

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**050823Orig1s000**

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

<b>BIOPHARMACEUTICS REVIEW</b>			
<b>Office of New Drug Quality Assessment</b>			
<b>Application No.:</b>	NDA 50-823	<b>Reviewer:</b> Mark R. Seggel	
<b>Submission Date:</b>	12-AUG-2011 (eCTD)		
<b>Division:</b>	Anti-infective Products	<b>Team Leader:</b> Angelica Dorantes, Ph.D.	
<b>Applicant:</b>	B. Braun Medical Inc.	<b>Supervisor:</b> Patrick J. Marroum, Ph.D.	
<b>Trade Name:</b>	Not applicable	<b>Date Assigned:</b>	31-MAY-2011
<b>Generic Name:</b>	Ceftazidime for Injection, USP and Dextrose Injection, USP in Duplex® Container	<b>Date of Review:</b>	07-JUN-2011
<b>Indication:</b>	Treatment of infections caused by susceptible bacteria	<b>Type of Submission:</b> 505(b)(2); RLD is GSK's NDA 50-578, Fortaz (ceftazidime for injection) in ADD-Vantage vial.	
<b>Formulation / strengths:</b>	Injection and Diluent; 1 g and 2 g, in 50 mL		
<b>Route of Administration:</b>	Intravenous Infusion		
<b>Type of Review:</b>	<b>BIOWAIVER REQUEST</b>	<b>PDUFA Date:</b>	<b>13-JUN-2011</b>
<p><b>SUMMARY:</b> This new drug application provides for Ceftazidime for Injection, USP and Dextrose Injection, USP packaged in B. Braun's Duplex® Container. The Duplex® container system is a dual chamber flexible bag consisting of a drug-containing chamber, a diluent chamber, and a setport for administration. The product is manually activated by application of pressure which releases diluent into the drug chamber. The application is being submitted as a 505(b)(2) because of the use of this unique packaging system. The RLD, GSK's Fortaz (ceftazidime for injection) is packaged in the ADD-Vantage® vial.</p> <p>A biowaiver has been requested by the applicant in accordance with 21 CFR 320.22 (b)(1)(i-ii). The new drug product and the RLD are both parenteral solutions for administration by injection, and both products contain dry-powdered mixtures of the same amounts of ceftazidime pentahydrate (equivalent to 1 g and 2 g ceftazidime) and sodium carbonate. Reconstitution of the B. Braun's ceftazidime with the accompanying 50-mL 5% Dextrose Injection and reconstitution of the GSK product with 50-mL 5% Dextrose Injection with Abbott ADD-Vantage Flexible diluent containers result in solutions with the same concentration. Note that ADD-Vantage diluents are also available containing 0.45% or 0.9% Sodium Chloride Injection, and in 100-mL configurations).</p> <p>Because B. Braun's packaging system does not allow for removal of other than the entire contents, and because Fortaz is also available in several other packaging configurations, certain indications covered under the Fortaz labeling will not be included in the new product's labeling.</p> <p>A side-by-side comparison of the proposed new product and the RLD is provided on the following page.</p>			
<p><b>RECOMMENDATION:</b> The in vivo bioavailability or bioequivalence of the proposed new drug product is self-evident, and the criteria for a waiver of evidence of in vivo bioavailability or bioequivalence required under 21 CFR 320.22 have been satisfied. It is, therefore, recommended that this NDA be approved.</p>			
<p><b>Signature</b> Mark R. Seggel Reviewer Office of New Drugs Quality Assessment cc: A.Dorantes, M.Sloan, D.Matecka, J.Pohlman, C.Davi</p>		<p><b>Signature</b> Patrick J. Marroum, Ph.D. Biopharmaceutics Supervisor Office of New Drugs Quality Assessment</p>	

## Review Notes

### 1.12.12 Comparison of Proposed Product and RLD:

	B. Braun Product (N50-823)	RLD (N50-578)
Product Name	Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container	Fortaz® (Ceftazidime for Injection) in ADD-Vantage® vial
Manufacturer	B. Braun Medical Inc.	GSK
Strength	1 g and 2 g ceftazidime (anhydrous basis)	1 g and 2 g ceftazidime (anhydrous basis)
Active Ingredient*	Ceftazidime pentahydrate	Ceftazidime pentahydrate
Inactive Ingredient*	Sodium carbonate, ca. 118 mg/g ceftazidime	Sodium carbonate, ca. 118 mg/g ceftazidime
Diluent	5% Dextrose Injection – 50 mL	5% Dextrose Injection – 50 mL or 100 mL 0.9% Sodium Chloride Injection – 50 mL or 100 mL 0.45% Sodium Chloride Injection – 50 mL or 100 mL
Dosage Form	Parenteral Solution	Parenteral Solution
Route of Administration	Intravenous Infusion	Intravenous Infusion
Packaging System	Duplex® Container	ADD-Vantage® Vials
Indications	The conditions of use prescribed, recommended or suggested in the labeling for Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container are identical to those approved for Fortaz® except for urinary tract infections as well as lung infections caused by Pseudomonas spp. in patients with cystic fibrosis with normal renal function.	See combined package insert for Fortaz (ceftazidime for injection) and (ceftazidime injection)

\*Ceftazidime for Injection, USP, is a sterile mixture of Sterile Ceftazidime and Sodium Carbonate or Arginine. It contains not less than 90.0 percent and not more than 105.0 percent of ceftazidime on the dried and sodium carbonate- or arginine-free basis, and not less than 90.0 percent and not more than 120.0 percent of the labeled amount of ceftazidime.

### 1.12.15 Request for Waiver For *in-vivo* Studies:

B. Braun Medical Inc., hereby, requests a waiver of the requirement for the submission of evidence of in-vivo bioequivalence/bioavailability in accordance with 21 CFR 320.22 (b)(1)(i-ii). Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container is a parenteral solution intended solely for administration by injection and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application (NDA 050578). The bioequivalence of Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container relative to Fortaz® is therefore self-evident, as well as its bioavailability by the intravenous administration route.

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/s/  
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MARK R SEGCEL  
06/08/2011

ANGELICA DORANTES  
06/08/2011

## CLINICAL PHARMACOLOGY NDA FILEABILITY CHECKLIST

NDA: 50-823  
 Drug Name: Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex container, 1 g and 2 g  
 Applicant: B. BRAUN Medical Inc  
 Submission Date: August 13, 2010  
 Filing Date: October 12, 2010  
 PDUFA Date: June 13, 2011  
 OCP Primary Reviewer: Yongheng Zhang, Ph D  
 OCP Team Leader: Charles Bonapace, Pharm D

<i>QUESTION</i>	<i>YES</i>	<i>NO</i>	<i>NA</i>	<i>COMMENTS</i>
<b><i>Fileability:</i></b> <b><i>Is the Clinical Pharmacology section of the application fileable?</i></b> <b><i>(if 'NO', please comment as to why it is not fileable)</i></b>	<b><i>YES</i></b>			<b>This is a 505(b)(2) submission for the drug product Ceftazidime/Dextrose Injection in the Duplex container. No Clinical Pharmacology section is submitted, nor is it expected.</b>
<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"/>	
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"/>	

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OCP Primary Reviewer

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Date

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OCP Team Leader

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Date

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YONGHENG ZHANG  
10/01/2010

CHARLES R BONAPACE  
10/01/2010

## OFFICE OF CLINICAL PHARMACOLOGY REVIEW

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NDA:	50-823
Submission Date(s):	Aug 13, 2010
Drug	Ceftazidime
Product/Formulation; Strength(s)	Ceftazidime for Injection and Dextrose Injection in the DUPLEX <sup>®</sup> container, 1 gram in 50 mL and 2 grams in 50 mL
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Kimberly Bergman, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	B Braun Medical Inc.
Submission Type	505(b)(2), Original

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### BACKGROUND

B. Braun Medical Inc. submitted a 505(b)(2) NDA for Ceftazidime for Injection and Dextrose Injection in the DUPLEX<sup>®</sup> Container of 1 g/50 mL and 2 g/50 mL. The DUPLEX<sup>®</sup> 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. Seven other DUPLEX<sup>®</sup> antimicrobial products by B. Braun have been approved by the Agency since 2000.

The basis for this 505(b)(2) NDA is to use the Ceftazidime product from GlaxoSmithKline (GSK), Fortaz<sup>®</sup> in ADDVantage<sup>®</sup> 1 g and 2 g vials (NDA 50-587, approved 07/19/1985), as the reference listed drug (RLD). Accordingly, B. Braun requested a waiver for submission of evidence of in vivo bioavailability based on 21 CFR §320.22(b)(1)(i-ii).

The Sponsor meets the requirements for waiver of evidence of in vivo bioavailability, based on the listed criteria in 21 CFR §320.22(b)(1)(i-ii). The Ceftazidime DUPLEX<sup>®</sup> product, intended solely for administration by injection, contains the same active (ceftazidime) and inactive (sodium carbonate) ingredients in the same concentration as the RLD (**Table 1**).

**Table 1:** Comparison of Ceftazidime Duplex® product by B. Braun versus the Fortaz® in ADD-Vantage vials by GSK

Item	B. Braun	RLD
1. Name	Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container	Fortaz® (Ceftazidime for Injection) in ADD-Vantage® vial
2. Packaging System	Duplex® Container	ADD-Vantage® Vials
3. API	Ceftazidime pentahydrate	Ceftazidime pentahydrate
4. Inactive Ingredient(s)	Sodium Carbonate 5% Dextrose Injection – 50 mLs	Sodium Carbonate 5% Dextrose Injection – 50 mLs or 100 mLs 0.9% Sodium Chloride Injection –50 mLs or 100 mLs 0.45% Sodium Chloride Injection –50 mLs or 100 mLs
5. Strength	1 g and 2 g of ceftazidime approximate concentration of sodium carbonate is 118 mg/g	1 g and 2 g of ceftazidime approximate concentration of sodium carbonate is 118 mg/g
6. Route of Administration	Intravenous Injection	Intravenous Injection
7. Use	After constitution in the DUPLEX bag	After constitution with the diluent in the ADD-Vantage bag

#### RECOMMENDATIONS

The office of Clinical Pharmacology, Division of Clinical Pharmacology IV has reviewed the submission, 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: 09/2010

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

21 pages of draft labeling has been withheld in full as B(4)  
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/s/  
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YONGHENG ZHANG  
03/10/2011

KIMBERLY L BERGMAN  
03/10/2011