

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206494Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206494

SUPPL #

HFD # 520

Trade Name Avycaz

Generic Name ceftazidime-avibactam

Applicant Name Forest Laboratories

Approval Date, If Known February 11, 2015

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5-years + 5 years {Qualified Infectious Product Designation}

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# NDA 50-278 Fortaz (ceftazidime)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

NDA 206494 contains avibactam, a new chemical entity, in combination with ceftazidime, a previously approved active moiety. Under the Agency's new interpretation described in the Agency's Guidance for Industry, New Chemical Entity Exclusivity for Certain Fixed-Combination Drug Products, a drug substance is eligible for 5-year exclusivity, provided it meets the regulatory definition of new chemical entity, regardless of whether that drug substance is approved in a single-ingredient drug product or in a fixed-combination with another drug substance that contains no previously approved active moiety, or in a fixed-combination with another drug substance that contains a previously approved active moiety. This NDA is thus eligible for 5-year new chemical entity exclusivity pursuant to the new interpretation.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application

and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
 !
YES ! NO
Explain: ! Explain:

Investigation #2 !
 !
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

ATTACHMENT: GAIN EXCLUSIVITY
Form OGD-011347

GAIN Exclusivity Summary

Application Number	206494
Product Name/Generic/Dosage Form	AVYCAZ (ceftazidime-avibactam) Injection
Sponsor	Forest Laboratories

1. Does this product have Qualified Infectious Disease Product (QIDP) designation?

YES	NO
X	

2. Is the indication(s) approved in this NDA or supplement the same as the indication(s) identified in the QIDP designation letter?

YES	NO
X	

3. Has this product previously received a 5-year GAIN exclusivity extension?

YES	NO
	X

We note that AVYCAZ is a combination of two drugs, ceftazidime and avibactam, the ceftazidime is a previously approved product, Fortaz (ceftazidime) for injection (NDA# 050279). The new combination represented by AVYCAZ does not fall within the limitations to GAIN exclusivity set forth in Section 505E(c)(2) of the FD&C Act (providing that GAIN exclusivity does not apply to a “subsequent application filed with respect to a product approved under section 505 that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength.”)

Name of person completing form: Carmen DeBellas, PharmD, RPh

Title: Regulatory Project Manager

Date: *<see electronic signature>*

Name of Office/Division Director signing form: Edward Cox, MD, MPH

Title: Director, Office of Antimicrobial Products

Date: *<see electronic signature>*

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

/s/

CARMEN L DEBELLAS
02/25/2015

EDWARD M COX
02/25/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206494	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Avycaz Injection Established/Proper Name: ceftazidime/avibactam Dosage Form: injection, for Infusion		Applicant: Cerexa/Forest Research Institute Agent for Applicant (if applicable): N/A
RPM: Carmen DeBellas		Division: Anti-Infective Products
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is _____ 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): 1S, 4S
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input checked="" type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |
| X Qualified Infectious Disease Product designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	N/A
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	February 25, 2015
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> • Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included June 25, 2014
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> • Review(s) <i>(indicate date(s))</i> 	September 5, 2014 December 14, 2014 August 28, 2014 November 26, 2014
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> DMEPA: January 8, 2015 DMPP/PLT (DRISK): January 21, 2015 OPDP: January 14, 2015 SEALD: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	August 8, 2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	February 4, 2015
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>January 14, 2015</u> 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	Included
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	N/A
<ul style="list-style-type: none"> ❖ Minutes of Meetings <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) • EOP2 meeting (<i>indicate date of mtg</i>) • Mid-cycle Communication (<i>indicate date of mtg</i>) • Late-cycle Meeting (<i>indicate date of mtg</i>) • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	<input checked="" type="checkbox"/> N/A
	December 19, 2013
	March 7, 2011
	October 20, 2014
	November 14, 2014
	N/A
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	December 5, 2014
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	February 25, 2015
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	February 25, 2015
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	February 19, 2015
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 5 templates 	February 17, 2015
Clinical	
<ul style="list-style-type: none"> ❖ Clinical Reviews <ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) • Clinical review(s) (<i>indicate date for each review</i>) • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
	February 12, 2015
	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>) 	Refer to page 21-Clinical Review
<ul style="list-style-type: none"> ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) 	<input checked="" type="checkbox"/> N/A

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	N/A N/A <input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	Review- February 4, 2015 Review-February 20, 2015
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	January 20, 2015
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	February 12, 2015
Statistical Review(s) (<i>indicate date for each review</i>)	January 15, 2015
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	January 20, 2015
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	February 20, 2015
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	February 18, 2015
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	November 24, 2014 February 23, 2015
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	February 3, 2015
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	November 24, 2014
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: February 11, 2015 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy(BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<i>N/A</i>
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

CARMEN L DEBELLAS
02/25/2015

**PeRC PREA/BPCA/iPSP
Committee Meeting Minutes
January 14, 2015**

PeRC Members Attending:

Lynne Yao
Wiley Chambers
Ruthanna Davi
Dianne Murphy
Kristiana Brugger
Andrew Mosholder
Greg Reaman
Hari Cheryl Sachs
Susan McCune
Lily Mulugeta
Karen Davis-Bruno
Rosemary Addy
Barbara Buch
Peter Starke
Cara Fiore
Daiva Shetty

PREA/BPCA/Initial Pediatric Study Plan

(b) (4)				
10:00	NDA	206494	AVYCAZ (CAZ104) ceftazidime/avibactam injection iPSP (Deferral/ Plan)	Treatment of the following infections caused by designated susceptible microorganisms, reserved for use when limited or no alternative treatments are available. (1) Complicated intra-abdominal infections (cIAI) (2) Complicated urinary tract infections (cUTI)
(b) (4)				

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AVYCAZ (CAZ104) ceftazidime/avibactam injection iPSP (Deferral/ Plan)

IND 206494

- Proposed Indication: Treatment of the following infections caused by designated susceptible microorganisms, reserved for use when limited or no alternative treatments are available.
 - (1) Complicated intra-abdominal infections (cIAI)
 - (2) Complicated urinary tract infections (cUTI)
- This application triggered PREA as a new molecular entity.
- The Division clarified that this application is under priority review under qualified infectious disease product program (QIDP). However also noted that the application was submitted without phase 3 data, and without an agreed iPSP. The

pending approval will likely be limited to specific conditions because of the lack of phase 3 data. The Division agrees with the sponsors plan to extrapolate efficacy from adult data for cIAI and cUTI in pediatric patients down to 3 months of age.

- The Division does not agree extrapolation of efficacy is acceptable for patients less than 3 months of age.
- *PeRC Recommendations:*
 - The PeRC agreed that because of the priority review granted for this application that the inclusion of an agreed iPSP for this application would not be required. However, the PeRC reminded the Division that failure to include an iPSP is part of any marketing application may be grounds for a refuse to file action.
 - The PeRC that (b) (4) in patients less than 3 months of age and the PMR for this age range should include an adequate and well controlled trial.
 - The PeRC recommended that the Division review the PREA PMRs again after the phase 3 data have been submitted for review. The Division may consider changes to the PREA PMRs with review by the PeRC after these data are reviewed.
 - See comments on the IPSP sent to the Division on January 14, 2015.

(b) (4)

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CARMEN L DEBELLAS
01/20/2015

From: DeBellas, Carmen
Sent: Thursday, January 08, 2015 1:03 PM
To: Howell, Ann (Ann.Howell@frx.com)
Subject: NDA 206494 Avycaz Carton and Container Label recommendations

Hi Ann,

Please find recommendations attached.

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

Reference ID: 3684448

file:///C:/...BELLASC/Downloads/Desktop/NDA%20206494%20Avycaz%20Carton%20and%20Container%20Label%20recommendations.txt[1/8/2015 3:28:59 PM]

Carton and Container Recommendations

We recommend Cerexa, Inc. to submit these revisions below and include labels and labeling that includes approved proprietary name prior to approval of this NDA 206494.

a) Container Label

1. Revise the word "TRADENAME" to read "Avycaz" using title case letters to improve readability.
2. Ensure the established name at least ½ the size of the proprietary name (21 CFR 201.10 (g)(2)).
3. Add parenthesis surrounding the established name "ceftazadime/avibactam". Revise the established name and dosage form to appear all on one line. Present the established name on the container labels separated by slashes. Relocate the strength presentation to appear under the established name and revise the strength presentation from (b) (4) to read "2.5 gram per vial" to appear as follows:

Avycaz
(ceftazadime/avibactam) for injection
2.5 gram per vial

4. Revise the statement from (b) (4) to read "Must be reconstituted then diluted. For Intravenous Infusion." to provide clarity of important product preparation and administration information.
5. Relocate the usual dose statement "See package insert for dosage...directions for use" from the principal display panel to appear on the side panel to reduce clutter and distraction from other important information. To make room on the side panel, consider revising the usual dose statement to read "See prescribing information".
6. Revise the word "Constitution" to read "Reconstitution" on the side panel for clarity of important information.
7. Revise the uncommon abbreviation "(b) (4)" to read "room temperature" on the side panel for clarity of important information.

B. Carton labeling

1. See A.1 above

2. See A.2 above

3. See A.3 above

4. Revise the statement from [REDACTED] (b) (4) to read “Must be reconstituted then diluted. For Intravenous Infusion.” to provide clarity of important product preparation and administration information.

5. See A.6 above

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/s/

CARMEN L DEBELLAS
01/08/2015



NDA 206494

MID-CYCLE COMMUNICATION

Cerexa, Inc.
Attention: Kristina Haeckl, RAC
Executive Director, Regulatory Affairs
2100 Franklin Street, Suite 900
Oakland, CA 94612

Dear Ms. Haeckl:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ceftazidime-avibactam injection.

We also refer to the teleconference between representatives of your firm and the FDA on October 20, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date: October 20, 2014

Application Number: NDA 206494
Product Name: ceftazidime-avibactam
Indications: Complicated Intra-abdominal Infections
Complicated Urinary Tract Infections including Pyelonephritis
Limited Use Indication: Aerobic Gram-negative Infections with
Limited Treatment Options

Applicant Name: Cerexa, Inc.

FDA ATTENDEES

Division of Anti-Infective Products:

Dr. Sumathi Nambiar	Director
Dr. Katherine Laessig	Deputy Director
Dr. Margaret Gamalo	Statistics Reviewer
Dr. Thamban Valappil	Statistics Team Leader
Dr. Benjamin Lorenz	Clinical Reviewer
Dr. Seong Jang	Clinical Pharmacology Reviewer
Dr. Kimberly Bergman	Clinical Pharmacology Team Leader
Dr. Wendelyn Schmidt	Pharmacology/toxicology Team Leader
Dr. Armand Balboni	Pharmacology/toxicology Reviewer
Dr. Ronald Wassel	Reviewer, Office of Pharmacovigilance and Epidemiology
Dr. Joyce Weaver	Senior Drug Risk Manager, Office of Medication Error Prevention and Risk Management
Mr. Christopher Sese	Contractor- PDUFA V Program
Dr. Carmen DeBellas	Project Manager

APPLICANT ATTENDEES

Cerexa, Inc.

Dr. Ian Critchley	Vice President, Clinical Microbiology
Dr. David Friedland	Vice President, Clinical Development, Anti-Infectives
Ms. Kristina Haeckl	Executive Director, Regulatory Affairs
Dr. Douglas Rank	Director, Clinical Development
Dr. Lily Lorenz	Senior Director, Biostatistics & Data Management
Dr. Angela Talley	Associate Director, Clinical Pharmacology

Forest Research Institute

Dr. Stephen Barat	Executive Director, Toxicology & Preclinical Pharmacology
Ms. June Bray	Senior Vice President, Regulatory Affairs
Dr. Timothy Carrothers	Senior Principal Scientist, Pharmacometrics
Dr. Scott Cassidy	Director, Method Development
Dr. Tristen Duong	Technical Writer IV, CMC
Dr. Parviz Ghahramani	Vice President, Scientific Affairs
Ms. Ann Howell	Associate Director, Regulatory Affairs
Dr. Reena Nadpara	Post-Doctoral Pharm D Fellow, Regulatory Affairs
Dr. Declan Kelly	Executive Director, Regulatory Affairs CMC
Dr. Lawton Graham	Associate Principal Scientist, Chemical Development
Dr. Steven Leili	Director, Toxicology
Dr. David Nicholson	Senior Vice President, Global Brands R & D
Dr. Michael Olchaskey	Executive Director, Regulatory Affairs
Dr. Todd Riccobene	Senior Director, Clinical Pharmacology
Dr. Brahma Singh	Associate Principal Scientist, Product Development

Actavis

Dr. Kathleen Reape	Vice President, Clinical Development
--------------------	--------------------------------------

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

No issues to report at this time.

3.0 INFORMATION REQUESTS

There are no pending information requests.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

At the time of the Mid-Cycle meeting, the Office of New Drugs and the Office of Surveillance and Epidemiology have not conclusively determined whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. A final determination on the need for REMS is expected to be made during the review of the application.

5.0 ADVISORY COMMITTEE MEETING

NDA 206494 will be taken to the Anti-Infective Drugs Advisory Committee on December 5, 2014. A Designated Federal Officer for the Anti-Infective Drugs Advisory Committee will be in contact with you for specific details regarding deliverables and due dates.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

November 14, 2014: This will be the date of your Late Cycle Review Meeting. You may elect to have this meeting by teleconference or in person with the review team at the White Oak Campus. We will provide a briefing document for this meeting to you electronically on or about November 10, 2014. Topics of discussion at the meeting include, but are not limited to substantive review issues, additional applicant data (e.g., to be submitted in response to any actions, potential PMRs/PMCs and major labeling issues (if applicable).

December 10, 2014: The Division will convey preliminary, proposed revisions to the product labeling to you electronically. Be advised that these revisions may be limited to a certain section (or sections) of the label in stepwise fashion, as reviews are ongoing. In addition, we will communicate to you regarding any preliminary assessment(s) as to whether or not there will be post marketing commitments (PMC) and /or requirements (PMR).

February 25, 2015: The Agency will take an action on your application.

7.0 ADDITIONAL MEETING DISCUSSION

The Sponsor has recently submitted information to the Agency concerning the Phase 3 cIAI trial in the form of a Type A meeting request. Results of the trial show that patients with moderate to severe renal impairment had lower cure rates than patients in the comparator arm. The meeting has been scheduled for November 10, 2014.

The Division requested some time at this meeting to discuss the findings. The Sponsor is reviewing information to see if dosing recommendations need to be implemented. The Sponsor stated that it looks like the changes in creatinine clearance in these patients occurred beginning on day three. It seems that the improvement in renal function may

result in suboptimal dosing. The Sponsor suggested that closer monitoring of creatinine clearance may be a solution to the problem with these patients. The Sponsor added that the patients who died were considered failures.

The Sponsor reported that there were eight deaths in the CAZ-AVI arm vs three deaths in the comparator arm. The Sponsor added that each death was reviewed and that results showed that two deaths were determined to be related to potentially inadequate exposure and lack of timely dose adjustment. The remaining six had confounding factors involved.

The Sponsor reported that the Phase 3 cUTI trial was completed but would not be unblinded until late February 2015.

Advisory Committee Discussion

- The Division stated that the meeting would be a full day meeting on December 5, 2014.
- Details regarding the December 4, 2014 meeting will be available when the Federal Register Notice is posted.
- The Division's Briefing document would be sent to the Sponsor on or around November 10, 2014.
- The Division informed the Sponsor that there would be an opening presentation explaining a 505(b)(2) submission and how it relates to this NDA.
- The Division would present all indications as submitted in the application and there would be some discussion on the appropriateness of using meta-analysis and bridging efficacy data to historical information.
- The Division informed the Sponsor that any study information made public was open for discussion.
- The Sponsor stated that the 120-day safety update will contain some information on Phase 3 trials but the Division felt the date of submission would not give adequate time for review.
- The Sponsor stated that they have concerns about Advisory Committee members asking about the Phase 3 studies that have not been completed or analyzed. The Division informed the Sponsor that they could not be silent regarding the available data.

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/s/

SUMATHI NAMBIAR
12/18/2014

From: DeBellas, Carmen
Sent: Wednesday, December 10, 2014 3:39 PM
To: khaeckl@cerexa.com
Subject: Some labeling IRs

Hi Kristina,

I sent this pharmacology Toxicology last week. We are trying to reproduce the numbers that the you have in your label in section 8.1. The following table shows the values we am basing my margins on.....Could you check with your people to see where their numbers are coming from?

Labeling margins for reproductive toxicity with intravenous avibactam
The human AUC is from the label section 12.4 and is 38.2 gush/mL

Study	Embryo fetal NOAEL	AUC @ NOAEL	Ratio animal/human	Sponsor ratio
Rat Sag II	1000 mg/kg	454 gush/mL	12	9
Rat Sag III	825 mg/kg (NOAEL for fertility, pup viability)	870 gush/mL	23	11
Rabbit Sag II	100 mg/kg	272 gush/mL	7	2

Also, I hope that you have received the letter approving the name (b) (4). We will need mock-up versions of carton and container labels submitted for review. Just a reminder.

Thanks
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
12/10/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206494

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Cerexa, Inc.
2100 Franklin St, Suite 900
Oakland, CA 94612

ATTENTION: Kristina Haeckl, RAC
Executive Director, Regulatory Affairs

Dear Ms. Haeckl:

Please refer to your New Drug Application (NDA), dated and received, June 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ceftazidime/Avibactam for Injection, 2000 mg/ 500 mg.

We also refer to your correspondence, dated and received, September 23, 2014, requesting review of your proposed proprietary name, Avycaz.

We have completed our review of the proposed proprietary name, Avycaz and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your September 23, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Carmen DeBellas, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
12/04/2014

From: DeBellas, Carmen
Sent: Tuesday, November 25, 2014 2:51 PM
To: Howell, Ann (Ann.Howell@frx.com); khaeckl@cerexa.com
Subject: NDA 206494 Information request

Hi, Please find additional information request.

We appreciate your response to the three information requests that were listed in the late cycle review meeting agenda. In addition to this data regarding the RECLAIM study, we have three more requests:

- 1) In Table 2-1 in your amendment submitted on 09 Oct 2014 you provided a summary of clinical cure rate at Test of Cure, by baseline renal function subgroup (mMITT analysis set). Although there are no dosage change recommendations for patients with mild renal impairment (CrCL = 50-80 ml/min), please provide clinical cure rates in separate subgroups for normal renal function and mild renal function.
- 2) Please provide numbers of subjects in each treatment arm for the ITT and mMITT populations.
- 3) Please clarify the total number of deaths RECLAIM for each treatment arm in the safety population. In the 120-day update submitted on 23 Oct 2014, 22 (2.1%) deaths were reported. According to our discussion during the late cycle meeting, there was a total of 21 (13 CAZ-AVI vs 8 meropenem).

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
11/26/2014

From: DeBellas, Carmen
Sent: Thursday, November 06, 2014 2:36 PM
To: Howell, Ann (Ann.Howell@frx.com); khaeckl@cerexa.com
Subject: IR Request for November 10



~~IR-CAZ-AM-REC...~~

Please find IR for November 10 teleconference.

Thanks,

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203



With regard to the RECLAIM trial, if possible please provide the following prior to the meeting scheduled on 10 November 2014:

1. For all subjects who died and had moderate to severe renal impairment at baseline, submit creatinine clearance values at all time-points taken as well as narratives of their deaths, if available.
2. Submit all PK and MIC data (for ceftazidime and CAZ-AVI) in subjects with moderate to severe renal impairment at baseline who were determined to be clinical failures.

3.  (b) (4)

4.  (b) (4)

Have you reviewed any available literature, including published studies about ceftazidime, regarding the effect of baseline renal function and adequacy of dosing adjustments on clinical cure rates and mortality in cIAI? If so, please provide that information. If you have not yet performed such a review, we recommend that you perform a literature review to assess if any data are available on [the](#) effect of baseline renal function in ceftazidime-treated patients.

It would also be helpful, if you can provide questions that you would like to discuss at the meeting.

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/s/

CARMEN L DEBELLAS
11/06/2014

From:DeBellas, Carmen
Sent:Sunday, November 02, 2014 10:27 AM
To:khaeckl@cerexa.com
Cc:'Howell, Ann'
Subject:NDA 206494- Labeling Comment

Hi, Christina,

Please our first labeling comment. This one is rather early but I wanted to make sure you get these as soon as they come along.

*The dose strength should be expressed as (b)(4) relative to each active ingredient. Please change the drug product name and dose strength to the following:

Trade Name
(ceftazidime/avibactam) for injection
(b)(4)
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
11/02/2014

From:DeBellas, Carmen
Sent:Friday, October 10, 2014 9:21 AM
To:khaeckl@cerexa.com
Subject:NDA 206494 cazavi meeting request question

Hi Kristina,
Can you provide data for the creatinine clearance and categorization of renal function/impairment for the 2 Phase 2 studies and the interim data for Phase 3 Resistant Study?
Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
10/10/2014



NDA 206494

INFORMATION REQUEST

Cerexa, Inc. (A Subsidiary of Forest Laboratories, Inc.)
Attention: Kristina Haeckl, RAC
Executive Director, Regulatory Affairs
2100 Franklin St., suite 900
Oakland, CA 94612

Dear Ms. Haeckl:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for of the Federal Food, Drug, and Cosmetic Act for ceftazidime/avibactam Injection, 2.5 g.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by October 10, 2014, in order to continue our evaluation of your NDA.

Drug Substance Avibactam

You note that risk based assessment has been conducted for the inorganic impurities. Please provide details of this risk assessment. Additionally, please provide ICP-MS batch data for the inorganic impurities to justify not including a test for (b) (4) in the drug substance specification. We acknowledge that (b) (4) is controlled via an in-process test.

Drug Substance Ceftazidime

Since the NDA was submitted, the DMF holder has updated the drug substance specification. Please submit to the NDA the revised specification to be consistent with the information in the DMF.

Drug Product

1. It is noted in section 3.2.P.2.4. that the levels of extractables are lower than the safety concern thresholds/threshold of toxicological concern level based on the extractable data from the manufacturer (b) (4) components. However,

- no data is provided in support of this statement. Please provide the data from this study with details of the calculations.
2. For the post market stability protocol and commitment, please provide commitment to report the stability results to the Agency and withdraw from the market any batch that fails approved specifications in accordance with 21 CFR 314.81(b)(1)(ii).
 3. Please update drug product stability data for any time point that may be available since the NDA was submitted.

If you have any questions, call Navdeep Bhandari, Regulatory Health Project Manager, at (240) 402 -3815.

Sincerely,

{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

DOROTA M MATECKA
09/26/2014
For Dr. Rapti Madurawe

From:DeBellas, Carmen
Sent:Monday, September 22, 2014 3:00 PM
To:khaeckl@cerexa.com
Subject:NDA 206494 Information request CMC

Hi Kristina,

Please find Chemistry information request.

1. For the drug substance Avibactam, please provide the following information
 - a. Elemental analysis data for the characterization of avibactam
 - b. A table of compounds and their molecule structures that are evaluated for the potential genotoxicity and the corresponding prediction.
 - c. batch data to demonstrate that (b)(4) are well below the TTC level (b)(4) in order to justify that testing these genotoxic impurities are not needed in the drug substance specification
2. You noted that (b)(4)% overfills are used for both Avibactam and Ceftazidime in the drug product. However, it is calculated from the composition Table provided in 3.2.P.1 that overfill is (b)(4)% for Avibactam and (b)(4)% for Ceftazidime. Please explain

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
09/22/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 101307
NDA 206494

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Cerexa, Inc.
2100 Franklin St., Suite 900
Oakland, CA. 94612

ATTENTION: Kristina Haeckl, RAC
Executive Director, Regulatory Affairs

Dear Ms. Haeckl:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act, and your New Drug Application (NDA), dated and received June 25, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ceftazidime/Avibactam Injection, 2.5 grams..

We also refer to your correspondences, dated and received, June 16, 2014 and June 25, 2014, requesting review of your proposed proprietary name, Cazavi.

We have completed our review of the proposed proprietary name, Cazavi, and have concluded that this name is unacceptable for the following reasons:

Your proposed name, Cazavi, may be confused with the currently marketed product, Cozaar. We identified this safety concern based upon the misinterpretation of Cazavi as Cozaar in our written prescription simulation study. Because the likelihood of observing an error in a small study is low, we consider this finding to be an important predictor of errors that could occur in actual use if the proposed name were to be approved and marketed. On this basis, we have concern that the name Cazavi is likely to lead to errors with Cozaar in actual use. The sample below was used in the FDA written prescription simulation study.

Cazavi 2.5g q8hrs

We also note that the Cazavi Safety Analysis prepared by (b) (4) and submitted as part of the request for proprietary name review identified Cozaar as having similar sound and similar appearance in the Prescription Interpretation and Safety Survey. The survey participants were all healthcare professionals which further supports the potential for confusion between the two names.

(b) (4) concluded that Cazavi and Cozaar had sufficient distinctions to alleviate the potential for confusion because they do not share any identical letter strings longer than two letters. However, both names have the same length (6 letters), start with same letter 'C', have the letter string 'za' in the 3rd and 4th positions, and have similar shape when scripted. Furthermore, FDA's Phonetic and Orthographic Computer Analysis (POCA) calculates a 61% orthographic match for this name pair, which suggests that Cazavi and Cozaar look similar to each other.

In addition to their orthographic similarity, these products also share overlapping product characteristics. Cazavi and Cozaar have numerical similarities in strength and dose (2.5 grams vs. 25 mg). Oversight of decimals is a wide known factor in medication errors, and post-marketing surveillance of other wrong drug errors due to numerical similarity in dose and strength demonstrates this risk. For example, the Institute for Safe Medication Practices (ISMP) describes a case of medication confusion where prescriptions written for Microzide (hydrochlorothiazide) 12.5 mg were misinterpreted as Micronase (glyburide) 1.25 mg due to their look-alike names.¹

We note that Cazavi and Cozaar have a single route of administration and dosage form, which may be omitted from a prescription without prompting a clarification. However, we find that these differences are insufficient to prevent and error due to overwhelming orthographic similarity between Cazavi and Cozaar as evident in our prescription simulation study where full characteristics were provided yet misinterpreted. For example, ISMP describes a case of medication confusion where a written order for Celebrex was misinterpreted as Cerebyx since no route of administration was noted.²

Therefore, based upon the orthographic similarity of the names and overlapping product characteristics, we conclude there is a risk of wrong drug errors if your proposed name were to be approved. We find the proposed proprietary name, Cazavi unacceptable.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

¹ Institute for Safe Medication Practices, Oral antidiabetic therapy: Not as easy as it used to be (part 2). ISMP Med Saf Alert Community/Ambulatory 2004; 3(9) 2-4

² Institute for Safe Medication Practices, Safety Briefs. ISMP Med Safe Alert Acute Care 1999; 4(3) 2

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301)796-5413. For any other information regarding this application, contact Carmen DeBellas, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

KELLIE A TAYLOR
09/05/2014

From: Izadi, Fariba
Sent: 8/21/2014 11:20:48 AM
To: 'khaeckl@cerexa.com'
CC: DeBellas, Carmen
Subject: NDA 206494-(CAZ AVI) -Information Request
Importance: High

Dear Ms. Haeckl:

I am the project manager covering for Dr. DeBellas this week. We are reviewing the clinical section of your submission dated June 25, 2014 for NDA 206494 (CAZ AVI) and have the following information request.

The Clinical Study Report for NXL104/2002, Table 6 (pg 43 of the report) indicates that a clinical site in India, **Ramesh**, had 26 subjects enrolled and included in the safety population for the study. However, in Module 5.3.5.1, List Description of Investigator Site, Appendix 12.1.4.1, List of Staff at Investigational Site(s), Dr. Ramesh is not included. Please provide information about Dr. Ramesh including Site #, first and last name, location (site address) and current contact information (phone and e-mail address).

Best regards

Fariba Izadi, Pharm.D.
Regulatory Health Project Manager
Division of Anti-Infective Products
Phone: (301) 796-0563
Fax: (301) 796-9881
E-mail: Fariba.Izadi@fda.hhs.gov

Please confirm receipt of this email

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/s/

FARIBA IZADI
08/21/2014

From: DeBellas, Carmen
Sent: Wednesday, August 13, 2014 7:27 AM
To: khaeckl@cerexa.com
Subject: NDA 206494 Information Request (Product Quality Micro)

Hi Kristina,

Please find information request from our microbiology group.

The draft labelling submitted in NDA 206494 has provisions for up to a 12 hour storage time at room temperature following reconstitution and further dilution of the drug product. It may also be held for up to 24h refrigerated followed by up to 12 hours at room temperature. However, no post-constitution hold-time data were submitted in support of these storage times.

Please provide microbiological data to demonstrate that the reconstituted product solution will not support microbial growth during the proposed storage period. Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the storage conditions. (Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.)

Generally, "no growth" is interpreted as not more than a 0.5 log₁₀ increase from the initial count; however other evidence of growth may be significant. The test should be run at the label's recommended storage conditions, be conducted for 2 to 3-times the label's recommended storage period, and use each of the label-recommended reconstitution fluids inoculated with low numbers (≤ 100 CFU/mL) of challenge microbes. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of these data, the product labeling should recommend that a post-constitution storage period of not more than 4 hours at room temperature.

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203



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/s/

CARMEN L DEBELLAS
08/13/2014

From: DeBellas, Carmen
To: khaeckl@cerexa.com
Subject: NDA 206494 Information Request
Date: Monday, August 11, 2014 10:52:00 AM
Attachments: [NDA 206494_IR.doc](#)

Hi welcome back. Please find an information request for NDA 206494.

Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

1. In order to help assess the contribution of avibactam in the combination with ceftazidime, please provide an estimate of clinical success for patients with cUTI and cIAI caused by CAZ-nonsusceptible (NS) pathogens who are treated with ceftazidime alone. This may be based on data from your literature search as well as PK/PD modeling.
2. Additionally, please determine the effect of meropenem on patients in the cIAI trial (NXL-104-2002) whose infection was caused by MER-S and MER-NS organisms. Provide similar information for imipenem/cilastatin in the cUTI trial (NXL-104-2001).
3. Please provide your assessment regarding the low cure rates (clinical and microbiologic response) in both arms of trial NXL-104-2001.
4. Please provide a list of patients, if any, who had their investigator-assessed outcomes overridden.
5. Please provide SAS code for the ADAM datasets as well as the key efficacy analyses in the case study reports. Also, please provide the data generated from the literature search that were eventually used for the meta-analysis of the treatment effect of ceftazidime in cIAI and cUTI.
6. Regarding trial NXL-104-2002, values for the standard reference ranges (LBSTNRLO and LBSTNRHI) were not provided in the LB dataset. ULN counts for any lab test will be much more difficult to produce since original units are not completely consistent for each test. Please resubmit this dataset if it is possible to provide values for these variables.

If some of the information requested here has already been submitted as part of your package, please identify where it can be located.

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/s/

CARMEN L DEBELLAS
08/11/2014

From: DeBellas, Carmen
Sent: Wednesday, July 09, 2014 7:36 AM
To: khaeckl@cerexa.com
Subject: NDA 206494 IR

Kristina,

The jumpstart team has discovered that in the 2001 study, You did not submit the following datasets, though they are all listed in the define file and were included in the IND submission:

TE, TI, TS, TV, VS, (b) (4)

We will need an answer ASAP.

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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CARMEN L DEBELLAS
07/09/2014

From: DeBellas, Carmen
Sent: Wednesday, July 09, 2014 11:40 AM
To: khaeckl@cerexa.com
Subject: Revised IR for NDA 206494

Hi Kristina,

Apparently, I missed an email. The correct missing datasets are TE, TI, TS, TV, VS, and XC.

Thanks,
Carmen

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-1203

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/s/

CARMEN L DEBELLAS
07/09/2014



NDA 206494

NDA ACKNOWLEDGMENT

Cerexa, Inc.
Attention: Kristina Haeckl, RAC
Executive Director, Regulatory Affairs
2100 Franklin Street, Suite 900
Oakland, CA 24612

Dear Dr. Haeckl:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ceftazidime-avibactam for injection

Date of Application: June 25, 2014

Date of Receipt: June 25, 2014

Our Reference Number: NDA 206494

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 24, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, PharmD, RPh
Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

CARMEN L DEBELLAS
07/01/2014



IND 101307

MEETING MINUTES

Cerexa, Inc.
Attention: Kristina Haeckl, RAC
Executive Director, Regulatory Affairs
2100 Franklin St, STE 900
Oakland, CA 94612

Dear Ms. Haeckl:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ceftazidime/Avibactam (CAZ-AVI) Injection.

We also refer to the meeting between representatives of your firm and the FDA on December 19, 2013. The purpose of the meeting was to discuss the format and filing of an NDA for CAZ-AVI based upon nonclinical data, Phase 1 data, data from two Phase 2 studies, and published ceftazidime data.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Guidance
Meeting Date: December 19, 2013
Application Number: IND 101307
Product Name: Ceftazidime/Avibactam Injection
Sponsor/Applicant Name: Cerexa, Inc.

FDA ATTENDEES

Agency Attendees

Dr. Edward Cox	Office Director
Dr. John Farley	Deputy Office Director
Dr. Katherine Laessig	Deputy Division Director
Dr. Sumathi Nambiar	Division Director
Dr. Benjamin Lorenz	Acting Clinical Team Leader
Dr. Carmen DeBellas	Project Manager
Dr. Kimberly Bergman	Clinical Pharmacology Team Leader
Dr. Seong Jang	Clinical Pharmacology Reviewer
Dr. Dmitri Iarikov	Clinical Reviewer
Dr. Thomas Smith	Clinical Team Leader
Dr. Kellie Reynolds	Deputy Director, Division of Clinical Pharmacology 4
Kerry Snow	Clinical Microbiology Team Leader
Dr. James Wild	Pharmacology/Toxicology Reviewer
Dr. Meg Gamalo	Statistical Reviewer
Dr. Thamban Valappil	Statistical Team Leader
Dr. Daniel Rubin	Statistical Reviewer
Dr. Dionne Price	Acting Director, Division Biostatistics 4
Dr. Ribhi Shawar	Branch Chief, DMD, CDRH
Dr. Joseph Toerner	Associate Director of Medical Affairs
Dr. Leonard Sacks	Office of Medical Policy
Dr. Rachel Sherman	Office of Medical Policy

SPONSOR ATTENDEES

Dr. Ian Critchley	Vice President, Clinical Microbiology, Cerexa
Dr. David Friedland	Vice President, Clinical Development, Cerexa
Ms. Kristina Haeckl	Executive Director, Regulatory Affairs, Cerexa

Ms. June Bray	Senior Vice President, Regulatory Affairs, Forest Research Institute
Dr. Lily Lorens	Senior Director, Biostatistics and Data Management, Cerexa
Dr. Douglas Rank	Director, Clinical Development, Cerexa
Dr. Todd Riccobene	Director, Clinical Pharmacology and Drug Dynamics, Forest Research Institute
Dr. Timothy Carrothers	Senior Principal Scientist, Modeling & Simulation, Forest Research Institute
Ms. Aurora Sosa	Associate Director, Regulatory Affairs, Cerexa
Dr. Angela Talley	Associate Director, Clinical Development, Cerexa
Ms. Renee Wible	Director, Global Regulatory, AstraZeneca
Dr. Maria Sunzel	Principal Clinical Pharmacology Scientist, AstraZeneca
Dr. James Li	Senior Clinical Pharmacometrician, AstraZeneca
By Telephone:	
Mr. Jon Armstrong	Global Product Scientist, AstraZeneca
Dr. Paul Newell	Medical Science Director, AstraZeneca
Dr. John Rex	Vice President and Head of Infection, Global Medicines Development, AstraZeneca

BACKGROUND

The purpose of the Type B Pre-NDA Meeting was to discuss the format and filing of an NDA for CAZ-AVI based upon nonclinical data, Phase 1 data, data from two Phase 2 studies, and published ceftazidime data. The Sponsor received the preliminary meeting responses to the questions in their meeting briefing package prior to the meeting. The Sponsor requested discussion on questions, 1, 2, 9, 11, 10A, 12, 15, 17 and 18.

DISCUSSION

The Agency began the meeting by stating that at the last meeting on June 17, 2013, the Agency had noted that (b) (4) approval was a potential pathway for a CAZ-AVI NDA, and that reliance on previous experience with ceftazidime safety and efficacy could be supportive. Since then the Agency has had several internal discussions, and recommends that a (b) (4) approach may not be the appropriate regulatory pathway as there is no surrogate endpoint that is reasonably likely to predict clinical benefit for CAZ-AVI. Therefore, the Agency recommends that the most appropriate pathway for the proposed NDA package is a 505(b)(2) application, whereby approval for the indications of complicated urinary infections (cUTI) and complicated intraabdominal infections (cIAI) will rely in part upon the Agency's finding of safety and efficacy of ceftazidime. The NDA will also need to include evidence of the safety of avibactam as well as the contribution of avibactam to the efficacy of CAZ-AVI (i.e. restoring the activity and treatment effect of ceftazidime in infections caused by ceftazidime-resistant organisms). The responses provided are based on the recommended 505(b)(2) approach, rather than (b) (4)

Questions for Discussion:

1. The Sponsor has conducted a series of nonclinical safety pharmacology and toxicology studies to support the clinical development and registration of CAZ-AVI. Does the Agency agree that the nonclinical program outlined in Section 14.3.1 and Appendix V meets the requirements of an NDA submission, and that no other studies are required?

FDA Response: The scope of the safety pharmacology and toxicology studies described in the meeting package and investigators brochure appears to be sufficient to support an NDA application for CAZ-AVI. A final evaluation of the sufficiency of the studies will be based on final study data included in complete study reports. Should unexpected findings occur in nonclinical or clinical studies, additional studies may be requested. Also, additional information regarding the final drug product formulation and drug substance and product impurities/degradants is needed in order to determine if additional qualifying studies are needed. In addition to the results of the 1-month toxicology studies with the combination of ceftazidime and avibactam, prior findings of safety for ceftazidime from the product label or from literature reports can be used to support the safety of ceftazidime unless rights of reference for further ceftazidime study data can be obtained.

Meeting Discussion:

The Sponsor stated that they would provide nonclinical information by referencing the ceftazidime package insert and the summary basis for approval to support a 505(b)(2) application. The Agency noted that although the Sponsor can refer to the ceftazidime package insert, reference to the summary basis for approval for ceftazidime cannot be made unless they have obtained a right of reference. Nonclinical information would have to be obtained from literature or the product label.

2. Does the Agency agree that the nonclinical drug metabolism and pharmacokinetic (DMPK) program (as outlined in Section 14.3.1.3 and Appendix VI) meets the requirements for an NDA submission, and that no other studies are required?

FDA Response: Yes, we agree. The scope of the DMPK studies described in the meeting package appears to be sufficient to support NDA application. However, a final evaluation will be based on final study data included in complete study reports.

Meeting Discussion:

The Sponsor reminded the Agency that the submission would contain ceftazidime information alone from pharmacokinetic studies already in existence and through literature references.

Questions 9 and 11 were discussed together.

9. The Sponsor does not plan to submit an Integrated Summary of Efficacy (ISE) for the CAZ-AVI NDA. CAZ-AVI efficacy will be summarized in 2 separate NDA Section 2.7.3 documents, one for cIAI and one for cUTI. Supporting tables, listing, and figures for Sections 2.7.3-cIAI and 2.7.3-cUTI will be located in Module 5 of the NDA. Does the Agency agree with the proposed plan for the summaries of efficacy?

FDA Response: We recommend that you plan to include an ISE. The ISE is considered a required part of an NDA submission and must include information stipulated under 21 CFR 314.50(d)(5)(v). Within the ISE, you should provide a clear and cohesive analysis of the collective evidence to support efficacy. We are cognizant of the fact that it may not be appropriate to pool the Phase 2 cIAI and cUTI studies. Where needed, however, you may provide reference to supporting tables, etc. with discussions that include the requisite concepts of the ISE, from Sections 2.7.3-cIAI and 2.7.3-cUTI in Module 5.

11. The Sponsor does not plan to submit an Integrated Summary of Safety (ISS) for the CAZ-AVI NDA. The Sponsor intends to provide an aggregate summary of the cumulative safety database for CAZ-AVI in NDA Section 2.7.4. Supporting tables, listings, and figures for Section 2.7.4 will be placed in Module 5 of the NDA. Does the Agency agree with the proposed plan for summary of safety?

FDA Response: We agree that much of your data will be in Module 5, so you may refer to the supporting data and analyses for Section 2.7.4 in Module 5. However, in keeping with our response to Question 9 and requirements under 21 CFR 314.50(d)(5)(vi), we request that you submit your integrated analysis of safety in an ISS. The ISS should provide a clear and concise summary suitable for risk/benefit analysis, particularly in patients with renal failure or patients with different levels of severity of the disease, for example.

Meeting Discussion:

The Sponsor stated that the ISE and ISS for the Phase 2 studies will be small enough to be placed in section 2.7 of the eCTD. Their first proposal was to include the narratives in section 2.7 with the tables for the ISE and ISS located in Module 5 (based on the April 2009 Guidance). The second proposal was to include all the narratives and tables in section 2.7 and duplicate the information in Module 5. The Agency replied that the first proposal was acceptable.

10. The Sponsor plans to analyze the clinical data from the Phase 2 studies as part of the totality of the data. These analyses will reference the established efficacy of ceftazidime, the active antibacterial agent in CAZ-AVI. Does the Agency agree with the proposed plan for analyses of efficacy? Specifically,

a. Does the Agency agree with the proposed analysis paradigm referencing the established historical efficacy of ceftazidime alone?

FDA Response: Should you choose to take a 505(b)(2) approach, whereby you rely on the Agency's previous finding of safety and efficacy of ceftazidime alone, you will also need to present a systematic review and summary of the efficacy of ceftazidime from any available published literature.

The conduct of the systematic review must have a comprehensive plan that is defined prior to the literature search. The search must establish the treatment effect of ceftazidime in cIAI and cUTI caused by CAZ-S pathogens through meta-analytic methods, which must be clearly described in the plan as well, as part of the supportive evidence. Please summarize any data if available on the treatment of cIAI and cUTI caused by CAZ-R pathogens with ceftazidime. Limitations of the derived treatment effect estimate that will potentially preclude effective comparison with data from the Phase 2 trials must be thoroughly discussed. It is important to note that, although hypothesis testing is not possible, these treatment effects will be compared to the treatment effect of CAZ-AVI in cIAI and cUTI caused by either CAZ-S or CAZ-R pathogens.

Meeting Discussion:

The Sponsor stated that any search terms used in acquiring literature would be defined a priori and listed in the NDA. A complete list of the publications with a description of the limitations of the publications would also be provided. Data from appropriate randomized trials could be used to perform a meta-analysis of the treatment effects.

The Agency stated that a summary of information concerning ceftazidime alone and CAZ-AVI in combination in susceptible and resistant organisms should be provided. The Sponsor noted that the safety information for ceftazidime could be obtained from the package insert and signal detection using the FDA Adverse Event Reporting System. The Agency stated that the approach was acceptable. The Sponsor added that they would provide a summary and complete copy of the original publication associated with any new safety information they could obtain from literature sources.

12. The Sponsor plans to pool the Phase 1 safety data for CAZ-AVI studies. Healthy subjects and special populations will be pooled for the safety analysis according to study drug groups (ie, CAZ-AVI, CAZ-AVI +MTZ, ceftazidime alone, avibactam alone, other comparators, and placebo) as outlined in the summary table prototype (Appendix VII). Pooled data for avibactam alone will also include data from the one completed study in the ceftaroline fosamil- avibactam (CXL) program, in which subjects received avibactam alone. Does the Agency agree with the proposed plan for the pooled Phase 1 studies?

FDA Response: We agree. Please include this assessment in the ISS as mentioned above. Pooled data for avibactam is acceptable, including data from the CXL program. Please provide a

summary of the safety of avibactam from the studies that used the dose and duration consistent with the regimen proposed to be marketed.

Meeting Discussion:

The Sponsor stated that they would submit a summary of experience with CAZ-AVI [REDACTED] (b) (4)

15. a) Based on the totality of evidence provided by nonclinical, Phase 1, and Phase 2 studies of CAZ-AVI in addition to the experience with ceftazidime alone, [REDACTED] (b) (4)

[REDACTED] Does the Agency agree that the proposed indication statement and list of pathogens are appropriate for CAZ-AVI labeling?

FDA Response: We do not agree. The Division believes that the indications of cUTI and cIAI would be appropriate given the data proposed in your NDA submission. Treatment of these infections would be indicated when alternatives are not suitable. Upon completion of either cUTI or cIAI Phase 3 trials, supplemental applications can be submitted to revise language on limitations for use for that specific indication(s).

Although the prescribing information for ceftazidime includes other indications at this time, we are willing to consider granting only the indications of cUTI and cIAI for which you have limited efficacy and safety data in patients treated with CAZ-AVI.

In order to include the indication for HABP/VABP or the other labeled indications in the ceftazidime label additional trial (s) will be needed. We will be willing to discuss with you the scope of such trials. Some options that we have considered are:

[REDACTED] (b) (4)

We note that the indication statement separates causative pathogens from the indications. We think it is important to associate a pathogen with a particular body site i.e. indication. For the final labeling, inclusion of specific pathogens for each indication will require further discussion.

[REDACTED] (b) (4)

(b) (4)

b) Does the Agency agree that the proposed labeling language provided in the draft TPP (Appendix I) is appropriate for CAZ-AVI?

FDA Response: Final agreement regarding the labeling will take place during the NDA review cycle.

Meeting Discussion:

The Agency restated that product labeling is based on the indication and associated pathogens studied. The Sponsor stated they understood the label would include cUTI and cIAI with the pathogens identified for these indications.

The Sponsor asked if the pathogens listed in the approved ceftazidime label would be included in the CAZ-AVI label even though some pathogens may not have been identified in the Phase 2 trials. The Agency replied that this would be a review issue. The Sponsor stated that if they did not have *Klebsiella spp.* or certain gram-negative organisms, they may not have a commercially viable product. In the case of *Enterobacteriaceae*, data from clinical and non-clinical models may be provided for review. Some *Pseudomonas* isolates may be found in Phase 2 data in the cIAI trial but numbers will be small. The Agency asked the Sponsor to provide scientific justification for any pathogens they wanted in the label. The information provided should be complete and of good quality in order for the Agency to link to the pathogens listed in the ceftazidime label.

There was some discussion of the placement of wording about mixed infections (susceptible and resistant isolates) in the package insert. The Sponsor noted that they would be interested in including language similar to that in the Zosyn label. The Agency pointed out that there would need to be further consideration of the wording regarding mixed infections in the context of the need for limited use of CAZ/AVI. The Agency stated that it wanted to be careful about the language in the CAZ-AVI labeling so that it would not replace ceftazidime. The label would need to express that the drug should only be used for ceftazidime-resistant organisms and should communicate clearly how to use the drug most efficiently.

The discussion then turned to the possibility of a Hospital-Acquired Bacterial Pneumonia/
Ventilator-Associated Bacterial Pneumonia (HABP/VABP) trial. (b) (4)

(b) (4)

(b) (4)

17. Does the Agency agree with the format of the clinical data to be included in the NDA as presented in Table 15.6.1-1 and Table 15.6.1-2?

FDA Response: We agree. Ideally, we request that you submit the data in both SDTM and ADAM format. We also encourage you to submit a sample dataset so that we can ensure there are no compatibility concerns with our review tools. Once submitted, we can consult our computational science colleagues. A sample dataset, such as one consisting of subjects with ceftazidime-resistant isolates, would also help us begin the process of review as well. In addition to case report forms (CRFs) for patients who died, had SAEs or discontinued treatment, please submit the CRFs for all cases in whom CAZ-r organisms were isolated.

Meeting Discussion:

The Agency asked the Sponsor to submit a sample dataset ahead of the NDA submission in order to make sure that the datasets are compatible with the Agency's review tools. The Sponsor stated that responses to information requests were submitted in June of 2013 and that case report forms and datasets were submitted on November 20, 2013.

18.

(b) (4)

The PSP will also include a request to defer the submission of data from additional pediatric studies until after approval of the supplemental NDA (sNDA) that will include the confirmatory Phase 3 cIAI and cUTI studies in adults. Does the Agency agree that the pediatric PK study data are not required for the (b) (4) NDA?

FDA Response:

Please clarify the status of your pediatric PK study (D4280C00014). If PK data are available in any of the pediatric age cohorts at the time of NDA submission, please include such information. If you plan to defer your pediatric studies, please submit a justification.

Meeting Discussion:

The Sponsor mentioned a single dose pediatric pharmacokinetic study which may not be completed at the time of NDA submission. The first cohort (ages 12 to 17 years), however, is complete. So far there are 15 patients from 6 to 17 years of age. Although some safety data is available, the PK analysis is not complete but they will try to have it done by the time of NDA submission. The target enrollment would be at least 8 evaluable subjects in each of the four

cohorts with an age range from 3 months to 17 years. The Sponsor stated they would provide a complete Pediatric Study Plan (PSP) in June of 2014.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements of Prescribing Information](#) website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents, and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

505(b)(2) REGULATORY PATHWAY

A 505(b)(2) application would be an acceptable approach at this time based on the information provided. The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry Applications Covered by Section 505(b)(2) (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's

finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency’s regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the “listed drug for which FDA has made a finding of safety and effectiveness,” and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
1. Example: Published literature	Nonclinical toxicology
2. Example: NDA XXXXXX “TRADENAME”	Previous finding of effectiveness for indication X
3. Example: NDA YYYYYY “TRADENAME”	Previous finding of safety for Carcinogenicity, labeling section XXX

4.	
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Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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

/s/

SUMATHI NAMBIAR
01/17/2014



IND 101307

MEETING MINUTES

AstraZeneca Pharmaceuticals, LP
Attention: Renee Wible, Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Wible:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CAZ104 (ceftazidime NXL104).

We also refer to the meeting between representatives of your firm and the FDA on March 7, 2011. The purpose of the meeting was to discuss the phase 3 development plan for CAZ104 (ceftazidime NXL104) in the treatment of complicated urinary tract infection (cUTI) and complicated intra-abdominal infections (cIAI).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kyong Hyon, Regulatory Project Manager, at (301) 796-0734.

Sincerely yours,

{See appended electronic signature page}

Sumathi Nambiar, M.D., MPH
Deputy Director for Safety
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2 (EOP2)

Meeting Date and Time: March 7, 2011, 11:00 AM – 12:00 Noon (EST)
Meeting Location: 10903 New Hampshire Avenue, Silver Spring, MD 20993, Building 22, Room 1309

Application Number: IND 101307
Product Name: CAZ104 (ceftazidime NXL104)
Indication: treatment of complicated urinary tract infection (cUTI) and complicated intra-abdominal infections (cIAI).

Sponsor/Applicant Name: AstraZeneca Pharmaceuticals, LP

Meeting Recorder: Kyong Hyon

FDA ATTENDEES

Office of Antimicrobial Products (OAP)

Edward Cox, MD, MPH, Director
John Farley, MD.MPH, Deputy Director
Nicole Mahoney, PhD, FDA Commissioner's Fellow

Division of Anti-Infective and Ophthalmology Products (DAIOP)

Wiley Chambers, MD, Acting Director
Katherine Laessig, MD, Deputy Director
Sumathi Nambiar, MD, MPH, Deputy Director for Safety
Thomas Smith, MD, Clinical Team Leader
Benjamin Lorenz, MD, Clinical Reviewer
Frederic Marsik, PhD, Clinical Microbiology Team Leader
Avery Goodwin, PhD, Clinical Microbiology Reviewer
Thamban Valappil, PhD, Statistical Team Leader
Mark Gamalo, PhD, Statistical Reviewer
Kimberly Bergman, PharmD, Acting Clinical Pharmacology Team Leader
Aryun Kim, PharmD, Clinical Pharmacology Reviewer
Houda Mahayni, RPh, PhD, Biopharmaceutics Reviewer, Office of New Drugs Quality Assessment (ONDQA)
Kyong Hyon, Regulatory Project Manager

SPONSOR ATTENDEES

AstraZeneca Pharmaceuticals, LP (AZ)

Jon Armstrong, MSc, BSc, Global Product Statistician

Phil Damstetter, MSc, Associate Director Regulatory Affairs
Shampa Das, PhD, Clinical Pharmacology and DMPK Leader
Leanne Gasink, MD, Clinical Research Director
Cindy Lancaster, MS, MBA, JD, Executive Director Regulatory Affairs, US region, Oncology and Infection Therapy Area
Paul Newell, MD, Medical Science Director, Infection
Wright Nichols, PhD, Development Microbiology Director
Renee Wible, BSN, RN, Director, Regulatory Affairs, Global Regulatory Leader
Lindsay Wright, PhD, Toxicology Program Leader

Cerexa/Forest (F/C)

June Bray, MBA, RPh, VP, Regulatory Affairs, Forest
Ian Critchley, PhD, VP, Clinical Microbiology, Cerexa
David Friedland, MD, VP, Clinical Sciences, Cerexa
Paul Grint MD, President, Cerexa
Lily Llorens, PhD, Sr. Director, Biometrics, Cerexa
Bruce Lu, PharmD, Senior Director, Regulatory Affairs, Cerexa
Doug Rank, MD, Director, Clinical Development, Cerexa
Todd Riccobene, PhD, Director, Clinical Pharmacology and Drug Dynamics, Forest

1.0 BACKGROUND

AstraZeneca (AZ) submitted an EOP2 meeting request on December 15, 2010 to discuss the phase 3 development plan for CAZ104 (ceftazidime NXL104) in the treatment of complicated urinary tract infection (cUTI) and complicated intra-abdominal infections (cIAI). The face-to-face meeting was granted on December 23, 2010 and scheduled to occur on March 7, 2011. The meeting package (MP) was submitted on January 25, 2011. The Division sent preliminary written responses to questions from the MP on March 2, 2011 via e-mail to which AstraZeneca responded on March 4, 2011 via e-mail (included below).

2. DISCUSSION

The following is a summary of the minutes of the face-to-face meeting held on March 7, 2011, including prior communication. AZ/F/C's questions from the MP are in bold followed by responses from the Division in italics, AZ/F/C's March 4, 2011 e-mail response, and the points discussed during the face-to-face meeting.

The meeting started with the introduction of the attendees and a brief description of the purpose of the meeting. AZ//F/C stated that they would like to focus the meeting questions 12, 17, 18, 14a, 11, 13, 9, and 15.

Chemical, pharmaceutical and biological development questions

Question 1: Method of preparation of CAZ104

AstraZeneca-Forest-Cerexa consider that the bioavailability of CAZ104 prepared by either of the 2 methods proposed will be equivalent as a) both methods will result in an equivalent

aqueous solution for infusion and b) no additional excipients that impact the solubility, stability or pharmacokinetics (PK) of the 2 agents will be employed by either method. Does FDA agree with this proposal?

Division Response (per 3-2-11 e-mail): *Yes, we consider the bioavailability of CAZ104 prepared by either of the 2 methods to be equivalent.*

Sponsor Response (per 3-4-11 e-mail): No further discussion is required.

3-7-11 Meeting Discussion: No further discussion was needed.

Non-clinical questions

Question 2: Pre-clinical toxicology program

AstraZeneca-Forest-Cerexa believe that the pre-clinical toxicology program will be sufficient to support registration for the use of CAZ104 for the treatment of patients with cIAI and cUTI including pyelonephritis. Does the FDA agree?

Division Response (per 3-2-11 e-mail): *Both NXL104 and ceftazidime were non-teratogenic when they were tested alone. An embryo-fetal study in rats or rabbits would be required to evaluate the teratogenic potential of the combination. The planned pre-postnatal developmental study should be conducted as soon as possible.*

Sponsor Response (per 3-4-11 e-mail): Further written clarification is requested. We had not planned to conduct a combination embryo-fetal study based on the ICH M3 (R2) guidance which states that ‘If nonclinical embryo-fetal studies **have** indicated that neither agent poses a potential human developmental risk, combination embryo-fetal studies are not recommended unless concerns exist, based on the properties of individual components, that their combination could give rise to a hazard for humans.’

3-7-11 Meeting Discussion: No further discussion was needed.

Clinical questions

General questions

Question 3: Clinical pharmacology program

AstraZeneca-Forest-Cerexa believe that the proposed clinical pharmacology program will be sufficient to support registration for the use of CAZ104 for the treatment of patients with cIAI and cUTI with pyelonephritis. Does the FDA agree?

Division Response (per 3-2-11 e-mail): *No. Certain in vitro drug-drug interaction (DDI) studies are outstanding and pending results from these recommended in vitro DDI studies or currently planned clinical pharmacology studies (e.g., ADME study), additional work may be required. See the following comments.*

- *In recent years, there has been increasing evidence to support the clinically important role of transporters in DDI. We recognize the significance of transporter-based DDI and believes evaluation of such mechanisms is warranted during drug development for new molecular entities. Consequently, we recommend you to perform in vitro studies investigating NXL104 as a substrate of the following transporters: P-gp (P-glycoprotein); BCRP (breast cancer resistant protein); and OAT1/OAT3 (organic anion transporter) and OCT2 (organic cation transporter) if active renal secretion is significant.*
- *Similarly, we recommend that you perform in vitro studies investigating NXL104 as an inhibitor of the following transporters: P-gp, BCRP, OATP1B1/OATP1B3 (organic anion transporting polypeptide), OAT1/OAT3, and OCT2.*
- *Ultimately, if no in vivo DDI studies are deemed necessary for the investigation of enzyme- or transporter-based DDI, we recommend that you perform a population PK analysis from Phase 3 patients to assess the effect of concomitant medications on the pharmacokinetics of NXL104.*
- *Refer to the following publications regarding enzyme- and transporter-based DDI: (i) Draft Guidance of Drug Interaction Studies dated 11 Sep 2006, (ii) Zhang L, et al. Toxicol Appl Pharmacol 2010;243:134-45., and (iii) International Transporter Consortium. Nat Rev Drug Discov 2010;9:215-36.*

Sponsor Response (per 3-4-11 e-mail): No further discussion is requested. These studies are planned.

3-7-11 Meeting Discussion: No further discussion was needed.

Question 4: Dose selection

Question 4a: Based on data from pre-clinical PK/PD studies and clinical population PK modeling from studies of CAZ104, AstraZeneca-Forest-Cerexa have selected a CAZ104 dose regimen for use in the Phase III cIAI studies which is different than that used in the Phase II cIAI study. Specifically, a longer infusion time (2 hours instead of 30 minutes) is proposed for the Phase III studies. Does the FDA agree with the dose regimen selected for use in the Phase III cIAI program?

Division Response (per 3-2-11 e-mail): Agree; see the following comments:

- *Provide a comprehensive table that clearly identifies dose regimens (dose, dose frequency, and infusion time) for each study drug according to renal function (includes renally-adjusted and non-renally-adjusted regimens). Currently, it is unclear what the dose regimens exactly are for all of the study drugs (ceftazidime, NXL104, metronidazole, and the active comparator, meropenem).*
- *Provide dose justification for the proposed regimen of NXL104 in patients with creatinine clearance (CrCL) of 31-50 mL/min (250 mg Q12h as 2-h infusions).*

Sponsor Response (per 3-4-11 e-mail):

The dosage regimens for each study drug according to renal function (non-renally adjusted and renally-adjusted regimens) are outlined in Table 1.

Table 1 Ceftazidime/NXL104 adjustments for patients with renal impairment

Creatinine clearance (mL/min) ^a	Ceftazidime/NXL104/Metronidazole		Meropenem/Metronidazole placebo	
	Ceftazidime/NXL104 dose, interval, duration	Metronidazole dose, interval, duration		Metronidazole placebo dose, interval, duration
CrCl >50ml/min	2000mg ceftazidime/500mg NXL104 every 8h ±30 min, 2h constant infusion	500mg metronidazole every 8h ±30 , 1h constant infusion	500mg meropenem every 8h ±30min, 30min constant infusion	0.9% saline every 8 hours ±30 minutes over 1h constant infusion
CrCL 31 to 50ml/min	1000 mg ceftazidime/ 250 mg NXL104 every 12 hours ±30 min over 2h constant infusion	500mg metronidazole every 8 hours ±30 min over 1h constant infusion	1000 mg meropenem every 12 hours ±30 min over 2h constant infusion	0.9% saline every 8 hours ±30 minutes over 1h constant infusion

The proposed dosing regimen and magnitude of dose reduction of NXL104 in patients with creatinine clearance (CrCL) of 31-50ml/min (250mg q12h as 2-h infusion) was selected based on population PK modeling and simulation of probability of PK/PD target attainment (PTA). Population PK models of NXL104 and CAZ104 were built from Phase 1 data in healthy volunteers (SAD, MAD, age and gender) and renally-impaired subjects) and also Phase 2 data from the complicated intra-abdominal infection patients. Because the pharmacokinetics of NXL104 and ceftazidime are similar and the impact of renal impairment on exposure is comparable, the dose adjustment recommended for NXL104 is the same as that recommended for ceftazidime (50% reduction in dose given q12h rather than q8h; FORTAZ[®] I.V. US PI).

As described in section 5.2 of the briefing document these population pharmacokinetic models were used in Monte Carlo simulations of patients to determine the dose of both compounds required to maintain unbound NXL104 plasma concentrations above the threshold concentration (Ct 1mg/L) and unbound ceftazidime plasma concentrations above an MIC of 8 mg/L for at least 50% of the dosing interval with a joint probability of target attainment of at least 90%. Using these targets and comparison of predicted exposure, dose adjustments for renal impairment were assessed.

The predicted exposure following the proposed dose adjustments are outlined in Table 2

Table 2 Predicted CAZ and NXL104 Exposure for Simulations of 1,000 Patients with CAZ104 Dosed in 120 Minutes iv Infusion for Different Renal Function Groups

Renal Function	Drug	Dose	C _{max,ss} (mg/L)		AUC _{ss} (mg.hr/L)		C _{av,ss} (mg/L)	
			Mean	SD	Mean	SD	Mean	SD
CrCL>80 mL/min	NXL104	500 mg, q8h	15.3	4.2	27.9	7.4	3.5	0.9
	CAZ	2000 mg, q8h	82.7	33.3	191.1	78.7	23.9	9.8
51 mL/min ≤CrCL≤80 mL/min	NXL104	500 mg, q8h	18.6	5.5	38.2	13.2	4.8	1.6
	CAZ	2000 mg, q8h	92.1	36.9	227.4	93.9	28.4	11.7
31 mL/min ≤CrCL≤50 mL/min	NXL104	250 mg, q12h	11.7	3.4	34.5	12.1	2.9	1
	CAZ	1000 mg, q12h	70.7	26.7	284.6	116.5	23.7	9.7

With the proposed dosage adjustment to 250mg q12h of NXL104 as 2-h infusion for subjects with CrCL of 31-50ml/min the predicted exposure in steady-state C_{max} (C_{max,ss}) and dose interval adjusted steady-state AUC (i.e., the average steady-state concentration over the dose interval, C_{av,ss}=AUC_{ss}/τ, where τ is the dose interval) is comparable to subjects with normal renal function. Likewise, this dosage adjustment is predicted to achieve the joint target of 50% T>8mg/L of ceftazidime and 50% T>1mg/L of NXL104, with a PTA of approximately >90% (Table 3). Overall the analysis predicts that NXL104 could be dose adjusted across patients with differing degrees of renal impairment, using the same guidelines agreed for Ceftazidime, maintaining a 4:1 ratio of ceftazidime: NXL104.

Table 3 Joint probability of target attainment for dose adjusted CAZ104 in patients with varying degrees of renal impairment for 120- minute iv infusion dose administration

Renal Function	Drug	Dose	PK/PD Target	
			50% T> Ct or MIC Ct/MIC (mg/L)	PTA (%)
CrCL>80 mL/min	NXL104	500 mg, q8h	1	96.1
	CAZ	2000 mg, q8h	8	96.0
	NXL104+CAZ	500mg NXL104+2000mg CAZ, q8h	Joint target	92.1
51 mL/min ≤CrCL≤80 mL/min	NXL104	500 mg, q8h	1	99
	CAZ	2000 mg, q8h	8	98.6
	NXL104+CAZ	500mg NXL104+2000mg CAZ, q8h	Joint target	97.6
31 mL/min ≤CrCL≤50 mL/min	NXL104	250mg, q12h	1	90.6
	CAZ	1000 mg, q12h	8	98.2
	NXL104+CAZ	250mg NXL104+1000mg CAZ, q12h	Joint target	89.1

CAZ: Ceftazidime; Ct: Threshold concentration of NXL104; MIC: Minimum inhibition concentration of ceftazidime; PTA Probability of target attainment

For the proposed Phase 3 studies, the inclusion of patients with renal impairment has been limited to patients with CrCL of no lower than 31 mL/min.

3-7-11 Meeting Discussion: No further discussion was needed.

Question 4b: Similar to the cIAI dose selection, AstraZeneca-Forest-Cerexa have selected a dosing regimen for the Phase III cUTI studies (based on pre-clinical PK/PD studies and clinical population PK modeling) that is different than the dose regimen used in the Phase II cUTI study. An increased CAZ104 dose (2000 mg ceftazidime / 500 mg NXL104 vs 500 mg ceftazidime / 125 mg NXL104) and longer infusion time (2 hours instead of 30 minutes) are proposed for the Phase III cUTI studies. Does the FDA agree with the dose regimen selected for use in the Phase III cUTI program?

Division Response (per 3-2-11 e-mail): Agree.

Sponsor Response (per 3-4-11 e-mail): No further clarification is requested.

3-7-11 Meeting Discussion: No further discussion was needed.

Questions on the overall clinical program for initial submission

Question 5: Suitability of the Phase III clinical program to support a new chemical entity (NCE) submission

AstraZeneca-Forest-Cerexa consider that positive data from the proposed Phase III clinical program would provide sufficient efficacy and safety data for CAZ104 in patients with cIAI and cUTI including acute pyelonephritis to form the basis of an NDA submission in these indications. Does the FDA agree?

Division Response (per 3-2-11 e-mail): Prior to the finalized submission of the NDA, the clinical development program will need to adequately address the contribution of each component. Further discussion with us may be warranted in this regard, but supportive evidence of the additional treatment effect provided by the combination may be demonstrated with in vitro data and with in vivo animal model data.

Sponsor Response (per 3-4-11 e-mail): No further clarification is requested, unless the FDA has specific information to share at this time.

3-7-11 Meeting Discussion: No further discussion was needed.

Question 6: Investigative site overlap between Phase III studies in the same indication

For each indication, AstraZeneca-Forest-Cerexa propose that some investigative sites will be allowed to recruit patients into both Phase III studies, such that up to 25% of the total

patient population randomized into either study could be recruited at sites participating in both studies. Does the FDA agree that this overlap will not compromise the reproducibility of efficacy and safety results obtained in the Phase III setting?

Division Response (per 3-2-11 e-mail): No. The clinical trials for each indication should not include the same investigators. The independence of these trials is maximized by the use of different investigators and sites for each trial. By using a fraction of sites to enroll for both studies, the results in both trials are correlated. Consequently, any unanticipated, undetected, systematic biases in one trial may be propagated to the other trial despite the best intentions of you and investigators.

Sponsor Response (per 3-4-11 e-mail): No further clarification is requested.

3-7-11 Meeting Discussion: No further discussion was needed.

Questions on the design of the proposed Phase III studies in patients with cIAI

Question 7: Inclusion criteria for Phase III cIAI studies

Question 7a: Does the FDA agree that the disease-specific inclusion criteria proposed by AstraZeneca-Forest-Cerexa for the Phase III studies in patients with cIAI are representative of the patient population expected for this indication?

Division Response (per 3-2-11 e-mail): Yes, we agree with the proposed disease-specific inclusion criteria.

Sponsor Response (per 3-4-11 e-mail): No further clarification is requested.

3-7-11 Meeting Discussion: No further discussion was needed.

Question 7b: In order to ensure enrollment of the ‘more complicated’ intra-abdominal cases, AstraZeneca-Forest-Cerexa propose to limit the number of patients with a diagnosis of perforated appendix/appendiceal abscess enrolled in the Phase III cIAI studies to a maximum of 25% of the patient population in each study. Does the FDA agree with this approach?

Division Response (per 3-2-11 e-mail): Yes, we agree with this approach.

Sponsor Response (per 3-4-11 e-mail): No further clarification is requested.

3-7-11 Meeting Discussion: No further discussion was needed.

Question 8: Choice of primary endpoint and timing of primary assessment for the Phase III cIAI studies

8a: AstraZeneca-Forest-Cerexa consider that the proportion of patients with clinical cure at test of cure (TOC) visit (4 to 6 weeks post treatment) is an appropriate primary endpoint to assess efficacy in the Phase III studies in patients with cIAI. Does the FDA agree with the choice of primary endpoint and timing of its assessment?

Division Response (per 3-2-11 e-mail): *Based on our current thinking, we recommend a primary endpoint of development of complications of cIAI by a fixed time point following randomization and initiation of treatment. These complications are similar to the failure criteria specified in your draft protocol. The optimal timing of this assessment is unclear. Your proposal should be supported by evidence from your phase II trial. In addition, it is important to understand the reasons for failure from your phase II trial. Providing us with a complete study report of your phase II trial as well as data sets in the very near future will assist our efforts to determine the recommended timing of primary endpoint assessment.*

Sponsor Response (per 3-4-11 e-mail):

- We request clarification on what are the areas of uncertainty with regard to the endpoint (definition of development of complications and optimal timing of the assessment).
- We will provide FDA with the clinical study report for the phase 2 study as soon as it is available. Please clarify which data are of greatest interest to the FDA.

3-7-11 Meeting Discussion: No further discussion was needed.

8b: AstraZeneca-Forest-Cerexa are currently assuming that in order to provide sufficient evidence of efficacy in patients with cIAI, it is necessary to demonstrate non-inferiority for the primary endpoint at the TOC visit (4 to 6 weeks post treatment) in both the microbiologically modified intention-to-treat (mMITT) and microbiologically evaluable (ME) populations, and consequently have included them both as co-primary populations. Does the FDA agree?

Division Response (per 3-2-11 e-mail): *The mMITT population should be considered the primary analysis population. Consistency of the results should be evaluated in all populations and any inconsistencies in the results of these analyses should be explored and explanations should be provided in the complete study report.*

Sponsor Response (per 3-4-11 e-mail): No further clarification is requested.

3-7-11 Meeting Discussion: No further discussion was needed.

Question 9: Non-inferiority margin for Phase III cIAI studies

AstraZeneca-Forest-Cerexa plan to investigate the non-inferiority of CAZ104 + metronidazole (MTZ) compared to meropenem for the treatment of cIAI by conducting 2 identically designed and sized Phase III studies, both using a margin of (b) (4) %. Does the FDA agree that this non-inferiority margin is appropriate to assess the efficacy of CAZ104 in patients with cIAI?

Division Response (per 3-2-11 e-mail): *At this time we anticipate recommending a non-inferiority margin of 10 percent; however, we are still deliberating on the justification for this margin. We appreciate the information you have provided to justify the NI margin and will consider this information while developing our recommendation.*

Sponsor Response (per 3-4-11 e-mail):

- We believe that a (b)(4)% margin is justified, and the proposed endpoint is appropriate for this indication (as detailed in the briefing document). However, we understand the need for FDA to deliberate on the appropriate endpoint, its timing and the corresponding margin. It is worth noting that the probability of concluding non-inferiority using a (b)(4)% margin in both trials, given that the true difference is less than or equal to (b)(4)% will be (b)(4)%. We still consider a (b)(4)% margin to be both statistically and clinically appropriate.
- We would like to know when the FDA anticipates a final decision will be made. Further, can the FDA confirm when the data/literature references and methods that underpin the 10% margin could be made available?

3-7-11 Meeting Discussion:

- The Division stated that they agreed with the methodology used for the NI margin, but will need to review the prophylaxis data and other data to determine their final decision on NI margin; a (b)(4)% margin is unlikely to be acceptable. The Division requested data on the timing of failure or success from the phase 2 trial and will provide a list of phase 2 data of interest. AZ/F/C agreed to provide these datasets.

Question 10: Analysis populations for Phase III cIAI studies

Does the FDA agree with the analysis populations proposed by AstraZeneca-Forest-Cerexa for the Phase III studies in patients with cIAI, as defined in Section 12.1 of the Study D4280C00001 Clinical Study Protocol (CSP)?

Division Response (per 3-2-11 e-mail): *The mMITT population should include all randomized subjects who met the disease definition of cIAI and have at least one etiologic pathogen identified at study entry regardless of susceptibility only. The additional requirement that they received any amount of study drug should be removed. Please also clarify whether the CE population refers to patients who met the definition for the ITT population or if it is a subset of the mMITT population.*

Sponsor Response (per 3-4-11 e-mail):

- The Division's response is noted. Please note that any patient not receiving study drug will be regarded as indeterminate (due to the reason "Patient did not receive 48 hours of IV study therapy") and therefore considered a failure in the mMITT analysis. This change in definition to the population will impact cure rates.
- The CE population is a subset of the mMITT population.

3-7-11 Meeting Discussion: No further discussion was needed.

Question 11: Prior antibiotics in the Phase III cIAI studies

AstraZeneca-Forest-Cerexa propose to allow limited prior antibiotic use in the Phase III cIAI studies. Does the FDA agree with this proposal?

Division Response (per 3-2-11 e-mail): *We would prefer excluding all patients who have received antibacterial drug therapy during the previous 48 hours. Ideally patients should be enrolled, randomized and given their first dose pre-operatively without any prior antibiotic use. It is unclear how significantly one or two doses of routine perioperative antibiotics would be expected to impact the treatment effect. We are currently developing our recommendation in this regard. Providing us with a complete study report of your phase II trial as well as data sets in the very near future will assist our efforts.*

Sponsor Response (per 3-4-11 e-mail):

- From a medical practice and standards perspective, avoidance of prior antibiotics is not feasible in every case, particularly because most patients are entered into the study after source control in order to verify the cIAI. The standard of care is to start antibiotics peri-operatively to prophylax against wound infection. Analyses comparing treatment groups in patients who received prior antibiotics and in patients without prior antibiotics will be performed.
- As mentioned in the response to question 8a, we will provide the phase 2 study report as soon as it is available. Please clarify which data is of greatest interest to the FDA.

3-7-11 Meeting Discussion:

- AZ/F/C sought the Division's position regarding the use of prior antibiotics in the study and asked whether the limited use of prior antibiotics would be acceptable or there should be no prior use of any antibiotics. The Division stated that they learned from the historical CAP data that prior antibiotic use is a confounding factor which affects the interpretation of the study. The Division suggested enrolling subjects at pre- and post-operative stages so that the impact of prior antibiotic use on the study drug could be determined and quantified.
- However, the Division would like to see AZ/F/C's phase 2 data regarding the antibiotic treatment given to patients between closure in the operating room and initiation of study drug and the percentage of patients receiving prior antibiotics. The Division will provide a list of requested data and will have further recommendations on this issue in the next month or so.
- It was agreed that more discussion would be warranted during a future teleconference.

Question 12: Concomitant antibiotics in the Phase III cIAI studies

AstraZeneca-Forest-Cerexa propose to allow limited concomitant antibiotic use for Gram-positive pathogens. Does the FDA agree with this proposal?

Division Response (per 3-2-11 e-mail): *We strongly recommend curtailing the use of concomitant antibiotics to the extent possible, since this may preclude evaluation of the study drugs' antibiotic treatment effect. Adding metronidazole to the CAZ104 arm may also confound interpretation of study results because under reduced conditions, such as those found in*

intraabdominal infections, metronidazole may have some activity against Enterobacteriaceae. We are presently considering recommendations for additional in-vitro testing which may address the concern of metronidazole activity against Enterobacteriaceae and will provide any recommendations to you in the near future.

Sponsor Response (per 3-4-11 e-mail):

- We acknowledge the concerns regarding the impact of concomitant antibiotics on the ability to make an assessment of efficacy of the study drug. Protocol defined Gram-positive agents have no Gram negative coverage and can be used in both treatment groups. Gram positive coverage will only be used in high risk patients for MRSA and enterococcus and use will be stopped upon a negative culture, consistent with existing medical guidelines.
- We would like clarity concerning the comments from the FDA about metronidazole. We consider that cover of anaerobes is essential in cIAI studies, and that because the clinical activity of metronidazole is limited to anaerobic organisms, this makes it an acceptable choice. There is no suitable alternative in our view either because of resistance issues or because other agents' spectra overlap that of the investigational agent.

3-7-11 Meeting Discussion:

- AZ/F/C stated that the proposed concomitant Gram-positive coverage will not have any Gram-negative activity, will be limited only to those patients suspected of having Gram-positive infection, and will be stopped upon a confirmed negative culture.
- AZ/F/C further stated that although metronidazole demonstrates some activity against facultative anaerobic bacteria, such as Enterobacteriaceae, in animal models, this is less clear with use in humans. AZ/F/C also stated that they would like to finalize these studies in the second quarter of 2011 and they do not see any other way to conduct their studies but to use metronidazole as proposed. The Division responded that the scientific literature from the 1970s – 1980s suggested that metronidazole has some activity against *E. coli in vitro* and suggested that AZ/F/C perform *in vitro* screening using a checkerboard model with and without metronidazole under aerobic, microaerophilic, and anaerobic conditions. This would provide information regarding potential effects of metronidazole. If there is an interaction, then animal testing would be recommended. The Division stated that this testing should be performed prior to the initiation of the phase 3 study.
- The Division stated that they will provide a list of references from 1970s – 1980s to AZ/F/C.

Questions on the design of the proposed Phase III Studies in patients with cUTI including pyelonephritis

Question 13: Inclusion criteria for Phase III cUTI study

Does the FDA agree that the disease-specific inclusion criteria proposed by AstraZeneca-Forest-Cerexa for the Phase III studies in patients with cUTI including acute pyelonephritis (eg, the inclusion of males with UTI) are representative of the patient population expected for this indication?

Division Response (per 3-2-11 e-mail): *Yes, we agree with the proposed inclusion criteria with a suggestion for clinical signs/symptoms (#2 on page 63 of the Briefing Document). Patients should have at least two of the following signs or symptoms:*

- *Chills or rigors or “warmth” accompanied by fever (e.g., oral temperature greater than 38 degrees Celsius)*
- *Flank pain (pyelonephritis) or pelvic pain (cUTI)*
- *Nausea or vomiting*
- *Dysuria, urinary frequency, or urinary urgency*
- *Costo-vertebral angle tenderness on physical examination*

Prior to receipt of drug therapy, all patients should have a urine specimen for culture and in vitro susceptibility testing. If a patient has an indwelling catheter, it is preferable to collect samples following placement of a new catheter or, if this is not feasible, it should be obtained using aseptic techniques through the collection port. Uropathogenic bacteria identified at 1×10^5 colony forming units per milliliter (CFU/mL) should be considered a bacterial pathogen.

Although patients with uncomplicated UTI are generally female, male patients should have a documented risk factor (e.g. BPH, indwelling catheter) when possible.

Sponsor Response (per 3-4-11 e-mail):

- We believe that the presence of fever is uncommon in complicated lower UTI and your suggested criteria would greatly limit enrollment of complicated lower UTI in comparison to acute pyelonephritis. We are concerned that, for example, there would be a risk of enrolling subjects without UTI on the basis of fever and nausea only. In contrast, patients with dysuria, frequency and urgency plus clear microbiological evidence of a cUTI, would be excluded if fever or pelvic pain were not also present. Does the agency have any information on the specificity and sensitivity of these criteria, especially with regard to complicated lower UTI?
- Currently, baseline urine cultures containing more than 2 organisms would be considered contaminated and these patients excluded from the study. In looking at your comments, would you clarify that:
 - If a patient has more than 2 organisms at baseline they can be enrolled.
 - More than 2 bacteria at $>10^5$ from a single specimen may be considered pathogens or will this be considered a contaminated specimen?
- Thank you for your comment about males with cUTI. We will document risk factors in males when present.

3-7-11 Meeting Discussion: No discussion due to time constraints.

Question 14: Choice of primary endpoint and timing of primary assessment for the Phase III cUTI studies

14a: AstraZeneca-Forest-Cerexa consider that the per-patient microbiological response at the TOC visit (5 to 11 days post treatment) is an appropriate primary endpoint for the

Phase III studies in patients with cUTI including acute pyelonephritis. Does the FDA agree with the choice of primary endpoint and timing of its assessment?

Division Response (per 3-2-11 e-mail): *Primary assessment should include both resolution of clinical signs/symptoms as well as microbiological response (a urine culture at TOC shows that the pathogen found at trial entry is reduced to less than 10^3 CFU/mL) at a fixed time point approximately 7 days after completion of antimicrobial therapy.*

Sponsor Response (per 3-4-11 e-mail):

- We would like to understand the rationale for a combined microbiological and clinical response. Currently, our proposed endpoint is in keeping with previous trials and consistent with the data used for the non-inferiority margin.
- Currently the clinical outcome is based on investigator assessment. Is this acceptable for documenting clinical response or is the resolution of signs and symptoms intended to be the determinant of cure?
- We would like to understand further the rationale for using $<10^3$ cfu/mL as the criterion for a post-baseline urine culture to be negative. Past FDA guidelines have advised that the cut-off would be $<10^4$ cfu/mL.

3-7-11 Meeting Discussion:

- AZ/F/C inquired if the endpoint should be co-primary or a composite of clinical and microbiological response. The Division responded that it should be co-primary, not a composite.
- AZ/F/C inquired whether the investigator's assessment of clinical outcome was acceptable. The Division stated that in the past there have been discrepancies between what the investigators reported and what the patients reported. Therefore, the use of a patient-reported outcome tool for assessing improvement of symptoms after treatment would also be recommended, and any discrepancies should be reported. Furthermore, microbiological eradication is also an important factor, and, therefore, the microbiological response should be a co-primary endpoint.
- The Division stated that they would consult the FDA Study Endpoints and Label Development (SEALD) review team regarding clinical assessment after 4-5 days of treatment and validation of measures of response. The Division will share SEALD's recommendations with AZ/F/C.
- Using both the clinical and microbiological responses, rather than separate assessments of each endpoint, the Division stated that they derived the NI margin from historical data. Specific references for this data will be sent to AZ/F/C in future correspondence.
- There was discussion about the timing of the primary endpoint and the Division responded that this will need further internal discussion and that at the follow up teleconference with AZ/F/C, the Division will provide further guidance.
- AZ/F/C requested the rationale for recommending a lower microbiological criterion for resolution of 10^3 CFU/mL. The Division responded that the reason was that the higher bacterial counts may be associated with recurrence of infection and development of resistance. The Division stated that they would like to learn about colony counts from AZ/F/C's phase 2 study, but AZ/F/C responded that they do not have data reported as 10^3

CFU/mL because labs do not routinely perform 10^3 CFU/mL counts. The Division and AZ/F/C agreed that the 0.001 mL (1 μ L) loop, which is a standard loop used by laboratories, was adequate and that AZ/F/C should report colony counts that fall between 10^3 and 10^4 since there is interest in seeing what number of patients fall into this range and how these numbers may correlate with clinical cure, recurrence of infection, and development of resistance. However, acceptable treatment results will remain as no growth at $\leq 10^4$ CFU/mL (colony count of 9 colonies or less). The Division asked AZ/F/C to provide the protocol that will be used to culture urine for review and comment prior to initiating phase 3 studies.

- The Division asked AZ/F/C when urine specimens would be collected according to the protocol. AZ/F/C stated that urine culture would be collected at the baseline and at 5 to 11 days after treatment. The Division suggested a timepoint at about day 17 post randomization (7 days after end of therapy) for the test of cure, but agreed to discuss this further with AZ/F/C during a future teleconference.

14b: AstraZeneca-Forest-Cerexa are currently assuming that in order to provide sufficient evidence of efficacy in patients with cUTI, it is necessary to demonstrate non-inferiority for the primary endpoint at the TOC visit (5 to 11 days post-treatment) in both the microbiologically modified intention-to-treat (mMITT) and microbiologically evaluable (ME) populations, and consequently have included them both as co-primary populations. Does the FDA agree?

Division Response (per 3-2-11 e-mail): The mMITT population should be considered the primary analysis population. Consistency of the results should be evaluated in all populations and any inconsistencies in the results of these analyses should be explored and explanations be provided in the complete study report.

Sponsor Response (per 3-4-11 e-mail): No further clarification is requested.

3-7-11 Meeting Discussion: No further discussion was needed.

Question 15: Non-inferiority margin for Phase III cUTI study

AstraZeneca-Forest-Cerexa plan to investigate the non-inferiority of CAZ104 compared to doripenem for the treatment of cUTI by conducting 2 identically designed and sized Phase III studies, both using a margin of (b) (4)%. Does the FDA agree that this non-inferiority margin is appropriate to assess the efficacy of CAZ104 in patients with cUTI including acute pyelonephritis?

Division Response (per 3-2-11 e-mail): Based on our current thinking, we recommend using a non-inferiority margin of 10 percent.

Sponsor Response (per 3-4-11 e-mail):

- We believe that a (b) (4)% margin is justified based on the M1 estimate of (b) (4)% for this indication. A (b) (4)% margin would be much smaller than any antibiotic effect over placebo and would rule out any clinically relevant difference.

- Can the FDA please provide the data/literature references and methods that underpin the 10% margin?

3-7-11 Meeting Discussion: Due to time constraints, it was agreed that this topic would be discussed during a future teleconference.

Question 16: Analysis populations for Phase III cUTI study

Does the FDA agree with the analysis populations proposed by AstraZeneca-Forest-Cerexa for the Phase III studies in patients with cUTI including acute pyelonephritis, as defined in Section 12.1 of the Study D4280C00002 CSP?

Division Response (per 3-2-11 e-mail): Please refer to the response for Question 10.

Sponsor Response (per 3-4-11 e-mail):

- The FDA response is noted. Please note that any patient not receiving study drug will be regarded as indeterminate (due to the reason “Patient did not receive 48 hours of IV study therapy”) and therefore considered a failure in the mMITT analysis. This change in definition to the population will impact cure rates.
- The CE population is a subset of the mMITT population.

3-7-11 Meeting Discussion: No further discussion was needed.

Question 17: Oral switch for Phase III cUTI study

AstraZeneca-Forest-Cerexa propose to allow an oral switch in the Phase III studies in patients with cUTI. Does the FDA agree with this proposal?

Division Response (per 3-2-11 e-mail): This proposal is not acceptable for the following reason: The timing of the oral switch, as well as the choice and duration of oral treatment may not be comparable between study groups. We strongly recommend for the purposes of this trial, that all patients receive the complete duration of treatment of the study drug or active control. If patients no longer require continued inpatient care, then outpatient intravenous administration should be arranged.

Sponsor Response (per 3-4-11 e-mail):

- We understand the FDA’s response to both questions 17 and 18, however, there appears to be some inconsistency in the FDA’s comments with regard to the rejection of an oral switch in our study and the advice to adhere to the doripenem label. In particular, the doripenem label indicates that the 10 day duration “includes a possible switch to an appropriate oral therapy, after at least 3 days of parenteral therapy, once clinical improvement has been demonstrated.” The doripenem trials also studied a clinically relevant treatment strategy that allowed for a switch to oral therapy after 3 days of treatment if certain endpoints were met as would be expected to occur after approval. In the doripenem cUTI randomized controlled trial, only 11% of subjects who completed the study received IV therapy only. The median duration of IV therapy in the ME

population was 5 days while the median duration of all therapy was 10 days. Further clarification is requested.

- Are there any changes that we can make to this study where an oral switch would be considered acceptable?

3-7-11 Meeting Discussion:

- AZ/F/C stated that they would like to conduct trials that will produce interpretable data. However, the challenges would be in recruitment and retention of the U.S. study population with prolonged IV therapy if there is no option of switching to oral therapy.
- AZ/F/C/ stated that they would have specific criteria for the switch to oral therapy from IV and would also limit the oral agent to a specific one and asked if this would be acceptable to the Division. AZ/F/C also asked if the Division would accept an IV only study from a non-U.S. population. The Division acknowledged the challenges, but they were concerned about the ability to interpret the efficacy of the study drug, especially when the oral agent is different from the study drug.
- The Division also stated that efficacy data should also be derived from the U.S. population if the product to be marketed is in the U.S.
- AZ/F/C stated that the oral switch would be done at the point when the patients would almost be cured and therefore, they believed that this switch would not have any effect on the treatment effect. Even in the doripenem cUTI study, about 89% of subjects changed to an oral agent. The Division stated that one option would be to keep the patients on IV therapy for a minimum of 4 days and perform an assessment at this time to measure the treatment effect before a change to an oral agent. The Division stated further that in the previous studies, including the doripenem studies, the average IV therapy length was 5 days, and an earlier timepoint for an oral switch might confound the efficacy results. The Division stated that it would be helpful to see more data on the timing of bacterial eradication and the timing of the oral switch and requested AZ/F/C to submit the bacterial eradication data and the timing of the oral switch on the patients from their phase 2 study. The Division would arrange to have a teleconference with AZ/F/C to discuss this topic further after reviewing the data from phase 2 study, hopefully within approximately 4 weeks.

Question 18: Duration of therapy for Phase III cUTI study

AstraZeneca-Forest-Cerexa propose a duration of treatment for the cUTI Phase III studies of 7 to 10 days, which is consistent with the registration trials for doripenem but differs from the duration of treatment in the doripenem label of 10 days. Does the FDA agree with this proposal?

Division Response (per 3-2-11 e-mail): The duration of treatment with CAZ104 for cUTI, as proposed for labeling purposes, will need to be evaluated following submission of the results of Phase III studies. For the purposes of this trial, doripenem should be administered for the duration of 10 days as indicated in the label.

Sponsor Response (per 3-4-11 e-mail): Please see the response to question 17.

3-7-11 Meeting Discussion:

The Division stated that they recommend AZ/F/C follow the duration indicated in the label, which is 10 days of treatment, unless AZ/F/C could show data to support a noninferiority margin for a shorter duration of treatment. This is another topic that the Division and AZ/F/C will need to discuss further.

Question on pediatric use information

Question 19: Request for deferral of pediatric use information

In accordance with 21 CFR 314.55(b) (1), AstraZeneca-Forest-Cerexa propose to defer submission of pediatric use information until after the approval of the drug product in adults. This proposal is based on the need to collect additional safety and efficacy data prior to initiation of pediatric studies. Does the FDA agree to defer the requirement for pediatric use information in an NDA for the proposed indications of cIAI and cUTI including acute pyelonephritis?

***Division Response (per 3-2-11 e-mail):** The prescribing information for ceftazidime contains dosing recommendations down to the neonatal period. You should begin work on your pediatric program; we expect the completion of pediatric pharmacokinetic studies by the time of NDA submission. Your NDA application must contain a pediatric plan. Submission of pediatric studies may be deferred if your drug is ready for approval in adults before pediatric studies are complete. You must submit your rationale for deferral, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the submission of each protocol, expected initiation of each study, expected completion of each study, and expected submission to the Agency of each full study report. Your deferral request and pediatric plan must be reviewed by the Agency's Pediatric Review Committee before NDA approval. If a satisfactory pediatric plan is submitted with the expected timelines, we anticipate approving your deferral request.*

Sponsor Response (per 3-4-11 e-mail): The FDA response is noted. Further clarification on the pediatric plan will be requested in the near future.

3-7-11 Meeting Discussion: No further discussion was needed.

Additional Comments (per 3-2-11 e-mail)

Clinical Pharmacology:

- *Pending results from the planned thorough QT study, ECG monitoring is warranted in all clinical studies and should always include assessment during therapy at or around the anticipated T_{max} .*

Sponsor Response (per 3-4-11 e-mail): No further clarification is required.

3-7-11 Meeting Discussion: No further discussion was needed.

Clinical Pharmacology:

- *Considering removing the upper limit of body weight/body mass index exclusion criterion from Phase 3 protocols to allow collection of valuable pharmacokinetic information in obese patients, however limited it may be.*

Sponsor Response (per 3-4-11 e-mail): The body weight/BMI exclusion is only for the cIAI study. We plan on obtaining this data from cUTI study.

3-7-11 Meeting Discussion: No further discussion was needed.

Statistics

- *The proposed method that missing data will result in a reduced sample size for that parameter is not acceptable. You also should present sensitivity analyses such as including all missing patients as failures or including all missing patients as successes. Furthermore, other appropriate sensitivity analyses should be carried out that does not necessarily use LOCF.*

3-7-11 Meeting Discussion: No further discussion was needed.

Sponsor Response (per 3-4-11 e-mail):

- The statement in the protocol “Missing data will result in a reduced sample size for that parameter” refers to the safety variables (labs, etc.) where we are planning to report the data and not employ any imputation approaches as the safety analyses will predominantly consist of summary tables and graphs.
- For the efficacy analysis we will be considering the missing data. Specifically, consistent with standard definitions, the mMITT population will count indeterminates in the denominator (thereby counting them as failures). However, for the ME population, indeterminates will be excluded from the population. Further sensitivity analyses may be employed depending on the number and nature of the missing data.

3-7-11 Meeting Discussion: No further discussion was needed.

Statistics

- *Provide other sensitivity analysis. An analysis of patients who initiate rescue antibacterial drug therapy between the treatment groups is a recommended secondary endpoint; imbalances between treatment groups in the proportion of patients who initiate rescue antibacterial drug therapy can be an important consideration for overall efficacy.*

Sponsor Response (per 3-4-11 e-mail): We will provide a summary of the number of patients who initiate rescue antibacterial drug therapy by treatment group. However we are not intending to undertake any formal statistical analysis on this. Is this acceptable?

3-7-11 Meeting Discussion: No further discussion was needed.

Statistics

- *Before initiation of any phase 3 trial, you should provide a detailed statistical analysis plan with the protocol for the phase 3 trial.*

Sponsor Response (per 3-4-11 e-mail): We plan to provide the statistical analysis plan with the protocol for the phase 3 trials.

3-7-11 Meeting Discussion: No further discussion was needed.

ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

/s/

SUMATHI NAMBIAR
03/28/2011

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 206494

LATE-CYCLE MEETING MINUTES

Cerexa, Inc.
Attention: Kristina Haeckl, RAC
Executive Director, Regulatory Affairs
2100 Franklin Street, Suite 900
Oakland, CA 94612

Dear Ms. Haeckl:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ceftazidime-avibactam injection.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on November 14, 2014.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Carmen DeBellas, Regulatory Project Manager at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: November 14, 2014

Application Number: NDA (b) (4)

Product Name: Ceftazidime-avibactam injection

Applicant Name: Cerexa, Inc.

FDA ATTENDEES

Office of Antimicrobial Products

Dr. Edward Cox Director
Dr. John Farley Deputy Director

Division of Anti-Infective Products

Dr. Sumathi Nambiar Director
Dr. Katherine Laessig Deputy Director
Dr. Margaret Gamalo Statistics Reviewer
Dr. Thamban Valappil Statistics Team Leader
Dr. Benjamin Lorenz Clinical Reviewer
Dr. Seong Jang Clinical Pharmacology Reviewer
Dr. Kimberly Bergman Clinical Pharmacology Team Leader
Dr. Wendelyn Schmidt Pharmacology/toxicology Team Leader
Dr. Ronald Wassel Reviewer, Office of Pharmacovigilance and Epidemiology
Dr. Joyce Weaver Senior Drug Risk Manager, Office of Medication Error Prevention and Risk Management

Mr. Christopher Sese Contractor- PDUFA V Program
Dr. Carmen DeBellas Project Manager

APPLICANT ATTENDEES

June Bray Sr. Vice President, Regulatory Affairs, FRI
Timothy Carrothers Sr. Principle Scientist, Pharmacometrics, FRI
Ian Critchley Vice President, Clinical Microbiology, CRX
Tristan Duong Technical Writer IV, CMC, FRI
David Friedland Vice President, Clinical Development, CRX
Kristina Haeckl Executive Director, Regulatory Affairs, CRX
Ann Howell Assoc. Director, Regulatory Affairs, FRI
Steven Leili Directory, Toxicology, FRI
Lily Llorens Senior Director, Biostatistics and Data Management, CRX
Reena Nadpara Post-Doctoral PharmD Fellow, Regulatory Affairs, FRI
David Nicholson Sr. Vice President, Global Brands R&D, Actavis

Michael Olchaskey	Exec Director, Regulatory Affairs, RFI
Douglas Rank	Director, Clinical Development, CRX
Todd Riccobene	Sr. Director, Clinical Pharmacology, FRI
Brahma Singh	Associate Principal Scientist, Product Development, FRI
Pomy Shrestha	Director, Global Drug Safety, FRI
Angela Talley	Associate Director, Clinical Development, CRX
Gavin Corcoran	Chief Medical Officer, FRI
Declan Kelly	Executive Director, Regulatory Affairs, CMC, FRI
David Melnick	Medical Science Director, AZ

1.0 BACKGROUND

NDA 206494 was submitted on June 25, 2014 for ceftazidime-avibactam injection.

Proposed indication(s): Complicated Intra-abdominal Infections
Complicated Urinary Tract Infections including Pyelonephritis
Limited Use Indication: Aerobic Gram-negative Infections with
Limited Treatment Options

PDUFA goal date: February 25, 2015

FDA issued a Background Package in preparation for this meeting on November 12, 2014.

2.0 DISCUSSION

1. Introductory Comments –

Welcome, introductions, ground rules, and objectives of the meeting

2. Discussion of Substantive Review Issues –

Each issue will be introduced by FDA and followed by a discussion.

- Discuss renal dosing recommendations and adequacy of available clinical information to provide dosing adjustments for patients with CrCl < 50 ml/min.

Discussion:

Based on their review of the available data, the Sponsor stated that they [REDACTED] (b) (4) [REDACTED] in line with the recommendation in the label for ceftazidime. The Division stated that this information was still under review. It seems that in moderate to severe renal impairment, some dosage adjustment may be needed. The Division enquired if more frequent monitoring of creatinine clearance will be needed in these patients in order to adjust the dose appropriately. The Sponsor noted that more time would be needed to review dosing calculations for moderate to severe renal impairment patients. The Division stated that review of

the Case Report Forms will be necessary since they were not convinced that lower cure rates were only because of CAZ-AVI dosing. The Division added that concentration time profiles would need to be reviewed to see if exposure targets were met.

3. Discussion of Minor Review Issues –

There are no additional review issues to discuss.

4. Additional Applicant Data –

- Meeting Background Materials including preliminary response to the Information Request sent on 06 November 2014.

5. Information Requests –

With regard to the RECLAIM trial, please provide responses to the following pending requests from our information request dated 06 November, 2014, as new information becomes available:

- For all subjects who died and had moderate to severe renal impairment at baseline, submit creatinine clearance values at all time-points taken.
- Submit all PK and MIC data (for ceftazidime and CAZ-AVI) in subjects with moderate to severe renal impairment at baseline who were determined to be clinical failures.

We have the following requests as discussed during the teleconference on 10 November 2014:

- When available, please submit PK and MIC data (for ceftazidime and CAZ-AVI), as well as post-baseline CrCl values, in all subjects with moderate to severe renal impairment at

-  (b) (4)

In addition, we have the following “new” information request:

- Please submit ceftazidime/avibactam dosing information (including all dose adjustments), creatinine clearance values at all time-points assessed, any available pharmacokinetic data and outcome data for all subjects with moderate to severe renal impairment at baseline.

Discussion:

The Sponsor informed the Division that the pharmacokinetic and MIC information for all patients who died had been submitted on  (b) (6). The information requested during

the November 10, 2014 teleconference would be submitted sometime next week. The Sponsor stated that they are reviewing the requested literature.

6. Discussion of Upcoming Advisory Committee Meeting –

- Preliminary Phase 3 cIAI results, including subgroup of subjects with CrCl < 50 ml/min.

Discussion: The Sponsor stated that the focus of their presentation will be on information provided in the NDA. They would also provide information from the ongoing analysis of the Phase 3 trial that has been mentioned publicly. The Division asked the Sponsor to add an addendum to their briefing document with information available regarding the Phase 3 cIAI trial as it was not included in the briefing document. The Sponsor expressed some concern about the level of discussion that may occur during the question and answer period and what level of detail should be provided in the addendum to the briefing document. They stated that the study report had not been written as yet. The Sponsor expressed concern about how differences in interpretation of the data may be confusing to the committee. The Sponsor also mentioned their concern about the committee's understanding of a 505(b)(2) submission. The Division stated they would discuss the 505(b)(2) regulatory pathway in their presentation.

The Sponsor enquired if any information was available about the December 4th AC meeting. The Division stated that they could not discuss any non-public information.

7. REMS or Other Risk Management Actions –

None at this time.

8. Postmarketing Requirements/Postmarketing Commitments –

- **Post Marketing Requirements:**

1. PREA

A. Ongoing: Phase I, single-dose Pharmacokinetic (PK) study in patients aged ≥ 3 months to < 18 years (Study D4280C00014).

B. Proposed

a. A Phase I, two-part, open-label single dose (Part A) and multiple dose (Part B) PK and safety study to define the dose in patients aged < 3 months who are receiving concomitant antibiotic therapy.

b. A Phase II, multicenter randomized, single-blind safety, tolerability and descriptive efficacy study in cIAI.

c. Phase II, multicenter, randomized, single-blind safety, tolerability and descriptive efficacy study in cUTI.

2. Microbiology Surveillance Study:

Conduct US surveillance studies for five years from the date of marketing ceftazidime-avibactam to determine if resistance to ceftazidime-avibactam has developed in those organisms specific to the indications in the label.

Final Protocol Submission:

First interim report:

Second interim report:

Third interim report:

Fourth interim report:

Fifth interim report:

Study completion:

Final report submission:

- **Post Marketing Commitments:**

Final study reports for Phase 3 cIAI/cUTI trials and the Resistant Pathogen Study. We are considering a potential study related to renal dosing. A decision will be made once we complete our review.

9. Major labeling issues –

- Clarify that you are seeking limited use indications for cUTI and cIAI.

- [REDACTED] (b) (4)

Discussion:

The Division asked the Sponsor to clarify the difference in the wording of the indications submitted in the NDA and those mentioned in the Agency's Advisory Committee Backgrounder. The Sponsor clarified that for the cIAI and cUTI indications they were seeking limited use labeling. The Sponsor asked the Division why the wording for the third question in the briefing document was different from the first two and stated that they preferred if the wording would be consistent across all three indications. The Division agreed to do so.

[REDACTED] (b) (4)

10. Review Plans –

Currently, discipline reviews are expected to be completed within pre-specified timelines.

11. Wrap-up and Action Items –

Await discussion at the December 5th AIDAC meeting.
Complete labeling discussions
Resolve renal dosing issue

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

SUMATHI NAMBIAR
12/19/2014