.21
15.63								374.8	148.50
31.25								235.4	91.51
62.5								110.9	39.47
125								53.6	13.60
250								33.6	6.80
500								25.6	5.38

Theoretical Drug Concentration in Spiking Solutions (ng/mL)	Proteasome Activity as Measured by the Linear Slope of Proteasome-Substrate Reaction Kinetics (RFU/min)								
	S1P2 (Plate 1)	S1P4 (Plate 2)	S2P1 (Plate 3)	S2P2 (Plate 4)	S2P3 (Plate 5)	S3P2 (Plate 6)	S3P3 (Plate 7)	Average	S.D.
3.91	(b) (4)							547.6	186.59
7.81								476.9	160.49
15.63								368.8	141.91
31.25								231.3	84.08
62.5								109.3	35.21
125								50.8	12.14
250								32.5	5.73
500								25.1	5.10

Theoretical Drug Concentration in Spiking Solutions (ng/mL)	Proteasome Activity as Measured by the Linear Slope of Proteasome-Substrate Reaction Kinetics (RFU/min)								
	S1P2 (Plate 1)	S1P4 (Plate 2)	S2P1 (Plate 3)	S2P2 (Plate 4)	S2P3 (Plate 5)	S3P2 (Plate 6)	S3P3 (Plate 7)	Average	S.D.
3.91	(b) (4)							541.9	164.62
7.81								483.4	165.35
15.63								361.6	128.87
31.25								226.8	72.80
62.5								109.9	31.34
125								51.3	10.50
250								33.4	5.45
500								25.8	5.18

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/s/

PEDRO L DEL VALLE

09/27/2013

This is a revision of the review filed on April 5, 2013. This review contains the correct calculations for excipients present in the final product. Use this version as the review from the Pharmacology/ Toxicology team

HALEH SABER

09/27/2013

This review is to replace the previous pharmacology/ toxicology review.