CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050823Orig1s000

OTHER REVIEW(S)

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 50-823 BLA# N/A	NDA Supplement #:S- N/A BLA STN # N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: Ceftazidime for Injection USP and Dextrose Injection in the Duplex Conatiner Dosage Form: Injection Established/Proper Name: Ceftazidime for Injection USP and Dextrose Injection in the Duplex Conatiner Dosage Form: Injection Strengths:1g and 2g		
Applicant: B. Braun Medical, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: August 12, 2010 Date of Receipt: August 13, 2010 Date clock started after UN: N/A		
PDUFA Goal Date: June 13, 2011	Action Goal Date (if different): N/A	
Filing Date: October 13, 2010	Date of Filing Meeting: October 1, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) : Type 5		
Proposed indication(s)/Proposed change(s): Indicated for the treatment of the following infections caused by susceptible isolates of the designated microorganisms: Lower respiratory tract infections, skin and skin-structure infections, bacterial septicemia, bone and joint infections, gynecologic infections, intra-abdominal infections and central nervous system infections.		
Type of Original NDA: AND (if applicable)		505(b)(2)
Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***		N/A
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		Standard
Resubmission after withdrawal? **No**		Resubmission after refuse to file? **No**
Part 3 Combination Product? **No** ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate	

	products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other: None of the above apply	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): None

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***			X	
If yes, explain in comment column.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: Paid (PD3010305)
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: Not in arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**		X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:		X		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	All electronic			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	N/A			
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	**X**			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English)	**X**			

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?			X	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?			X	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*			X	No studies were conducted by applicant
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***			X	
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and***	X			

the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			**X**	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver	X			

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***				
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]			X	
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***			X	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	Package Insert (PI) Immediate container labels			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	**Not Applicable**			
Check all types of labeling submitted.	N/A			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			OSE consult completed March 29, 2011 (Renal Failure)
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***			X	
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***			X	

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 1, 2011

BLA/NDA/Supp #: NDA 50-823 (505(b)(2) application)

PROPRIETARY NAME: Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex Conatiner

ESTABLISHED/PROPER NAME: Ceftazidime for Injection USP and Dextrose Injection USP in the Duplex Conatiner

DOSAGE FORM/STRENGTH: Injection; 1g and 2g

APPLICANT: B. Braun Medical, Inc.

PROPOSED INDICATION(S): Indicated for the treatment of the following infections caused by susceptible isolates of the designated microorganisms: Lower respiratory tract infections, skin and skinstructure infections, bacterial septicemia, bone and joint infections, gynecologic infections, intra-abdominal infections and central nervous system infections.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	J. Christopher Davi, MS	Y
	CPMS/TL:	Maureen Dillon-Parker	N
Cross-Discipline Team Leader (CDTL)	Janice K. Pohlman, MD		Y
Clinical	Reviewer:	Alma Davidson, MD	Y
	TL:	Janice K. Pohlman, MD	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (*for antimicrobial products*)	Reviewer:	Kerian Grande, PhD	Y
	TL:	Frederic Marsik, PhD	Y

Clinical Pharmacology	Reviewer:	Yongheng Zhang, PhD	Y
	TL:	Charles Bonapace, PharmD	Y
Biostatistics	Reviewer:	Daniel Rubin, PhD	Y
	TL:	Thamban Valappil, PhD	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Wendelyn Schmidt, PhD	Y
	TL:	N/A	
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Milton Sloan, PhD	Y
	TL:	Rapti Madurawe, PhD	Y
Quality Microbiology *(for sterile products)*	Reviewer:	Stephen Fong, PhD	Y
	TL:	James McVey, PhD	N
CMC Labeling Review	Reviewer:	Milton Sloan, PhD	Y
	TL:	Rapti Madurawe, PhD	Y
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	N/A	
	TL:		
OSE/DRISK (REMS)	Reviewer:	Ronald Wassel, PharmD	N
	TL:	Kelly Cao, PharmD	N
OC/DCRMS (REMS)	Reviewer:	N/A	
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	N/A	
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers	None		
Other attendees	Wiley Chambers, MD, Acting Division Director		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	YES
• Electronic Submission comments **List comments**: None	None
CLINICAL **Comments**: None	FILE
• Clinical study site(s) inspections(s) needed? **If no,** explain: No studies conducted	NO
• Advisory Committee Meeting needed? **Comments**: No, no studies were conducted. ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety***	NO

or efficacy issues ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**: None	Not Applicable
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**: None	Not Applicable
CLINICAL MICROBIOLOGY **Comments**: None	FILE
CLINICAL PHARMACOLOGY **Comments**: None	FILE
• Clinical pharmacology study site(s) inspections(s) needed?	NO
BIOSTATISTICS **Comments**: None	FILE
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: None	FILE

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**: None	Not Applicable
PRODUCT QUALITY (CMC) **Comments**: See 74-day letter	Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: None	YES
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: See review by Stephen Fong, PhD	YES
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**: All facilities deemed compliant through 22-Sept-2012	YES YES YES
Facility/Microbiology Review (BLAs only) **Comments**: None	Not Applicable

CMC Labeling Review **Comments**: None	

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Katherine A. Laessig, MD, Deputy Division Director, DAIP **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**: None

REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. Review Issues: Review issues have been identified for the 74-day letter. List (optional): CMC (see letter) Review Classification: Standard Review

ACTIONS ITEMS	
X	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
N/A	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
N/A	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
N/A	BLA/BLA supplements: If filed, send 60-day filing letter
N/A	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
X	Send review issues/no review issues by day 74

N/A	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH C DAVI
05/25/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 50-823	NDA Supplement #: S- N/A	Efficacy Supplement Type SE- N/A
Proprietary Name: N/A Established/Proper Name: Ceftazidime for Injection USP and Dextrose Injection in the Duplex Container Dosage Form: Solution for Injection Strengths: 1g and 2g		
Applicant: B. Braun Medical, Inc.		
Date of Receipt: August 13, 2010		
PDUFA Goal Date: June 13, 2011	Action Goal Date (if different):N/A	
Proposed Indication(s): For treatment of patients with infections caused by susceptible strains of the designated microorganisms.		

GENERAL INFORMATION

1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

NO

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Refers to the approved Drug, Fortaz® 1 g and 2 g vials as the reference listed drug (RLD) – NDA 50-578	• Waiver of evidence of *in vivo* bioavailability • Prior finding of safety and efficacy; Safety and efficacy information contained in the FULL PRESCRIBING INFORMATION section of the label.
Published literature articles	Safety update

*each source of information should be listed on separate rows

3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Applicant proposes only to package Fortaz® in the Duplex® container. No bridging studies are necessary from a bioequivalence standpoint.

RELIANCE ON PUBLISHED LITERATURE

4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

NO

*If "**NO**," proceed to question #5.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

N/A

*If "**NO**", proceed to question #5.*

*If "**YES**", list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

N/A

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES

*If "**NO**," proceed to question #10.*

6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Fortaz®	50-578	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer **"N/A"**.*

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

8) Were any of the listed drug(s) relied upon for this application:

a) Approved in a 505(b)(2) application?

NO

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

b) Approved by the DESI process?

NO

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

c) Described in a monograph?

NO

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph: Fortaz® (NDA 50-579)

d) Discontinued from marketing?

NO

*If "**YES**", please list which drug(s) and answer question d) i. below.*
*If "**NO**", proceed to question #9.*

Name of drug(s) discontinued from marketing: N/A

i) Were the products discontinued for reasons related to safety or effectiveness?

N/A

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for the packaging of the bioequivalent RLD Fortaz in the Duplex® packaging system.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.*

NO ☐

*If "**NO**" to (a) proceed to question #11.*
*If "**YES**" to (a), answer (b) and (c) then proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

N/A

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

N/A

*If "**YES**" to (c) <u>and</u> there are no additional pharmaceutical equivalents listed, proceed to question #12.*
*If "**NO**" <u>or</u> if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s): N/A

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

***Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.*

YES
*If "**NO**", proceed to question #12.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES

*If "**YES**" <u>and</u> there are no additional pharmaceutical alternatives listed, proceed to question #12.*

*If "**NO**" <u>or</u> if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do <u>not</u> have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s): Fortaz® (NDA 50-578)

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): There are no unexpired patents listed.

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s): N/A

14) Which of the following patent certifications does the application contain? *(Check all that apply <u>and</u> identify the patents to which each type of certification was made, as appropriate.)*

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

B. Braun Medical Inc., hereby states that, in its opinion and to the best of its knowledge, the reference listed drug, Fortaz® drug product, applicant GlaxoSmithKline, is subject to the exemption provisions of Section 125 of Title 1 of the Food and Drug Administration Modernization Act of 1997. For this reason, patent certification is not required.

15) Complete the following checklist ***ONLY*** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

N/A

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOSEPH C DAVI
05/24/2011

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	May 02, 2011
Application Type/Number:	NDA 050823
To:	Wiley A Chambers, MD, Acting Director Division of Anti-Infective and Ophthalmology Products
Through:	Melina Griffis, RPh, Team Leader Kellie Taylor, PharmD, MPH, Associate Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Lubna Merchant, M.S., Pharm.D, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Ceftazidime for Injection and Dextrose Injection in the Duplex Container, 1 g and 2 g
Applicant/sponsor:	B Braun Medical
OSE RCM #:	2011-284

CONTENTS

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling of the container labels and carton labeling for Ceftazidime for Injection and Dextrose Injection in the Duplex Container (NDA 050823). Seven other Duplex products by B. Braun have been approved by the Agency for other antimicrobial products. DMEPA did not evaluate these labels and labeling of the prior submissions.

2. METHODS AND MATERIALS

Since Ceftazidime is currently marketed, the Division of Medication Error Prevention and Analysis (DMEPA) conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify any medication errors relevant to the labels or labeling of Ceftazidime. In addition, we also searched AERS for any medication errors related to the other seven Duplex products marketed by B Braun. Additionally, we evaluated the proposed container labels, and carton labeling submitted by the Applicant.

2.1. ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

An AERS search was conducted on February 24, 2011 using the tradename "Fortaz," active ingredient 'Ceftazidime, and verbatim term "Forta%," and "Ceftazidim%." The reactions used were the HLGT term, "Medication Errors," and the PT term, "Product Quality Issue."

A second AERS search was conducted on April 25, 2011 to identify errors occurring with products marketed in the Duplex container. The following search terms were used: active ingredients 'Cefazolin, Cefuroxime, Cefotaxime, Ceftriaxone, Cefoxitin, Cefotetan, and Cefepime'. The reactions used were the HLGT term, "Medication Errors," and the PT term, "Product Quality Issue." The manufacture was limited to B Braun and the dates were limited from 7/27/200 to 4/25/2011.

Reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. Reports that did not describe a medication error or did not describe an error applicable to this review (e.g. adverse events related to ceftazidime or other medications, accidental exposure, intentional or accidental overdose, no medication errors, errors due to knowledge or performance deficit) were excluded from further analysis. If an error occurred, the reports were categorized by type of error and evaluated for contributing factors to the medication errors. Additionally the reports were reviewed to determine if the error could be applicable to the labels and labeling of Ceftazidime and thus pertinent to this review.

2.2 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA),[1] the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the container labels, and carton labeling. This review focuses on labels and labeling submitted as part of August 13, 2010

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

submission. See Appendices A-B for images of the proposed container labels and carton labeling. In addition, we also reviewed our recommendations made in the previous labeling review for Cefepime/dextrose duplex containers (OSE# 2010-444).

3. RESULTS

The following section describes the results of AERS and our label and labeling review.

3.1 AERS RESULTS

A total of 91 cases were retrieved in the AERS search, however after excluding cases as described in section 2.1, only 26 cases involved a medication error. These cases are categorized below:

- Wrong dose error (n=11). These cases involve an overdose of Ceftazidime in patients with renal impairment and reported a failure to adjust dosage based on the renal function.
- Wrong drug errors (n=9), which involved the following products:
  - One case involved the products Forteo and Fortaz, one case involved Tazidime and Trazodone, one case involved Ceftazidime and Cefuroxime, one case involved Ceftazidime and Ceftizoxime and the last case reported the labeling of bulk bottle of Fortaz -ceftazadime- (b) (4) and individual bottle are identical and have a potential for error.
  - Four cases involved Fortaz and Zinacef, the reporter in all four cases stated that the labels on the Fortaz 1 gram and 2 gram add-vatage vials and the Zinacef 750 mg and 1.5 gram vials made by Glaxo are very similar to each other. These cases are not relevant to this review and will be assessed in a separate review.
- Wrong route errors (n=3), two cases involved Ceftazidime being given via intra-arterial route instead of intravenous route and one case reported that Ceftazidime was inhaled over 3 minutes.
- Wrong patient (n=2), in one case the drug was entered on the wrong patient and the other case the drug was administered to the wrong patient.
- Wrong technique error (n=1), involved a case in which Ceftazidime was reconstituted with sodium chloride instead of sterile water for an intramuscular injection.

3.2 LABELS AND LABELING

The container label risk assessment identified the following deficiencies:

- The information on the container label needs to be condensed to improve readability.
- The proposed container labels for Ceftazidime/dextrose duplex containers are not adequately differentiated from other available duplex containers products by B Braun.

We provide labeling recommendations in section 5 to address these deficiencies.

4. DISCUSSION

The Applicant states the Duplex system is designed for single use administration. Seven other Duplex products by B. Braun have been approved by the Agency for other antimicrobial products. The Ceftazidime for Injection and Dextrose for Injection in the Duplex Container application is the eight cephalosporin duplex container application submitted to the FDA. According to the Applicant, the advantages of this system includes a decreased potential for admixture errors or contamination of the drug product and a decreased risk of needle stick injuries with the needle-free system. The Duplex Container packages Ceftazidime powder and dextrose solution in separate chambers together in one dual chamber bag. To reconstitute the Ceftazidime powder and Dextrose diluent, the seal between the two separated chambers are broken by applying pressure to the container. The Duplex system simplifies the steps needed to reconstitute the admixture and does not require a syringe or needle in reconstituting the product. We agree that the Ceftazidime for Injection and Dextrose Injection in the Duplex Container reduces potential for admixture errors or contamination of the drug product and decreases the risk of needle stick injuries with the needle-free system. However, we note that with this design there may be a risk of administering the diluent without mixing the drug. Our AERS search for similar duplex products did not identify any existing medication error cases related to admixture error and thus we are satisfied that the current labeling helps to manage this risk.

Additionally, we note that the proposed Ceftazidime for Injection and Dextrose Injection in the Duplex Container cannot provide for all dosages and thus the risk of infusing the wrong amount of drug is still present. For patients with decreased renal function, partial volume infusion of Ceftazidime contained in the Duplex Container will be required.

In our search of AERS, we identified several cases of overdose due to failure to adjust doses based on creatinine clearance. However, this error is not likely due to the labeling because the renal dosing provided in SECTION 2.3 DOSAGE AND ADMINISTRATION is adequate.

We also note that the labels for Ceftazidime for Injection and Dextrose Injection in the Duplex Container are identical to the labels of Cefepime for Injection and Dextrose Injection in the Duplex Container. The similarity can lead to selection errors and administration of the wrong drug. To avoid selection errors adequate differentiation between the two products is warranted.

In addition, the duplex container label is too cluttered. This clutter decreases the readability of the label. The Agency, in conjunction with the U.S. Pharmacopeia (USP) and the Institute of Safe Medication Practices (ISMP), held a public meeting to discuss changes to the information on parenteral drug products to improve the safety of their use.[2] Following that meeting, DMEPA, USP and ISMP compiled a list of essential and none essential information that currently appears on infusion bags labels. We provide recommendations to minimize some of the clutter to improve readability of the labels based on this list.

[2] Improving Patient Safety by Enhancing the Container Labels for Parenteral Infusion Drug Products, a Public Meeting, on January 11, 2007.

5. CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling identified areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations in Section 5.2 Comments to the Applicant for the container labels and carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Brantley Dorch at 301-796-0150.

5.2 COMMENTS TO THE APPLICANT:

A. Ceftazidime/Dextrose Duplex Container Label (all strengths)

1. The Ceftazidime/Dextrose Duplex containers look identical to the Cefepime/Dextrose Duplex containers. Revise the duplex containers so that these products are adequately differentiated from each other. This can be achieved by increasing the prominence of the established name and utilizing different colors or boxing or different font or layouts in the presentation of the established names and strength.
2. The duplex container label is too cluttered, which decreases the readability of the information on the labels. Additionally, we request you make the following revisions to improve readability and prominence of information on the proposed labels:
    a. Delete the following statements to minimize label clutter:

(b) (4)

    b. Use a different font or other means such as boxing to highlight the reconstitution directions of the product so that this information is displayed prominently
    c. Relocate the reconstitution information so that it appears prior to the “drug chamber contains ....” statement
    d. The size of the company logo is more prominent than the established name. Decrease the size of the company logo.

B. Ceftazidime/Dextrose Duplex Container Label - Drug Chamber Label (all strengths)

1. Revise the statement [redacted] (b) (4) with "Peel foil strip only when ready for use to visually inspect drug prior to reconstitution"

2. Delete the statement [redacted] (b) (4) as this information is included on the Container Label.

C. Other approved Duplex Container Label (Cefazolin, Cefuroxime, Cefotaxime, Ceftriaxone, Cefoxitin, Cefotetan, and Cefepime)

At the time of next printing or within one year, revise all the approved Duplex Container products you manufacture to incorporate the above comments A2, A3, A4, B1, and B2.

[redacted] (b) (4)

Appendix C: AERS cases

ISR #		ISR #		ISR #		ISR #	
382786	9	1977746	8	4609455	0	5588765	7
422111	8	1982605	0	4623716	0	5612626	8
469433	2	3038564	5	4632194	7	5692962	X
573996	6	3049575	8	4657836	1	5731837	4
605027	3	3219295	5	4783154	7	5793561	1
631407	6	3229147	2	4823667	2	5845250	2
639379	5	3396207	5	5007788	X	5901997	0
737836	4	3545795	4	5007789	1	5975873	1
749535	3	3724351	9	5039145	4	6038592	1
772358	6	3924037	1	5074260	0	6056887	2
794210	2	3976106	8	5078367	3	6086524	2
843950	5	4002392	4	5081658	3	6088769	4
913603	3	4097978	5	5106554	4	6098183	3
946032	7	4209013	6	5115707	0	6124633	X
1358527	5	4264855	6	5170007	8	6406745	6
1419175	1	4303489	1	5215025	6	6651558	3
1444833	2	4515879	2	5267285	3	6679675	2
1494184	5	4516076	7	5269857	9	6772127	0
1518955	1	4534352	9	5275810	1	6775076	7
1584566	5	4535620	7	5500843	7	6779442	5
1676330	3	4606682	3	5504177	6	7020648	8
1822319	0	1921866	0	5554288	4	7291368	X
1914689	X			5564965	7		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUBNA A MERCHANT
05/02/2011

MELINA N GRIFFIS
05/03/2011

KELLIE A TAYLOR
05/04/2011

CAROL A HOLQUIST
05/04/2011

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Pre-Decisional Agency Information

Date: April 13, 2011

To: J. Christopher Davi, MS, Regulatory Project Manager
Division of Anti-Infective and Ophthalmology Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications

Sheila Ryan, Pharm.D., Group Leader
Division of Drug Marketing, Advertising and Communications

Subject: NDA 50823
Ceftazidime for Injection USP and Dextrose Injection USP in Duplex Container, for intravenous use

As requested in your consult dated March 18, 2011, DDMAC has reviewed the draft labeling for Ceftazidime for Injection USP and Dextrose Injection USP in Duplex Container.

DDMAC's PI comments are based on the substantially complete version of the labeling titled, "50823PLR18Mar11clean.doc" which was sent via email from Christopher Davi on March 21, 2011.

DDMAC's comments are provided in the attached, clean version of the labeling.

If you have any questions about DDMAC's comments on the PI, please contact Christine Corser at 6-2653 or at Christine.Corser@fda.hhs.gov.

Thank you for the opportunity to provide comments on this label.

22 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE G CORSER
04/13/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 29, 2011
To:	Wiley Chambers, MD, Acting Director Division of Anti-Infective and Ophthalmology Products
From:	Ronald Wassel, PharmD, Safety Evaluator Division of Pharmacovigilance II
Through:	Kelly Cao, PharmD, Team Leader Division of Pharmacovigilance II Robert Boucher, MD, MPH, Director Division of Pharmacovigilance II Office of Surveillance and Epidemiology
Subject:	Evaluation of acute renal failure associated with ceftazidime
Application Type/Number:	Ceftazidime for Injection and Dextrose Injection in the Duplex Container NDA #: 50-823
Applicant/sponsor:	B. Braun Medical, Inc.
OSE RCM #:	2011-93

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (AERS) cases of acute renal failure reported in association with ceftazidime. The Division of Anti-Infective and Ophthalmology Products (DAIOP) requested this review by the Division of Pharmacovigilance II (DPV II) to determine if the cases we have in AERS support the sponsor's proposed labeling change concerning renal impairment.

DPV II finds the sponsor's proposed change to the POSTMARKETING EXPERIENCE section regarding renal failure acceptable, but suggests the following wording (add the word *which*):

> nephropathy, which may be severe (e.g. renal failure)

This review includes 20 cases of acute renal failure in association with ceftazidime, as per our case definition.

Given the information available, the temporal association, and the reported association of renal impairment with ceftazidime and toxic nephropathy with cephalosporins in general, it is reasonable to conclude that the renal impairment induced by ceftazidime may be severe and result in acute renal failure.

1 BACKGROUND

The Division of Anti-Infective and Ophthalmology Products (DAIOP) consulted the Division of Pharmacovigilance II (DPV II) to conduct an analysis of Adverse Event Reporting System (AERS) reports of renal adverse events associated with ceftazidime. B.Braun submitted a marketing application to market Glaxo's Fortaz (ceftazidime) in a Duplex® container and is converting Glaxo's label into the Physician Labeling Rule (PLR) format. B.Braun's submission included a safety update of literature articles related to the ceftazidime drug product that was prepared by an outside consultant. The consultant's review included recommendations for labeling changes, which included new wording for renal toxicity (a labeled event). The Review Division consulted us to determine if the cases we have in AERS support that change.

1.1 INTRODUCTION

Ceftazidime is a third-generation cephalosporin with broad spectrum activity against Gram-positive and Gram-negative bacteria. Unlike most third-generation agents, it is active against *Pseudomonas aeruginosa*; however, it has weaker activity against Gram-positive microorganisms and is not used for such infections. Ceftazidime is used to treat a wide range of severe urinary, respiratory, and wound infections, mostly due to enterobacteria or *Pseudomonas aeruginosa*, often combined with an aminoglycoside. Reference is made to its use in pneumonia, septicemia, meningitis, peritonitis, osteomyelitis, neonatal sepsis, burns, and melioidosis. It is also used in the empirical therapy of febrile neutropenia, alone or in combination with other antibiotics.

1.2 REGULATORY HISTORY

Ceftazidime was approved in 1985 (NDA # 50-578; Fortaz—GlaxoSmithKline). It is also marketed under several ANDAs. B. Braun Medical submitted a marketing application (NDA # 50-823) on July 30, 2010 to market ceftazidime in the Duplex® drug delivery system.

1.3 CURRENT LABELING OF RENAL ADVERSE REACTIONS FOR CEFTAZIDIME (FORTAZ LABEL USED AS RLD)

In the PRECAUTIONS/Drug Interactions section:

> Nephrotoxicity has been reported following concomitant administration of cephalosporins with aminoglycoside antibiotics or potent diuretics such as furosemide. Renal function should be carefully monitored, especially if higher dosages of the aminoglycosides are to be administered or if therapy is prolonged, because of the potential nephrotoxicity and ototoxicity of aminoglycosidic antibiotics. Nephrotoxicity and ototoxicity were not noted when ceftazidime was given alone in clinical trials.

In the ADVERSE REACTIONS/Laboratory Test Changes section (noted during clinical trials):

> As with some other cephalosporins, transient elevations of blood urea, blood urea nitrogen, and/or serum creatinine were observed occasionally.

In the POSTMARKETING EXPERIENCE section:

> Renal and Genitourinary: Renal impairment.

Under Cephalosporin-Class Adverse Reactions:

> toxic nephropathy

1.4 SPONSOR'S PROPOSED LABELING

The sponsor proposes to change the wording in the POSTMARKETING EXPERIENCE section from (b) (4)

In addition, the sponsor will include the following disclaimer in the POSTMARKETING EXPERIENCE section:

> The following adverse reactions have been reported during postapproval use of ceftazidime. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to readily estimate their frequency or establish a causal relationship to drug exposure.

2 METHODS AND MATERIALS

2.1 AERS SELECTION OF CASES

This reviewer conducted an AERS search on 1/13/2011 with ceftazidime using the MedDRA High Level Group Terms (HLGT) Nephropathies, and Renal Disorders (Excl Nephropathies), for all cases reported in the database.

2.2 CASE DEFINITION[1]

This review includes cases of renal failure based on the following:

One of the following satisfies the inclusion criteria:

1. Any case reporting a diagnosis of new onset renal failure or acute renal failure
2. Any case requiring recent dialysis or kidney transplant due to drug-induced renal failure

3. Any case specifying "renal insufficiency/impairment" and accompanied by at least **one** of the following lab data: increase in baseline serum creatinine of ≥ 0.5 mg/dL or decrease in baseline GFR of ≥ 25% in patients with previous normal renal function OR increase of ≥ 1 mg/dL in baseline creatinine in patients with chronic kidney disease OR anuria, oliguria (decreased urinary output)
4. Any case reporting nephrocalcinosis, interstitial nephritis per histology (may not be explicitly stated in report, but these events can lead to ARF)

3 RESULTS

3.1 ADVERSE EVENT CASES

The AERS search retrieved 590 cases using the broad search terms noted above. To obtain a manageable case series, the cases were exported to an Excel spreadsheet, and this reviewer excluded cases from further review that listed multiple suspect medications, leaving a total of 77 cases in which ceftazidime was the only suspect product reported. These cases underwent a hands-on review for inclusion based on the case definition, which resulted in the exclusion of 57 cases because they were either non-specific, not temporally related, the patient had pre-existing renal dysfunction that did not change, or the renal dysfunction was attributed to the patient's underlying condition or other causes, leaving a total of 20 cases. The Individual Safety Report (ISR) numbers of the 20 cases are presented in Appendix 1.

These 20 cases were received by the FDA between 1985 (year of approval) and 2007, with the majority (16) received prior to 1996. The age of the patients ranged from 34 days to 90 years (median—71 years; mean—61.1 years). The source of the reports included 11 domestic cases and 9 foreign cases. Reported indications for the use of ceftazidime included sepsis, *Pseudomonas* infection, pneumonia, endocarditis, osteomyelitis, cellulitis, urinary tract infection, biliary tract infection, and post-operative use.

The case series included two cases in which the patients underwent hemodialysis, and seven cases with a reported outcome of death. In five of the seven cases, renal failure was listed as contributory to the patient's death.

3.2 SELECTED CASES

The majority of cases had only minimal information, which made a causality assessment difficult. The following representative cases were chosen because of their adjudication as possible cases. The full case narratives, if not complete here, are presented in Appendix 2.

3.2.1 Deaths in which renal failure was considered contributory

- ISR # 371259 (1985; Costa Rica; Clinical Trial)—a 34–day–old male born prematurely with congenital agenesis of the left kidney and insufficiency of the right kidney was prescribed ceftazidime for septicemia due to *Enterococcus* at a dose of 119 mg/kg/day for

7 days (dose in current package insert for neonates 0 to 4 weeks is 30 mg/kg every 12 hours). After five doses the patient did not look septic and was more active. However, the severe underlying renal insufficiency progressed to oliguria and he died due to renal failure and cardiac arrest. The reporter assessed the death as not related to ceftazidime.

- ISR # 407050; Glaxo Mfr. Report # CG001379 (1984; Germany; Clinical Trial)—a 46–year–old male with a history of alcoholism and impaired renal function was treated with ceftazidime 4 grams daily for 8 days for osteomyelitis. He developed acute renal failure, which did not respond to daily hemodialysis, and died due to ventricular fibrillation following hyperkalemia. (Extent of information from Adverse Event Report.)

- ISR # 393072; Glaxo Mfr. Report # CG001185 (1986; Germany; Clinical Trial)—a 50–year–old male with alcoholism, lung pathology, pneumonia, and an extensive infected soft tissue injury was treated with ceftazidime 2 grams three times a day (reduced to 1 gram twice daily after 6 days) for a total of 8 days. The patient died due to renal failure and shock lung. (Extent of information from Adverse Event Report.)

- ISR # 478096; Glaxo Mfr. Report # CG002291 (1987; Japan)—a 75–year–old female was treated with ceftazidime 2 grams twice daily (reduced to 2 grams once daily after 3 days) for a total of 4 days for pyelonephritis and cystitis. The patient died due to heart and renal failure. Hepatic dysfunction (elevation in GOT and GPT, mild) and renal dysfunction (elevation in BUN and CR, severe). Doctor's comment: It is not clear whether renal failure was due to pyelonephritis or to drug treatment. (Extent of information from Adverse Event Report.)

- ISR # 912100; Glaxo Mfr. Report # G0016042 (1992; United States)—a 90–year–old female with no history of renal impairment was hospitalized for gallbladder surgery. She received ceftazidime 3 grams daily and died 4 to 5 days later due to renal failure. (Extent of information from Adverse Event Report.)

3.2.2 Additional cases

- ISR # 3168521; Glaxo Mfr. Report # B0060261 (1998; Japan)—a 4–month–old female received ceftazidime for a *Pseudomonas* infection and developed aggravated renal failure. Serum creatinine (mg/dL) increased from 0.16 to 1.32 and returned to 0.09 following discontinuation of ceftazidime and treatment with furosemide. Urinary volume (mL/24hr) decreased from 278 to 85 and returned to 324.

- ISR# 710902; Glaxo Mfr. Report # G004763 (1990; Japan)—a 68–year–old female was treated with ceftazidime for a suspected biliary tract infection. After one day, the patient was noted to have a decreased urine volume and became anuric the next day. The patient was treated with furosemide, mannitol, and hemodialysis and ceftazidime was discontinued. The acute renal failure resolved after approximately three weeks.

- ISR# 571610; Direct Report (1988; United States)—a 76–year–old male with kidney stones and recurrent UTIs secondary to *Pseudomonas* and *Proteus* received ceftazidime and developed an erythematous rash, eosinophiluria, and non-oliguric acute renal failure. Ceftazidime was replaced with aztreonam after which the rash resolved and the renal function returned to baseline. (Extent of information from Adverse Event Report.)

- ISR# 565903; Glaxo Mfr. Report # G0002002 (1988; United States)—a 78–year–old male with an elevated BUN (34) and sodium (146-157) was treated with ceftazidime for a *Proteus* UTI. Two days later the BUN and sodium were even higher (104 and 187-190, respectively) and he had a decreased urine output. Serum creatinine was also increased (1.0 to 2.6). On day three, BUN, creatinine, and sodium were 113, 2.9, and 193, respectively. The patient lapsed into a coma and died four days later due to underlying factors. (Extent of information from Adverse Event Report.)

4 DISCUSSION

This review includes 20 cases of acute renal failure in association with ceftazidime, as per our case definition.

The labels of other intravenous cephalosporins generally include information with respect to renal failure/nephrotoxicity in the Adverse Reactions and Postmarketing Experience sections of their labels. Two exceptions are the cefuroxime and ceftriaxone labels, which include statements in the Precautions section.

The cases with ceftazidime are generally older reports (> 15 years) and lack sufficient detailed information. It is possible that in many of these cases, the renal failure could have been related to the patients' underlying condition, or other unknown factors. However, given the information available, the temporal association, and the reported association of renal impairment with ceftazidime and toxic nephropathy with cephalosporins in general, it is reasonable to conclude that the renal impairment induced by ceftazidime may be severe and result in acute renal failure.

Although deaths due to renal failure have been reported in a few of the cases, it is unclear if ceftazidime contributed based on the available information and whether this represents a significant risk.

5 RECOMMENDATIONS

DPV II finds the sponsor's proposed change to the POSTMARKETING EXPERIENCE section regarding renal failure acceptable, but suggests the following wording (add the word *which*):

nephropathy, which may be severe (e.g. renal failure)

6 REFERENCES

1. Kortepeter C, Mackey A. Case Definition: Acute Renal Failure. OSE Case Definition Working Group. November 2002 (revised August 2008).

APPENDIX 1

ISR Numbers of Reports Included in Case Series

365317
371259
393072
407044
407050
478096
503595
563252
571610
710902
772787
840105
878958
912100
1644927
1684129
1749450
3168521
4519305
5453898

APPENDIX 2

ISR # 371259 (1985; Costa Rica; Clinical Trial)

A 34–day–old male patient was born prematurely at 33 weeks gestation. The child had a seizure disorder, congenital agenesis of the left kidney, insufficiency of the right kidney, and a colostomy, which was performed due to a perforated anus. He subsequently developed septic symptoms due to *Enterococcus* and was treated with ceftazidime, 119 mg/kg/day for seven days. On day two of ceftazidime therapy (after 5 doses), this patient did not look septic and was more active. However, the severe underlying renal insufficiency progressed to oliguria and five days later he died due to renal failure and cardiac arrest. The reporter assessed the death as not related to ceftazidime.

ISR # 3168521; Glaxo Mfr. Report # B0060261 (1998; Japan)

A 4–month–old female with a history of congenital myopathy was diagnosed as having multiple organ failure and experienced a cardiac arrest. The next day, the patient was diagnosed as having a *Pseudomonas* infection and was started on ceftazidime 100 mg/kg twice daily. After this, symptoms of renal failure began to appear and the patient was started on furosemide. Four days after starting ceftazidime, the patient was given a transfusion of microtubule associated protein. Four days later a conducting vein was inserted into the external jugular vein under local anesthetic. Four days after this a diagnosis of disseminated intravascular coagulation was made and the patient was given a platelet transfusion. On the next day, the patient was given a preserved blood transfusion. One day after this, ceftazidime was withdrawn and on the following day the blood concentration of ceftazidime showed considerable elevation. The renal failure improved and the diuretics were stopped six days later. Laboratory data included BUN (mg/dL): 9/10—10.7, 9/11—44.3, 9/12—65, 9/22—4.7; Creatinine (mg/dL): 9/10—0.16, 9/11—0.67, 9/12—1.32, 9/22—0.09; Urinary volume (mL/24hr): 9/10—278, 9/11—170, 9/12—85, 9/22—324. Other medications included lignocaine, cimetidine, bromhexine, and aminophylline.

ISR# 710902; Glaxo Mfr. Report # G004763 (1990; Japan)

A 68–year–old female developed a sore throat, fever, fatigue, and malnutrition. She was treated with cefpimizole, but shortly after discontinuing the drug the symptoms recurred. Cefpimizole was restarted but was stopped 13 days later after wheals appeared on the body. Two days later a fever developed and a biliary tract infection was suspected. Ceftazidime was started and the next day the patient was noted to have a decreased urine volume (400 mL/day). A day later, she became anuric and acute renal failure was diagnosed. Furosemide and mannitol were administered. The next day heart failure and dyspnea were observed and hemodialysis was commenced. The patient underwent plasma exchange and received prednisolone. Two weeks later, micturation was restored and the acute renal failure resolved five days later. Laboratory data included BUN 47 and serum creatinine 7.3 two days after ceftazidime was discontinued. A renal biopsy showed atrophy, hyaline casts, interstitial edema, lymphocyte infiltration, and tuble inflammation.

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/s/

RONALD T WASSEL
03/29/2011

KELLY Y CAO
03/30/2011

ROBERT M BOUCHER
03/30/2011

RPM Memo to File
NDA 50-823

This NDA was taken before the pediatric review committee (PeRC) on March 9, 2011, and it was determined by the committee that the application did not trigger PREA.

J. Christopher Davi, MS
Senior Regulatory Project Manager
DAIOP

Concurrence:

Janice K. Pohlman, MD, MPH
Medical Team Leader

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JOSEPH C DAVI
03/18/2011

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03/18/2011