CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206494Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **Feb 23, 2015**

From: **Zhengfang Ge, Ph.D.**
CMC Reviewer, Branch 2
Division of Process Assessment I
OPF/OPQ

Through: **Dorota Matecka, Ph.D.**
Acting Branch Chief, Brach III
Division of New Drug Product I, ONDP/OPQ

To: **CMC Review #1 of NDA 206494**

Subject: **Final Recommendation - Approval**

The CMC Review #1 has noted the following issues: 1) pending the Final "Acceptable" recommendation from the Office of Compliance, 2) pending resolution of the labeling deficiency, 3) pending microbiology review. Therefore, this NDA was not recommended for approval in the CMC Review #1.

On Jan 26, 2015, the applicant withdrew Dr. Reddy's Laboratories as one of the manufacturing facilities of avibactam starting material and intermediates. On Feb 23, 2015, the Division of Inspectional Assessment issued an "Approve" recommendation for the manufacturing facilities (see Attachment 1).

On Jan 27, 2015, the microbiology reviewer Dr. Mello recommended "Approval" of the NDA.

On Jan 30, 2015, the applicant submitted updated container and carton labels (see **Attachment 2,** Drug Product Carton Label). The updated container and carton labels are acceptable from CMC perspective.

Also on Feb 9, 2015, Division of Pharmaceutical Analysis concluded that the analytical methods are acceptable for control and regulatory purposes.

Final Recommendation:

This NDA is **now** recommended for approval from the CMC perspective.

Chemistry Review Data Sheet

NDA 206494

AVYCAZ
(ceftazidime & avibactam) Injection
2000/500 mg

Cerexa, Inc.

Zhengfang Ge, Ph.D.

Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

For

Division of Anti-Infection Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 206494

2. REVIEW #: 1

3. REVIEW DATE: Jan 15, 2015

4. REVIEWER: Zhengfang Ge, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	25-June-2014
Amendment	9-July-2014
Amendment	2-Oct-2014
Amendment	9-Oct-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Cerexa, Inc. (subsidiary of Forest Lab)
Address:	2100 Frank St, Ste 900, Oakland, CA 94612
Representative:	Kristina Haeckl
Telephone:	510-285-9200

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Avycaz
b) Non-Proprietary Name (USAN): avibactam sodium and ceftazidime
c) Code Name/# (ONDQA only): NXL104 for avibactam sodium
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: ceftazidime is a cephalosporin-class antibacterial, and avibactam is a β-lactamase inhibitor

11. DOSAGE FORM: IV injection

12. STRENGTH/POTENCY: ceftazidime 2000 mg, avibactam 500 mg

13. ROUTE OF ADMINISTRATION: IV injection

14. Rx/OTC DISPENSED: _X_Rx ___OTC

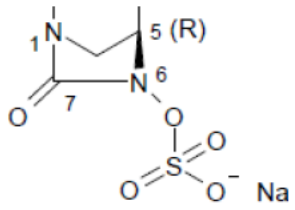
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Avibactam Sodium:
Chemical Name (IUPAC): Sodium;[(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulfate
CAS Name: Sulfuric acid, mono[(1R,2S,5R)-2-(aminocarbonyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester, sodium salt (1:1)

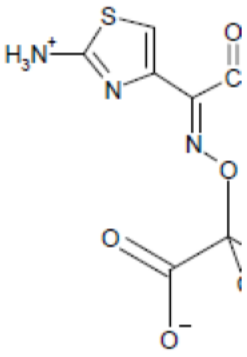


Molecular Formula: $C_7H_{10}N_3O_6SNa$
Molecular Weight: 287.23

Ceftazidime:

CAS Name: Pyridinium, 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, inner salt, hydrate (1:5)

IUPAC Name: (6R,7R)-7-[[(2E)-2-(2-amino-1,3-thiazol-4-yl)-2-(1-hydroxy-2-methyl-1-oxopropan-2-yl)oxyiminoacetyl]amino]-8-oxo-3-(pyridin-1-ium-1-ylmethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate pentahydrate



Molecular Formula: $C_{22}H_{32}N_6O_{12}S_2$
Molecular Weight: 636.6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug	1	Adequate	Sep 15, 2014	

Chemistry Review Data Sheet

		(b) (4)	Substance				
(b) (4)	III		(b) (4)	3	Adequate	4/42007	Reviewed by Dr. S. Read.
	III			3	Adequate	*19-Jan-2011*	*Review by Dr. L. Moussa*
	III			1	Adequate	Sep 16, 2014	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 101307		ceftazidime/avibactam [CAZ-AVI]
IND (b) (4)		(b) (4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		
Pharm/Tox	Acceptable	11/13/2014	Dr. A. Balboni
Biopharm	Acceptable	8/28/2014	Dr. H. Mahayni
LNC	N/A		
Methods Validation	pending		
DMEPA	pending		
EA	N/A		
Microbiology	pending		

The Chemistry Review for NDA 206494

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product *but is pending recommendation from microbiology reviewer Dr. R. Mello*.

However, the Office of Compliance has ***not*** issued an overall "Acceptable" recommendation.

Labeling deficiency listed at the end of this review on page 134 regarding the dose strength need to be resolved during the labeling review.

Therefore, from the ONDQA perspective, this NDA is ***not*** recommended for "***Approval***" in its present form until all pending issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Avibactam Sodium

Avibactam sodium is an NME with two chiral centers. (b) (4) (2S, 5R) is produced as a sterile drug substance by (b) (4) (b) (4) Also, stability studies have shown that (b) (4) does not convert to any other solid form under the proposed storage conditions. Avibactam sodium (b) (4) is freely soluble in water, therefore a specification for the particle size is not proposed. The drug substance structural characterization is confirmed using element analysis, (b) (4).

Avibactam sodium is (b) (4) Control strategy for the critical quality attributes and the impact of the process parameters have been

identified and developed following ICHQ11 and risk based approach. In-process parameters and controls for each intermediates have been properly established. Assessment of potential impurities and their potential genotoxicity through the manufacturing process and storage is provided in the submission. The potential genotoxic impurities (b) (4) are controlled through in process control and estimated well below the threshold of toxicology concern (TTC) level in the avibactam sodium batches based on the assessment. Specified impurity (b) (4) is qualified at NMT (b) (4)% as proposed in the drug substance specification and NMT (b) (4)% in the drug product specification. The controls and the qualification of the impurities are acceptable, and are also confirmed by the pharmtox reviewer, Dr. A. Balboni.

Stability data including 18 months stored at 25°C/60%RH and 6 months stored at 40°C/75%RH are provided for three primary avibactam sodium batches. These batches were manufactured at production scale at the proposed commercial manufacturing site ((b) (4)). The stability data supports the (b) (4) months retest period at (b) (4) condition, as proposed.

Drug Substance: Ceftazidime

Ceftazidime is a semisynthetic, cephalosporin antibiotic for parenteral administration. It is manufactured by (b) (4) as a ceftazidime pentahydrate/sodium carbonate blend. It has been approved in US with registered trade names Fortaz® (NDA 50578) and Zinacef® (NDA 50558). DMF (b) (4) is cross referenced for the CMC information. The DMF was reviewed previously and concluded ***Adequate*** by Dr. A. Banerjee dated 28-June-2011 for NDA 50578 and NDA 50634. Amendments received since Dr. Banerjee's review has been reviewed for this NDA. The DMF has been found adequate to support this NDA.

Drug Products

The proposed drug product is a sterile (b) (4) 20 mL, clear, Type I glass vial containing white to yellow powder of 500 mg avibactam ((b) (4) mg avibactam sodium) and 2000 mg ceftazidime (2635 (b) (4) ceftazidime pentahydrate/sodium carbonate). No excipients are used in the drug product. The vial presentation is designed for single dose use and will be reconstituted with sterile water for injection, 0.9% sodium chloride, 5% dextrose, 2.5% dextrose/0.45% sodium chloride (combined diluent) and Lactated Ringer's solution. The reconstituted vial is then further diluted with a suitable infusion fluid prior to administration by intravenous infusion.

The drug product is manufactured via a (b) (4) fills the vials with ceftazidime carbonate blend and avibactam sodium. (b) (4) The CQAs at the main process stages include (b) (4) Proper in-process controls are proposed to achieve the drug product quality.

The drug product specification includes tests for ID, degradation products, content uniformity (for both drug substances), as well as description on dry powder and reconstitution, reconstitution time, pH, (b) (4), particulate matter, sterility and bacteria indotoxins. The identified degradation products include (b) (4) (b) (4) from dug substance avibactam sodium with acceptance criteria at NMT (b) (4)% and (b) (4) from drug substance ceftazidime at NMT (b) (4)%. Qualification of (b) (4) at NMT (b) (4)% in the drug product has been confirmed by Pharmtox reviewer Dr. A. Balboni

18 month stability data at 25°C/60% RH and 6 months at 40°C/75% RH are provided for 3 primary drug product batches. The stability results from all time points meet specification and no significant changes have been observed. The stability data supports 24 months expiration as proposed. Therefore, the drug product is granted a 24 months expiration dating period when stored at USP controlled room temperature condition and protected from light.

The applicant conducted in-use stability and compatibility studies for the reconstituted drug product including evaluation of the drug product with common infusion diluents, intravenous (IV) bags and infusion lines. The tests were conducted using new released and aged drug products. These in-use stability results support a shelf life of 12 hours at room temperature after 24 hours under refrigerate for the reconstituted drug product as described in the drug product labeling.

The methods were found acceptable by this reviewer. Method validation for assay and impurities in the drug substance avibactam sodium and drug product has been consulted to the Division of Pharmaceutical Analysis (DPA) and is pending evaluation. Any DPA comments can be conveyed after NDA action.

Inspection of the manufacturers/facilities has been requested through EES and is pending recommendation from the OC.

The dose strength and established name to be present in the drug product labeling should be revised as required in the Deficiency at the end of this review on page 134. The revision will be communicated to the applicant during the labeling review.

Risk Assessment of the Drug Product

Product attribute/CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	Lifecycle Considerations/Comments
Assay for Avibactam and Ceftazidime	Quality of the incoming API; analytical method;	L	Incoming DSs and COAs are controlled by adequate assay method.	Acceptable	
Uniformity of dosage	Filling process	L	Filling process is well controlled	Acceptable	

unit			with in process weight tests		
Impurities/ degradation products including extractables / leachables	Quality of the incoming API; (b) (4)	M	Potential impurities are understood though risk assessment and controlled as shown by batch data. Analytical methods are adequate pending method validation by (b) (4) (b) (4)	Acceptable (pending method validation by (b) (4)	When Avibactam supplier changes, evaluate manufacturing, process as some impurities are controlled by the process and not listed in the specification. Evaluate DP impurity profiles for the supplier changes
Particulate matter	Sterile manufacturing process and packaging	M	USP<788> is met on DP stability and 'in-use" storage. Pending satisfactory validation of the sterilization process.	Acceptable (pending Product Quality Micro review)	Manufacturing process control
Sterility	Sterility of the API, (b) (4) filling process, sterilization of container closures	H	Pending satisfactory validation of the sterilization process, see Product Quality Micro review	pending Product Quality Micro review	

B. Description of How the Drug Product is Intended to be Used

- Complicated intra-abdominal infections (cIAI)
- Complicated urinary tract infections (cUTI), including acute pyelonephritis (AP)
- Infections with Limited Treatment Options Infections with Limited Treatment Options

C. Basis for Not-Approval Recommendation

1. The overall "Acceptable" recommendation has ***not*** been issued from the Office of Compliance.
2. The microbiology review is pending

III. Administrative

A. Reviewer's Signature

Zhengfang Ge, Ph.D.
Reviewer/ONDQA

Rapti Madurawe, Ph.D.
Branch Chief/ONDQA

B. Endorsement Block

Dorota Matecka, Ph.D.
CMC Lead/ONDQA

C. CC Block

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

/s/

ZHENGFANG GE

01/22/2015

This version of the review is to correct mistakes for the NDA #. The actual content of the review is the same as the one entered previously.

NDA 206494

Cazavi
(ceftazidime & avibactam) Injection
2000/500 mg

Cerexa, Inc.

Zhengfang Ge, Ph.D.

Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

For

Division of Anti-Infection Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 206494

2. REVIEW #: 1

3. REVIEW DATE: Nov 24, 2014

4. REVIEWER: Zhengfang Ge, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	25-June-2014
Amendment	9-July-2014
Amendment	2-Oct-2014
Amendment	9-Oct-2014

7. NAME & ADDRESS OF APPLICANT:

Name: Cerexa, Inc. (subsidiary of Forest Lab)

Address: 2100 Frank St, Ste 900, Oakland, CA 94612

Representative: Kristina Haeckl

Telephone: 510-285-9200

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cazavi
b) Non-Proprietary Name (USAN): avibactam sodium and ceftazidime
c) Code Name/# (ONDQA only): NXL104 for avibactam sodium
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: ceftazidime is a cephalosporin-class antibacterial, and avibactam is a β-lactamase inhibitor

11. DOSAGE FORM: IV injection

12. STRENGTH/POTENCY: ceftazidime 2000 mg, avibactam 500 mg

13. ROUTE OF ADMINISTRATION: IV injection

14. Rx/OTC DISPENSED: _X_Rx ___OTC

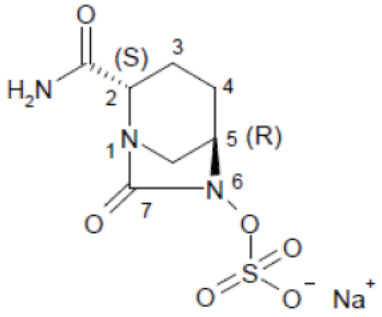
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Avibactam Sodium:
Chemical Name (IUPAC): Sodium;[(2S,5R)-2-carbamoyl-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl] sulfate
CAS Name: Sulfuric acid, mono[(1R,2S,5R)-2-(aminocarbonyl)-7-oxo-1,6-diazabicyclo[3.2.1]oct-6-yl] ester, sodium salt (1:1)

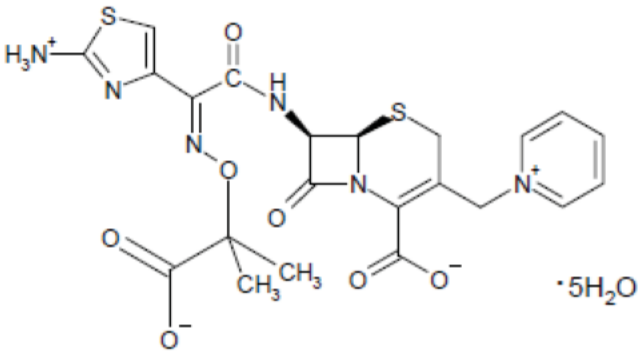


Molecular Formula: $C_7H_{10}N_3O_6SNa$
Molecular Weight: 287.23

Ceftazidime:

CAS Name: Pyridinium, 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-, inner salt, hydrate (1:5)

IUPAC Name: (6R,7R)-7-[[(2E)-2-(2-amino-1,3-thiazol-4-yl)-2-(1-hydroxy-2-methyl-1-oxopropan-2-yl)oxyiminoacetyl]amino]-8-oxo-3-(pyridin-1-ium-1-ylmethyl)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate pentahydrate



Molecular Formula: $C_{22}H_{32}N_6O_{12}S_2$
Molecular Weight: 636.6

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Drug	1	Adequate	Sep 15, 2014	

Chemistry Review Data Sheet

[redacted]	III	[redacted]	3	Adequate	4/42007	Reviewed by Dr. S. Read.
	III		3	Adequate	*19-Jan-2011*	*Review by Dr. L. Moussa*
	III		1	Adequate	Sep 16, 2014	

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND 101307		ceftazidime/avibactam [CAZ-AVI]
IND [redacted]		[redacted]

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending		
Pharm/Tox	Acceptable	11/13/2014	Dr. A. Balboni
Biopharm	Acceptable	8/28/2014	Dr. H. Mahayni
LNC	N/A		
Methods Validation	pending		
DMEPA	pending		
EA	N/A		
Microbiology	pending		

The Chemistry Review for NDA 205628

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product *but is pending recommendation from microbiology reviewer Dr. R. Mello*.

However, the Office of Compliance has ***not*** issued an overall "Acceptable" recommendation.

Labeling deficiency listed at the end of this review on page 134 regarding the dose strength need to be resolved during the labeling review.

Therefore, from the ONDQA perspective, this NDA is ***not*** recommended for "***Approval***" in its present form until all pending issues are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Avibactam Sodium

Avibactam sodium is an NME with two chiral centers. (b) (4) (2S, 5R) is produced as a sterile drug substance by (b) (4) Also, stability studies have shown that (b) (4) does not convert to any other solid form under the proposed storage conditions. Avibactam sodium of (b) (4) is freely soluble in water, therefore a specification for the particle size is not proposed. The drug substance structural characterization is confirmed using element analysis, (b) (4).

Avibactam sodium is (b) (4) Control strategy for the critical quality attributes and the impact of the process parameters have been

identified and developed following ICHQ11 and risk based approach. In-process parameters and controls for each intermediates have been properly established. Assessment of potential impurities and their potential genotoxicity through the manufacturing process and storage is provided in the submission. The potential genotoxic impurities (b) (4) are controlled through in process control and estimated well below the threshold of toxicology concern (TTC) level in the avibactam sodium batches based on the assessment. Specified impurity (b) (4) is qualified at NMT (b) (4)% as proposed in the drug substance specification and NMT (b) (4)% in the drug product specification. The controls and the qualification of the impurities are acceptable, and are also confirmed by the pharmtox reviewer, Dr. A. Balboni.

Stability data including 18 months stored at 25°C/60%RH and 6 months stored at 40°C/75%RH are provided for three primary avibactam sodium batches. These batches were manufactured at production scale at the proposed commercial manufacturing site ((b) (4)). The stability data supports the (b) (4) months retest period at (b) (4), as proposed.

Drug Substance: Ceftazidime

Ceftazidime is a semisynthetic, cephalosporin antibiotic for parenteral administration. It is manufactured by (b) (4) as a ceftazidime pentahydrate/sodium carbonate blend. It has been approved in US with registered trade names Fortaz® (NDA 50578) and Zinacef® (NDA 50558). DMF (b) (4) is cross referenced for the CMC information. The DMF was reviewed previously and concluded ***Adequate*** by Dr. A. Banerjee dated 28-June-2011 for NDA 50578 and NDA 50634. Amendments received since Dr. Banerjee's review has been reviewed for this NDA. The DMF has been found adequate to support this NDA.

Drug Products

The proposed drug product is a sterile, (b) (4) 20 mL, clear, Type I glass vial containing white to yellow powder of 500 mg avibactam (b) (4) mg avibactam sodium) and 2000 mg ceftazidime (2635 (b) (4) mg ceftazidime pentahydrate/sodium carbonate). No excipients are used in the drug product. The vial presentation is designed for single dose use and will be reconstituted with sterile water for injection, 0.9% sodium chloride, 5% dextrose, 2.5% dextrose/0.45% sodium chloride (combined diluent) and Lactated Ringer's solution. The reconstituted vial is then further diluted with a suitable infusion fluid prior to administration by intravenous infusion.

The drug product is manufactured (b) (4) fills the vials with ceftazidime carbonate blend and avibactam sodium. (b) (4) The CQAs at the main process stages include (b) (4) Proper in-process controls are proposed to achieve the drug product quality.

The drug product specification includes tests for ID, degradation products, content uniformity (for both drug substances), as well as description on dry powder and reconstitution, reconstitution time, pH, (b) (4), particulate matter, sterility and bacteria indotoxins. The identified degradation products include (b) (4) from dug substance avibactam sodium with acceptance criteria at NMT (b) (4)% and (b) (4) from drug substance ceftazidime at NMT (b) (4)%. Qualification of avibactam decarbonyl at NMT (b) (4)% in the drug product has been confirmed by Pharmtox reviewer Dr. A. Balboni

18 month stability data at 25°C/60% RH and 6 months at 40°C/75% RH are provided for 3 primary drug product batches. The stability results from all time points meet specification and no significant changes have been observed. The stability data supports 24 months expiration as proposed. Therefore, the drug product is granted a 24 months expiration dating period when stored at USP controlled room temperature condition and protected from light.

The applicant conducted in-use stability and compatibility studies for the reconstituted drug product including evaluation of the drug product with common infusion diluents, intravenous (IV) bags and infusion lines. The tests were conducted using new released and aged drug products. These in-use stability results support a shelf life of 12 hours at room temperature after 24 hours under refrigerate for the reconstituted drug product as described in the drug product labeling.

The methods were found acceptable by this reviewer. Method validation for assay and impurities in the drug substance avibactam sodium and drug product has been consulted to the Division of Pharmaceutical Analysis (DPA) and is pending evaluation. Any DPA comments can be conveyed after NDA action.

Inspection of the manufacturers/facilities has been requested through EES and is pending recommendation from the OC.

The dose strength and established name to be present in the drug product labeling should be revised as required in the Deficiency at the end of this review on page 134. The revision will be communicated to the applicant during the labeling review.

Risk Assessment of the Drug Product

Product attribute/CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation Approach	Risk Evaluation	Lifecycle Considerations/Comments
Assay for Avibactam and Ceftazidime	Quality of the incoming API; analytical method;	L	Incoming DSs and COAs are controlled by adequate assay method.	Acceptable	
Uniformity of dosage	Filling process	L	Filling process is well controlled	Acceptable	

unit			with in process weight tests		
Impurities/ degradation products including extractables / leachables	Quality of the incoming API; (b) (4)	M	Potential impurities are understood though risk assessment and controlled as shown by batch data. Analytical methods are adequate pending method validation by (b) (4)	Acceptable (pending method validation by (b) (4)	When Avibactam supplier changes, evaluate manufacturing, process as some impurities are controlled by the process and not listed in the specification. Evaluate DP impurity profiles for the supplier changes
Particulate matter	Sterile manufacturing process and packaging	M	USP<788> is met on DP stability and 'in-use" storage. Pending satisfactory validation of the sterilization process.	Acceptable (pending Product Quality Micro review)	Manufacturing process control
Sterility	Sterility of the API, (b) (4) filling process, sterilization of container closures	H	Pending satisfactory validation of the sterilization process, see Product Quality Micro review	pending Product Quality Micro review	

B. Description of How the Drug Product is Intended to be Used

- Complicated intra-abdominal infections (cIAI)
- Complicated urinary tract infections (cUTI), including acute pyelonephritis (AP)
- Infections with Limited Treatment Options Infections with Limited Treatment Options

C. Basis for Not-Approval Recommendation

1. The overall "Acceptable" recommendation has ***not*** been issued from the Office of Compliance.
2. The microbiology review is pending

III. Administrative

A. Reviewer's Signature

Zhengfang Ge, Ph.D.
Reviewer/ONDQA

Zhengfang Ge -A

Digitally signed by Zhengfang Ge -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Zhengfang Ge -A, 0.9.2342.19200300.100.1.1=1300225581
Date: 2014.11.24 11:14:13 -05'00'

Rapti Madurawe, Ph.D.
Branch Chief/ONDQA

Rapti D. Madurawe -A

Digitally signed by Rapti D. Madurawe -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300220251, cn=Rapti D. Madurawe -A
Date: 2014.11.24 12:43:58 -05'00'

B. Endorsement Block

Dorota Matecka, Ph.D.
CMC Lead/ONDQA

C. CC Block

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

/s/

ZHENGFANG GE
11/24/2014