

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
050823Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 2, 2011
From	Janice Pohlman, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	50-823
Supplement#	
Applicant	B. Braun, Inc.
Date of Submission	August 12, 2010
PDUFA Goal Date	June 13, 2011
Proprietary Name / Established (USAN) names	Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container
Dosage forms / Strength	1 and 2 grams
Proposed Indication(s)	<ol style="list-style-type: none"> 1. Lower respiratory tract infections 2. Skin and skin structure infections 3. Bacterial septicemia 4. Bone and joint infections 5. Gynecologic infections 6. Intra-abdominal infections 7. Central nervous system infections
Recommended:	Approval for indications 1-7

1. Introduction

Ceftazidime is a cephalosporin antibacterial agent. Ceftazidime shares the same mechanism of action of other β -lactam antibacterial agents that inhibit cell wall synthesis by binding to penicillin-binding proteins (PBPs). Ceftazidime was approved by the Agency on July 19, 1985, for the following indications:

- Lower respiratory infections, including pneumonia caused by *Pseudomonas aeruginosa* and other *Pseudomonas* spp., *Haemophilus influenzae*, including ampicillin-resistant isolates, *Klebsiella* spp., *Enterobacter* spp., *Proteus mirabilis*, *Escherichia coli*, *Serratia* spp., *Citrobacter* spp., *Streptococcus pneumoniae*, and *Staphylococcus aureus* (methicillin-susceptible isolates)
- Skin and skin-structure infections caused by *P. aeruginosa*, *Klebsiella* spp., *E. coli*, *Proteus* spp., including *P. mirabilis* and indole-positive *Proteus*, *Enterobacter* spp., *Serratia* spp., *S. aureus* (methicillin-susceptible isolates), and *Streptococcus pyogenes* (group A beta-hemolytic streptococci)

- Urinary tract infections, both complicated and uncomplicated, caused by *P. aeruginosa*, *Enterobacter* spp., *Proteus* spp., including *P. mirabilis* and indole-positive *Proteus*, *Klebsiella* spp., and *E. coli*
- Bacterial septicemia caused by *P. aeruginosa*, *Klebsiella* spp., *H. influenzae*, *E. coli*, *Serratia* spp., *S. pneumoniae* and *S. aureus* (methicillin-susceptible isolates)
- Bone and joint infections caused by *P. aeruginosa*, *Klebsiella* spp., *Enterobacter* spp., and *S. aureus* (methicillin-susceptible isolates)
- Gynecologic infections, including endometritis, pelvic cellulitis, and other infections of the female genital tract caused by *E. coli*
- Intra-abdominal infections, including peritonitis caused by *E. coli*, *Klebsiella* spp., and *S. aureus* (methicillin-susceptible isolates) and polymicrobial infections caused by aerobic and anaerobic organisms, and *Bacteroides* spp. (many isolates of *Bacteroides fragilis* are resistant)
- Central nervous system infections, including meningitis, caused by *H. influenzae* and *Neisseria meningitidis*. Ceftazidime has also been used successfully in a limited number of cases of meningitis due to *P. aeruginosa* and *S. pneumoniae*.

The approved dosing regimens of ceftazidime are shown in the table below.

	Dose	Frequency
Adults		
Usual recommended dosage	1 gram IV or IM	Every 8-12 h
Uncomplicated urinary tract infections	250 mg IV or IM	Every 12 h
Bone and joint infections	2 grams IV	Every 12 h
Complicated urinary tract infections	500 mg IV or IM	Every 8-12 h
Uncomplicated pneumonia, mild skin and skin-structure infections	500 mg-1 gram IV or IM	Every 8 h
Serious gynecologic and intra-abdominal infections	2 grams	Every 8 h
Meningitis	2 grams	Every 8 h
Very severe life-threatening infections, especially in immunocompromised patients	2 grams	Every 8 h
Lung infections caused by <i>Pseudomonas</i> spp. in patients with cystic fibrosis with normal renal function	30-50 mg/kg IV to a maximum of 6 grams per day	Every 8 h
Neonates (0-4 weeks)	30 mg/kg	Every 12 h
Infants and children (1 month-12 years)	30-50 mg/kg IV to a maximum of 6 grams per day	Every 8 h

2. Background

B. Braun Medical Inc. submitted this new drug application (NDA) for Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® Container in 1 and 2 gram strengths on August 12, 2010. The NDA was submitted as a 505(b)(2) application because of the new drug delivery system for Ceftazidime for Injection. The review of this NDA relies on the Agency's prior determination of safety and efficacy for the reference listed drug (RLD), Fortaz® (NDA 50578, Ceftazidime for Injection manufactured by GlaxoSmithKline), which

was approved on July 19, 1985. The Applicant states that Ceftazidime for Injection and Dextrose Injection in the Duplex® container is bioequivalent to the RLD, Fortaz®, in the 1 and 2 gram strengths.

The Duplex® container is a drug delivery system that contains both drug substance (ceftazidime for injection) and diluent (5% dextrose) in a sterile, dual chamber, single use container. A peelable seal separates the diluent and drug chambers. The contents of each chamber remain separated until manual activation by the application of pressure to the diluent chamber. This allows for aseptic reconstitution of the drug product. The Duplex® container is designed to maintain the integrity of the contents of the drug chamber and diluent chamber during shipping and storage while maintaining them in a ready to administer configuration without the need for freezing or special storage conditions.

Six cephalosporin drug products are currently approved and marketed in the United States in the Duplex® container system. These products are:

- Cefazolin for Injection USP and Dextrose for Injection USP in the Duplex® Container (NDA 50779)
- Cefuroxime for Injection USP and Dextrose Injection USP in the Duplex® Container (NDA 50780)
- Ceftriaxone for Injection USP and Dextrose Injection USP in the Duplex® Container (NDA 50796)
- Cefoxitin for Injection USP and Dextrose Injection USP in the Duplex® Container (ANDA 65214)
- Cefotetan for Injection USP and Dextrose Injection USP in the Duplex® Container (ANDA 65430)
- Cefepime for Injection USP and Dextrose Injection USP in the Duplex® Container (NDA 50821)

3. CMC/Device

The chemistry, manufacturing, and controls review was conducted by Milton Sloan, Ph.D., who recommends approval of the application.

Crude ceftazidime (b) (4) is manufactured by (b) (4) into the sterile drug substance, ceftazidime (pentahydrate) and buffered with sterile sodium carbonate to produce Ceftazidime for Injection, USP. Ceftazidime for Injection is the subject of an official monograph in the United States Pharmacopeia (USP).

The finished drug product consists of Ceftazidime for Injection USP in one chamber and 5% Dextrose Injection USP in the other chamber of the sterile, nonpyrogenic, single use Duplex® (b) (4) Container. Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex® container will supply the equivalent of either 1.0 or 2.0 grams of ceftazidime. The manufacture of the finished Duplex® product will occur at B. Braun Medical, Inc., Irvine, CA, a dedicated production facility for cephalosporin drug products.

All facilities including that of the Applicant, (b)(4) and Irvine, CA, have been found to be acceptable by the Office of Compliance as noted in the Establishment Evaluation System (EES) reports.

The Applicant submitted a request for waiver of the requirement for submission of evidence of bioequivalence/bioavailability in accordance with 21 CFR 320.22(b)(1)(i-ii). Ceftazidime for Injection and Dextrose Injection in the Duplex® container is a parenteral solution intended solely for administration by intravenous injection and contains the same active and inactive ingredients in the same concentration as the RLD, Fortaz®. The Applicant claims that the bioequivalence of this product is self-evident. FDA review of the waiver is pending at this time.

The product quality microbiology assessment was performed by Steven Fong, Ph.D. who recommends approval of the application. The drug product consists of 1 gram or 2 grams of Ceftazidime for Injection powder and 50 mL of sterile 5% Dextrose Injection. The Duplex® containers are sterilized and (b)(4) filled with the ceftazidime and dextrose. The fill process, container closure, and package integrity have been found to be acceptable. The Applicant's proposal for drug product expiry of 9 months under room temperature conditions (25°C ± 2°C/60% ± 5%RH) was found to be acceptable.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology or toxicology information was submitted with this 505(b)(2) application. There are no objections to the approval of Ceftazidime for Injection and Dextrose Injection in the Duplex® container as noted in the memo by Wendelyn Schmidt, Ph.D., Pharmacology/Toxicology supervisor.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer, Yongheng Zhang Ph.D., performed a review of the clinical pharmacology portion of the Applicant's proposed label in the physician labeling rule (PLR) format.

6. Clinical Microbiology

There was no new clinical microbiology information submitted with this application. A review of the Applicant's proposed label in PLR format was conducted by Kerian Grande, Ph.D.

7. Clinical/Statistical- Efficacy

There was no new clinical data submitted with this 505(b)(2) application. The Applicant is relying on the Agency's prior determination of efficacy and safety of the RLD, Fortaz® for the listed indications.

There was no statistical review required for this application.

8. Safety

The Applicant submitted a safety update in the form of a literature review for the period of August 2009 to August 2010 for citations referencing “ceftazidime and safety or adverse events in humans”. Five citations were identified, two of which were felt to be pertinent and reviewed by the Applicant’s safety consultant, (b) (4)

The first citation by Hubert, et al described a cross-over study comparing continuous infusion of ceftazidime with multiple short infusions of ceftazidime in patients with cystic fibrosis.¹ Based on this article, the Applicant wanted to add decreased concentrations of C-reactive protein (CRP) to the post-marketing adverse reactions section of the label. Since a decrease in CRP most likely reflects an improvement in the infection, this term was not added as an adverse reaction.

The second article by Steadman, et al, used ceftazidime-calcium interactions as a comparator to explore ceftriaxone-calcium interactions and likelihood of embolic adverse drug events (ADE).² Adverse drug events were categorized into probable, possible, and possible nonrenal, nonpulmonary embolic events based on the likelihood that an ADE was related to an embolic event where ceftriaxone or ceftazidime was listed as a primary or secondary drug in combination with calcium. The article was unclear on how some adverse reactions were considered to be related to an embolic event. Based on this article, the Applicant proposed the following be added to the postmarketing adverse reaction section of the label (b) (4)

Based on the Applicant’s review of the Steadman article, the Applicant’s proposed additions to the postmarketing section of the label, and review of the current label for Fortaz®, the Office of Surveillance and Epidemiology (OSE) was consulted to explore renal-related adverse drug reactions. Ron Wassel, PharmD, Safety Evaluator, OSE explored acute renal failure associated with ceftazidime to support the Applicant’s proposed labeling change regarding “nephropathy, which may be severe (e.g. renal failure)”. Based on his review, he agreed with the Applicant’s conclusion that renal impairment induced by ceftazidime may be severe and result in acute renal failure.

Also included in the application were two published literature reports and two abstracts about adverse reactions related to dextrose containing solutions that occurred in patients with corn allergy/hypersensitivity. The article by Randolph describes five subjects with a history of corn sensitivity who developed various symptoms following administration of IV dextrose; three of these subject’s symptoms may be consistent with anaphylaxis.³ The second article described a nurse with a history of contact urticaria due to corn allergy who suffered from hand dermatitis likely related to cornstarch powder in gloves.⁴

This literature was used to support the inclusion of the following statement in the proposed product label:

The clinical reviewer, Alma Davidson, M.D., found three additional literature articles related to allergic reactions and corn-derived dextrose containing solutions.

- In an article from 1991, Guharoy et al describes a 23 year old woman admitted for Caesarean-section who was administered lactated Ringer's with 5% dextrose IV and experienced an anaphylactic reaction manifested by orofacial swelling, difficulty breathing, hypotension, and frequent premature ventricular contractions. Intravenous therapy was discontinued and the patient received diphenhydramine and hydrocortisone. Intravenous administration of lactated Ringer's without dextrose did not produce a similar reaction.⁵
- A 1980 report by Czarny et al describes two patients with a history of extrinsic asthma and insulin-dependent diabetes mellitus who developed anaphylaxis after the administration of 50% dextrose solution.⁶
- In a 2001 article by Tanaka, et al, a 44 year-old was referred for evaluation of corn allergy presenting as pruritus, urticaria, vomiting, and diarrhea. When given an oral challenge with corn, the patient developed anaphylaxis.⁷

Dr. Davidson then reviewed FDA's Adverse Event Reporting System (AERS) for cases of anaphylactic reactions/shock, allergic reactions, and type 1 hypersensitivity reactions with dextrose listed as a potential etiology. The search retrieved 108 cases with 22 serious adverse reactions where dextrose was suspect. Most of the events were confounded by concomitant medications or contained insufficient detail to determine whether dextrose was related to the event.

Based upon FDA review, the following statement was added to the Warnings and Precautions section of the label, in lieu of the Applicant's proposed contraindication statement.

“Hypersensitivity reactions, including anaphylaxis, have been reported with administration of dextrose containing products. These reactions have been reported in patients receiving high concentrations of dextrose (i.e. 50% dextrose). The reactions have also been reported when corn-derived dextrose solutions were administered to patients with or without a history of hypersensitivity to corn products.”

9. Advisory Committee Meeting

No Advisory Committee meeting was convened for this 505(b)(2) application.

10. Pediatrics

The Applicant requested a waiver of pediatric assessment requirements for all pediatric age groups. The reason for the request is that Ceftriaxone for Injection and Dextrose for Injection

in the Duplex® container is a single use container designed to deliver 1 or 2 grams of ceftazidime and is not appropriate for use in children who do not require the full designated doses because of concerns related to potential overdose.

However, the application did not require a pediatric assessment under Pediatric Research Equity Act (PREA) since the drug product does not contain or involve a new 1) active ingredient(s); 2) indication(s); 3) dosage form; 4) dosage regimen; or 5) route of administration.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues for this application.

12. Labeling

The Applicant provided a proposed product label based on that of the RLD, Fortaz®, with information in PLR format.

The Applicant agreed to the Agency's changes to the proposed product label.

The Division of Medication Error Prevention and Analysis (DMEPA) recommended that information on the container label be presented more clearly and concisely and be differentiated from its appearance on other Duplex® container labels. DMEPA cited recommendations from a September 7, 2007 public meeting involving members of FDA Division of Medication Errors and Technical Support (DMETS), Institute for Safe Medication Practices (ISMP), and United States Pharmacopeia (USP). The Division and CMC reviewer accepted most changes but felt that the following statements should be maintained on the container label as deleting them could compromise the safety of the product.

- “Use only if prepared solution is clear and free of particulate matter”
- “Prior to administration check for minute leaks by squeezing container firmly. If leaks are found, discard container as sterility may be impaired.”

The decision was made to retain these statements in the present container label, but recommended B. Braun, Inc., design future labels to conform to these recommendations.

In addition to changes previously recommended and agreed upon, DMEPA and CMC recommended the following additional changes to the container label on May 27, 2011:

- Change the statement (b) (4) to “The DUPLEX Container is not manufactured with latex, PVC, and DEHP”.
- Delete the (b) (4)
- Delete the statement that (b) (4)

A final container label is pending at the time of this review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Based upon the reviews and recommendations from the reviewers, I recommend that this application be approved for the following indications for infections due to susceptible bacteria:

1. Lower respiratory tract infections
2. Skin and skin structure infections
3. Bacterial septicemia
4. Bone and joint infections
5. Gynecologic infections
6. Intra-abdominal infections
7. Central nervous system infections

- Risk Benefit Assessment

This 505(b)(2) application relies on the prior finding of efficacy and safety of the RLD, Fortaz®. The drug is bioequivalent to Fortaz®.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

A postmarketing risk evaluation and management strategy is not necessary for this application.

- Recommendation for other Postmarketing Requirements and Commitments

There are no postmarketing requirements and commitments for this application.

- Recommended Comments to Applicant

There are no deficiencies or comments to be communicated to the Applicant.

References

1. Hubert D, Le Roux E, Lavrut T, et al. Continuous versus intermittent infusions of cefazidime for treating exacerbation of cystic fibrosis. *Antimicrob Agents Chemother* 2009;53:3650-6.
2. Steadman E, Raisch DW, Bennett CL, et al. Evaluation of a potential clinical interaction between ceftriaxone and calcium. *Antimicrob Agents chemother* 2010;54:1534-40.
3. Randolph TG, Rollins JP, Walter CK. Allergic reactions Following the Intravenous Injection of Corn Sugar (Dextrose). *Archives of Surgery* 1950;61:554-564.
4. Liu W, Nixon RI. Corn contact urticaria in a nurse. *Australian Journal of Dermatology* 2007;48:130-131.
5. Guharoy SR, Barajas M. Probable anaphylactic reaction to corn-derived dextrose solution. *Vet Hum Toxicol* 1991 Dec;33:609-610.
6. Czarny D, Prichard PJ, Fennessy M, Lewis S. Anaphylactoid reaction to 50% solution of dextrose. *Med J Aust.* 1980;2:255-258.
7. Tanaka LG, El-Dahr JM, Lehrer SB> Double-blind, placebo-controlled corn challenge resulting in anaphylaxis. *J Allerg Clin Immunol* 2001;107:744.

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/s/

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06/02/2011