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RESEARCH**

APPLICATION NUMBER:
50-821

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 50-821	Submission Date(s): 26SEP2008
Drug	Cefepime Hydrochloride
Product / Formulation; Strength(s)	Cefepime for Injection USP and Dextrose Injection USP in the Duplex [®] Container, 1 gram in 50 mL and 2 grams in 50 mL
OCP Reviewers	Aryun Kim, Pharm.D.
OCP Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND division	DAIOP (520)
Sponsor	B. Braun Medical, Inc.
Submission Type; Code	Original, 505(b)(2)

BACKGROUND

B. Braun Medical, Inc. submitted a New Drug Application (NDA) for cefepime for injection and 5% dextrose injection in Duplex[®] containers of 1 g/50 mL and 2 g/50 mL for intravenous administration. The Duplex[®] container is a dual chamber bag filled with powder and diluent in separate chambers. When pressure is applied to the diluent chamber, the seal between the two chambers breaks allowing the powder to be reconstituted. Six other Duplex[®] products by B. Braun have been approved by the Agency for other antimicrobial agents.

In a 07/11/2008 email correspondence from the Agency in response to the Sponsor's 05/09/2008 meeting packet, the Agency agreed the Cefepime Duplex[®] product was appropriate for a 505(b)(2) application by using the cefepime hydrochloride product from Bristol-Myers Squibb (BMS), Maxipime[®] in ADD-Vantage 1 g and 2 g vials (NDA 50-679; approved 01/18/1996), as the reference listed drug (RLD). Accordingly, B. Braun requested a waiver for submission of evidence of in vivo bioavailability based on 21 CFR §320.2(b).

The Sponsor meets the requirements for waiver of evidence of in vivo bioavailability, based on the listed criteria in 21 CFR §320.2(b). The Cefepime Duplex[®] product contains the same active (cefepime hydrochloride) and inactive (L-Arginine) ingredients in the same concentration as the RLD (**Table 1**). Indications, route of administration, and dosing regimen (frequency and duration) for B. Braun's Cefepime for Injection and Dextrose for Injection in Duplex[®] container will be identical to BMS's Maxipime[®] in ADD-Vantage vials when reconstituted with 5% dextrose for intravenous administration.

Table 1. Comparison of Cefepime Duplex[®] product by B. Braun versus the Maxipime[®] in ADD-Vantage vials by BMS

Item	B. Braun	RLD
1. Name	Cefepime for Injection USP and Dextrose Injection USP	Maxipime [®] (Cefepime Hydrochloride, USP) for Injection
2. Container	DUPLEX (Dual Chamber Plastic)	ADD-Vantage Vial
3. Use	After Constitution in the DUPLEX bag	After Constitution with the diluent in the ADD-Vantage bag
4. Storage	Manufactured State: Room Temperature, 25°C Constituted State: 25°C, 5°C	Manufactured State: Room Temperature, 25°C Constituted State: 25°C, 5°C
6. API	Cefepime: 1.0g and 2.0g L-Arginine, USP (~725mg/g Cefepime)-Added to control the pH of the constituted solution at 4.0 to 6.0	Cefepime: 1.0g and 2.0g L-Arginine, USP (~725mg/g Cefepime) -Added to control the pH of the constituted solution at 4.0 to 6.0
7. Diluent	5% Dextrose Injection, USP	5% Dextrose Injection, USP 0.9% Sodium chloride Injection, USP
8. Diluent Volume, mL	50mL	50mL 100mL
9. Route of Administration	I.V.	I.V.

LABELING RECOMMENDATIONS

The proposed labeling recommendations in **Appendix 1** should be communicated to the Sponsor.

RECOMMENDATIONS

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed NDA 50-821, and it is acceptable from a clinical pharmacology perspective.

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/s/

Aryun Kim
5/22/2009 02:22:40 PM
PHARMACOLOGIST

Charles Bonapace
5/22/2009 02:24:56 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA(s): 50-821	Submission Date(s): 6 Nov 2009 (SDN 12) and 8 Dec 2009 (SDN 13)
Drug	Cefepime Hydrochloride
Product / Formulation; Strength(s)	Cefepime for Injection USP and Dextrose Injection USP in the DUPLEX® Container, 1 gram in 50 mL and 2 grams in 50 mL
OCP Reviewer	Aryun Kim, Pharm.D.
OCP Team Leader	Charles Bonapace, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP (520)
Sponsor	B. Braun Medical Inc., Allentown, PA
Submission Type; Code	Resubmission/Class 2; 505(b)(2)

BACKGROUND

B. Braun Medical Inc. originally submitted a 505(b)(2) NDA for Cefepime for Injection USP and Dextrose Injection USP in the DUPLEX® Container of 1 g/50 mL and 2 g/50 mL on **26 Sep 2008**. On **21 Jul 2009**, a Complete Response letter was issued, citing product quality issues. On **6 Nov 2009**, the Sponsor provided a response to the Complete Response letter and resubmitted the 505(b)(2) NDA, and an updated draft product label was provided on **8 Dec 2009**.

This review only reflects the Clinical Pharmacology Reviewer's edits to the Sponsor's currently proposed label. For all other details, reference is made to the Clinical Pharmacology Review of the original 505(b)(2) NDA submission dated 22 May 2009.

RECOMMENDATIONS

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the resubmission of NDA 50-821, and it is acceptable from a clinical pharmacology perspective. Product labeling should be revised as indicated in **Appendix 1**.

Appendix 1. Proposed Labeling with Revisions

Sponsor's draft label version date: 8 Dec 2009

The following proposed labeling has been marked with revisions made by the Clinical Pharmacology Reviewer.

15 pages have been withheld in full immediately following this page as B4 (Draft Labeling)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50821	ORIG-1	B BRAUN MEDICAL INC	CEFEPIME

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/s/

ARYUN KIM
04/29/2010

CHARLES R BONAPACE
05/03/2010

CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA: 50-821
 Drug Name: Cefepime
 Applicant: B. Braun
 Submission Date: 09-25-08
 Filing Meeting Date: 11-03-08
 PDUFA Date: 07-25-09
 OCP Primary Reviewer: Aryun Kim, Pharm.D.
 OCP Team Leader: Charles Bonapace, Pharm.D.

<i>QUESTION</i>	<i>YES</i>	<i>NO</i>	<i>NA</i>	<i>COMMENTS</i>
<i>Fileability:</i> <i>Is the Clinical Pharmacology section of the application fileable?</i> <i>(if 'NO', please comment as to why it is not fileable)</i>			<i>NA</i>	<i>No new clinical pharmacology data has been submitted.</i>
<i>Fileability Review Components</i>				
1. Is the clinical pharmacology section of the NDA organized in a manner to allow substantive review to begin (including a table of contents, proper pagination, reference links, etc.)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Note: Draft proposed labeling is not in the current PLR-format, and will need to be revised.
2. Are the clinical pharmacology studies of appropriate design and breadth of investigation to meet the basic requirements for approvability of this product?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3. If multiple formulations were used in the clinical development of the product, does the NDA contain appropriate biopharmaceutics information to allow comparison between the clinical development and to-be-marketed product(s) (i.e. pivotal BE)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4. If unapproved products or altered approved products were used as active controls, was bioequivalence to the approved product demonstrated?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5. Are complete and relevant bioanalytical reports included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6. If applicable, was the sponsor's request for a waiver of the requirement for submission of in vivo bioavailability data included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7. Are complete datasets supporting the clinical pharmacology studies included in the NDA submission?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

OCP Primary Reviewer

Date

OCP Team Leader

Date

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/s/

Aryun Kim
11/12/2008 11:19:10 AM
PHARMACOLOGIST

Charles Bonapace
11/14/2008 09:13:06 PM
BIOPHARMACEUTICS