CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200327

CHEMISTRY REVIEW(S)

NDA 200-327

Teflaro (Ceftaroline fosamil) for Injection
Review #2

Cerexa, Inc.

Andrew Yu
HFD-520

APPEARS THIS WAY ON ORIGINAL

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA 200-327

2. REVIEW#: 2

3. REVIEW DATE: 10/2/10

4. REVIEWER: Andrew Yu, PhD

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
IND 71371	October 02, 2009

6. Submission being review: Original

Submission(s) Reviewed	Document Date
200-327 Original NDA	12 /30 /09
Amendment (response to IR)	4/14/10
Amendment (response to IR2)	5/14/10
Amendment (Stability update)	6/23/10
Amendment (New carton label)	7/14/10
Amendment (Response to IR3)	8/2/10

7. NAME & ADDRESS OF APPLICANT:

Name:	Cerexa, Inc.
Address:	2100 Franklin Street, Suite 900 Oakland, CA 94612
Representative:	Bruce Lu, RPh RAC, Senior Director Regulatory Affairs
Telephone:	510-285-9200

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Teflaro
b) Non-Proprietary Name (USAN): Ceftaroline fosamil for injection
c) Code Name/# (ONDC only): FIJ
d) Chem. Type/Submission Priority (ONDC only): New molecular entity

- Chem. Type: 1

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b(1)

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Powder for injection

12. STRENGTH/POTENCY: 400 mg and 600 mg of Ceftaroline fosamil

13. ROUTE OF ADMINISTRATION: Intravenous

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:

A) CAS : 229016-73-3

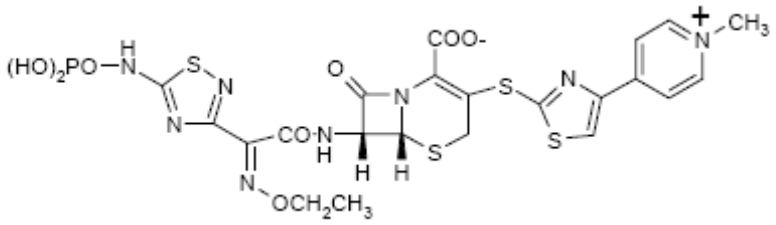
USAN: Ceftaroline Fosamil

(6R,7R)-7-{(2Z)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido}-3-{[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-yl]sulfanyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

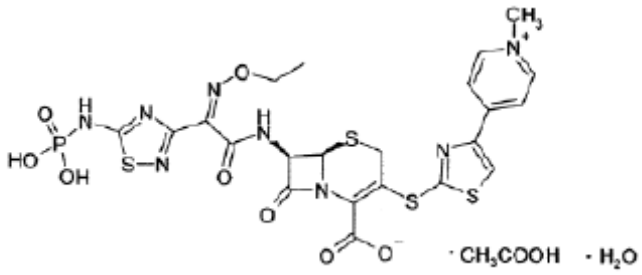
Molecular weight 684.68

Formula $C_{26}H_{21}N_8O_8PS_4$

Structural Formula:



B) Ceftaroline Fosamil monoacetate monohydrate
Ceftaroline Fosamil is not stable in the anhydrous form and is available as:
(6R,7R)-7-{(2Z)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido}-3-{[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-yl]sulfanyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate monoacetate, monohydrate



Molecular Formula: $C_{22}H_{21}N_8O_8PS_4 \bullet CH_3COOH \bullet H_2O$
Molecular Weight: 762.75
CAS: 866021-48-9

CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

The Chemistry Review for NDA 200-327

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective, this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made.

In review #1, product sterility assurance was pending and minor CMC recommendation for container/carton labels were made to the team and DMEPA. Product sterility assurance is now completed with an acceptable recommendation on 10/2/10 by Product Quality Microbiology. The vial/carton labels review is completed in this review. From the CMC perspective, "Approval" is recommended for this NDA.

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

NA

II. Summary of Chemistry Assessments

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

Teflaro for infusion is a new cephalosporin antibiotic containing sterile Ceftaroline fosamil powder in a vial. Ceftaroline fosamil is a prodrug synthesized from the active moiety in order to increase the water solubility. The drug substance is available as acetate, monohydrate which is a stable solvate. (b) (4) Throughout this review, "ceftaroline fosamil" will generally be used to refer to the drug substance, with clarification where this is important (e.g., labeling).

Ceftaroline fosamil is manufactured by ACS Dobfar under DMF 23167. Information requests to the DMF holder concerning impurity level, specifications and other quality issues have been adequately resolved and the DMF is acceptable. Ceftaroline fosamil has (b related impurities (b) (4) which are chemically characterized and controlled by specifications in the DMF and NDA. Three batches of sterile Ceftaroline fosamil were submitted with adequate stability data to support the shelf life proposed of 24 months stored at refrigerated condition. The drug substance is (b) (4) but is stable stored in the recommended container.

The drug product (Teflaro) consists of Ceftaroline fosamil formulated with (b) (4) arginine. Teflaro is supplied in single-use, clear glass vials containing either 400 mg or 600 mg of sterile Ceftaroline fosamil (calculated on an (b) (4) and anhydrous basis). Teflaro (b) (4) must be stored refrigerated. Ceftaroline fosamil is manufactured by ACS dobfar and (b) (4) and packaged by Facta Farmaceutica in Italy. (b) (4) arginine is supplied by (b) (4) under DMF (b) (4) The DMF is adequate for sterility and quality. The DMFs for the container components (b) (4) are also adequate. Two manufacturing issues were identified for Teflaro and were adequately resolved: 1) (b) (4) The applicant provided data in the IR response indicating that adequate protective measures were taken with no stability loss. 2) (b) (4)

[redacted] However, additional batch data submitted indicated that the product is still within acceptance limits (90-110%). The applicant will study another 3 batches of each strength to assure [redacted] and report the [redacted] result to FDA in annual reports. This issue is adequately resolved. Teflaro 600 mg or 400 mg are adequately controlled with product specifications for appearance, potency, uniformity, individual and total impurities, moisture, pH, endotoxin, sterility, particulate matter and other USP tests. The 24-month shelf life of the product is supported by three batches of stability for 24 months at long term storage condition for the 600 mg vials and 12 months for the lower strength. The shelf life is acceptable for 24 months for both strengths as proposed. Compatibility data with infusion media in normal saline, D_5W, [redacted] and lactated Ringer's solution are included in the NDA. The drug is not compatible with [redacted] but is compatible with D_5W when prepared for infusion as described in the package insert. Compatibility evaluation includes appearance, particulate matter, turbidity and stability. During development, arginine [redacted] with the drug in infusion solutions. [redacted] is controlled within qualified level of NMT [redacted] The qualification study was consulted to Pharm/Tox and acceptable. The [redacted] remains at less than [redacted] in all reconstituted infusion studies presented, well within the qualification limit.

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

Teflaro for injection is a powder containing either 400 or 600 mg of sterile ceftaroline fosamil. The recommended dose is 400 mg or 600 mg (1 vial) every 12 hours as indicated in the package insert. The drug product should be constituted by addition of 20 mL of Water for Injection, USP. The entire volume of constituted solution must be further diluted in ≥ 250 mL before infusion. Appropriate infusion solutions include: 0.9% Sodium Chloride Injection, USP (normal saline); 5% Dextrose Injection, USP; 2.5% Dextrose and 0.45% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP. The resulting solution should be administered over approximately 1 hour. Constitution time is less than 2 minutes. Mix gently to constitute and check to see that the contents have dissolved completely. Parenteral drug products should be inspected visually for particulate matter prior to administration. Studies have shown that the constituted solution in the infusion bag should be used within 6 hours when stored at room temperature or within 24 hours when stored under refrigeration at 2 to 8º C (36 to 46º F). The color of Teflaro infusion solutions range from clear, light to dark yellow depending on the concentration and storage conditions; however, when stored as recommended, the product potency is not affected. The compatibility of Teflaro with other drugs has not been fully established, however a list of chemically incompatible drugs based on preliminary studies are included in the NDA (see Appendix 4 of this review). The package insert states that the product should not be mixed with or physically added to solutions containing other drugs.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submissions and the Drug Master File provide adequate information on the chemistry and manufacturing controls for the production of this product for injection. All CMC deficiencies or comments communicated to the sponsor have been adequately addressed. The remaining [redacted] manufacturing consuls are pending in the Product Quality Microbiology review. All manufacturing sites have been found acceptable by the CDER Office of Compliance. Teflaro for injection is supplied in single-use, clear glass vials containing: 600 mg - individual vial (NDC 0456-0600-01) and carton containing 10 vials (NDC 0456-0600-10), 400 mg - individual vial (NDC 0456-0400-01) and carton containing 10 vials (NDC 0456-0400-10).Teflaro vials should be stored refrigerated at 2 to 8° C (36 to 46° F), and the shelf life of the drug product is 24 months stored under those conditions.

viewer's Signature

DARRTS

B. Endorsement Block

DARRTS

C. CC Block

DARRTS

9 Pages has been withheld as b4 (CCI/TS) immediately following this page.

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

/s/

ANDREW B YU
10/06/2010

STEPHEN P MILLER
10/06/2010
I concur - this NDA is recommended for approval from the CMC perspective

NDA 200-327

Teflaro (Ceftaroline fosamil) for Injection

Cerexa, Inc.

Andrew Yu
HFD-520

Table of Contents

Chemistry Review Data Sheet

1. NDA 200-327

2. REVIEW#: 1

3. REVIEW DATE: 8/2/10

4. REVIEWER: Andrew Yu, PhD

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
IND 71371	October 02, 2009

6. Submission being review: Original

Submission(s) Reviewed	Document Date
200-327 Original NDA	12 /30 /09
Amendment (response to IR)	4/14/10
Amendment (response to IR2)	5/14/10
Amendment (Stability update)	6/23/10
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Telephone:	510-285-9200

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a) Proprietary Name: Teflaro
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c) Code Name/# (ONDC only): FIJ
d) Chem. Type/Submission Priority (ONDC only): New molecular entity

- Chem. Type: 1

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505b(1)

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: Powder for injection

12. STRENGTH/POTENCY: 400 mg and 600 mg of Ceftaroline fosamil

13. ROUTE OF ADMINISTRATION: Intravenous

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:

A) CAS : 229016-73-3

USAN: Ceftaroline Fosamil

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Molecular weight 684.68

Formula $C_{26}H_{21}N_8O_8PS_4$

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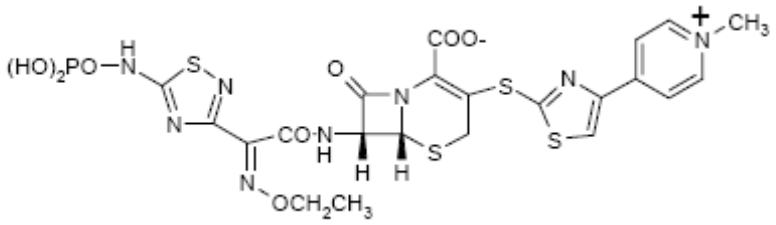
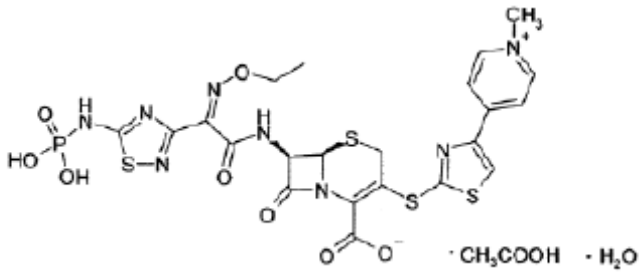


B) Ceftaroline Fosamil monoacetate monohydrate
Ceftaroline Fosamil [redacted] is available as:
(6R,7R)-7-{(2Z)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido}-3-{[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-yl]sulfanyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, acetic acid solvate, monohydrate



Molecular Formula: $C_{22}H_{21}N_8O_8PS_4 \cdot CH_3COOH \cdot H_2O$
Molecular Weight: 762.75
CAS: 866021-48-9
Comment: The drug substance as manufactured is the acetate hydrate, the structure is provided in B) above. The molecular formula and structure originally submitted did not reflect the solvate hydrate. Upon request for information, the appropriate structure and molecular weight for the acetate is provided. [redacted] *The title of the USAN monograph for this drug substance is Ceftaroline fosamil according to the current USAN dictionary online (8/30/10). The USAN monograph currently lists as the chemical name the monoacetate monohydrate (Structure B). The Ceftaroline Fosamil USAN monograph may be changed in the future to show instead the chemical name and Structure A .*

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
23167	II	ACS Dobfar	Ceftaroline fosamil	1	Adequate	8/10/10	Adequate
[redacted]	II	[redacted]	Arginine	1	Adequate	8/10/10 Consulted to microbiology for sterility.	[redacted]

(b) (4)	III	(b) (4)		4	CMC in NDA is adequate	Sterility consulted to microbiology	March 21, 2007 S. Read Review #3 acceptable
	V		(b) (4)	4		Consulted to microbiology	Facility DMF for microbiology
	III	(b) (4)	Glass vials	4	Acceptable (b) (4) glass)		Type I USP glass appropriate for parenteral use.
	III	(b) (4)	Vial Stopper	3	Sterilization is consulted to Microbiology	Stopper (b) (4) is adequate on previous review. No change made.	(b) (4) reviewed by M. Shih on 2/27/02, Stopper micro reviewed by E. Adeeku dated 7/15/08
	V	(b) (4)		4	Facility GMP operations	Consulted to microbiology	

[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		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			

EES	Acceptable	8/4/10	April Inyard
Methods Validation	Lab MV not needed	8/4/10	Andrew Yu
OPDRA (DMETS)	Pending (Teflaro)		DMETS staff
EA	Categorical exclusion claimed-Adequate	8/4/10	Andrew Yu
Microbiology	Pending	2/5/10	V. Pawar/Jessica Cole
Pharm/Tox	Acceptable	7/19/10	A. Ellis

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.
__x__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 200-327

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective, this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. Minor CMC recommendation for the vial and carton labels have been given to the review team and DMEPA for consideration. An "Acceptable" site recommendation from the Office of Compliance has been made.

From the CMC perspective approval cannot be recommended until the sterility assurance has been determined to be acceptable by the Product Quality Microbiology reviewer, and the vial/carton labels are finalized.

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

NA

II. Summary of Chemistry Assessments

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

Teflaro for infusion is a new cephalosporin antibiotic containing sterile Ceftaroline fosamil powder in a vial. Ceftaroline fosamil is a prodrug synthesized from the active moiety in order to increase the water solubility. The drug substance is available as acetate, monohydrate which is a stable solvate. (b) (4) Throughout this review, "ceftaroline fosamil" will generally be used to refer to the drug substance, with clarification where this is important (e.g., labeling).

Ceftaroline fosamil is manufactured by ACS Dobfar under DMF 23167. Information requests to the DMF holder concerning impurity level, specifications and other quality issues have been adequately resolved and the DMF is acceptable. Ceftaroline fosamil has (related impurities (b) (4) which are chemically characterized and controlled by specifications in the DMF and NDA. Three batches of sterile Ceftaroline fosamil were submitted with adequate stability data to support the shelf life proposed of 24 months stored at refrigerated condition. The drug substance is (b) (4) but is stable stored in the recommended container.

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(b) (4) during manufacturing. However, additional batch data submitted indicated that the product is still within acceptance limits (90-110%). The applicant will study another 3 batches of each strength to assure adequate (b) (4) and report the (b) (4) result to FDA in annual reports. This issue is adequately resolved. Teflaro 600 mg or 400 mg are adequately controlled with product specifications for appearance, potency, uniformity, individual and total impurities, moisture, pH, endotoxin, sterility, particulate matter and other USP tests. The 24-month shelf life of the product is supported by three batches of stability for 24 months at long term storage condition for the 600 mg vials and 12 months for the lower strength. The shelf life is acceptable for 24 months for both strengths as proposed. Compatibility data with infusion media in normal saline, D_5W, (b) (4) and lactated Ringer's solution are included in the NDA. The drug is not compatible with (b) (4) but is compatible with D_5W when prepared for infusion as described in the package insert. Compatibility evaluation includes appearance, particulate matter, turbidity and stability. During development, arginine (b) (4) with the drug in infusion solutions. (b) (4) is controlled within qualified level of NMT (b) (4) The qualification study was consulted to Pharm/Tox and acceptable. The (b) (4) remains at less than (b) (4) in all reconstituted infusion studies presented, well within the qualification limit.

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

Teflaro for injection is a powder containing either 400 or 600 mg of sterile ceftaroline fosamil. The recommended dose is 400 mg or 600 mg (1 vial) every 12 hours as indicated in the package insert. The drug product should be constituted by addition of 20 mL of Water for Injection, USP. The entire volume of constituted solution must be further diluted in ≥ 250 mL before infusion. Appropriate infusion solutions include: 0.9% Sodium Chloride Injection, USP (normal saline); 5% Dextrose Injection, USP; 2.5% Dextrose and 0.45% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP. The resulting solution should be administered over approximately 1 hour. Constitution time is less than 2 minutes. Mix gently to constitute and check to see that the contents have dissolved completely. Parenteral drug products should be inspected visually for particulate matter prior to administration. Studies have shown that the constituted solution in the infusion bag should be used within 6 hours when stored at room temperature or within 24 hours when stored under refrigeration at 2 to 8º C (36 to 46º F). The color of Teflaro infusion solutions range from clear, light to dark yellow depending on the concentration and storage conditions; however, when stored as recommended, the product potency is not affected. The compatibility of Teflaro with other drugs has not been fully established, however a list of chemically incompatible drugs based on preliminary studies are included in the NDA (see Appendix 4 of this review). The package insert states that the product should not be mixed with or physically added to solutions containing other drugs.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submissions and the Drug Master File provide adequate information on the chemistry and manufacturing controls for the production of this product for injection. All CMC deficiencies or comments communicated to the sponsor have been adequately addressed. The remaining sterility and aseptic manufacturing consuls are pending in the Product Quality Microbiology review. All manufacturing sites have been found acceptable by the CDER Office of Compliance. Teflaro for injection is supplied in single-use, clear glass vials containing: 600 mg - individual vial (NDC 0456-0600-01) and carton containing 10 vials (NDC 0456-0600-10), 400 mg - individual vial (NDC 0456-0400-01) and carton containing 10 vials (NDC 0456-0400-10).Teflaro vials should be stored refrigerated at 2 to 8° C (36 to 46° F), and the shelf life of the drug product is 24 months stored under those conditions.

III. Administrative

A. Reviewer's Signature

DARRTS

B. Endorsement Block

DARRTS

C. CC Block

DARRTS

102 Pages has been withheld as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200327	ORIG-1	CEREXA INC	ceftaroline fosamil for injection

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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/

ANDREW B YU
09/01/2010
Please sign

STEPHEN P MILLER
09/01/2010
I concur - we cannot recommend approval from the CMC perspective until the sterility assurance review has been concluded, and the vial/carton labeling has been finalized.

Initial Quality Assessment
Branch IV
Pre-Marketing Assessment Division II

OND Division:	Division of Anti-Infective and Ophthalmology Products
NDA:	200,327
Applicant:	Cerexa Inc., a wholly-owned subsidiary of Forest Laboratories, Inc.
Stamp Date:	30-Dec-2009
PDUFA Date:	30-Oct-2010 (for standard review). Priority review requested.
Trademark:	To be decided. (b) (4).
Established Name:	Ceftaroline fosamil
Dosage Form:	For injection
Route of Administration:	Intravenous
Indication:	Complicated skin and skin structure infections and community acquired bacterial pneumonia
PAL:	Rapti D. Madurawe
	YES NO
ONDQA Fileability:	☒ ☐
Comments for 74-Day Letter:	☒ ☐

Summary and Critical Issues:

A: Summary, Review and Discussion

(1) Introduction
NDA 200,327 provides for ceftaroline fosamil for injection, for the treatment of complicated skin and skin structure infections and community acquired bacterial pneumonia. The applicant has proposed the proprietary names (b) (4).

Ceftaroline fosamil drug substance (DS) is manufactured as an acetic acid solvate monohydrate. DS is a sterile, semi-synthetic new molecular entity (NME) of the cephalosporin class of beta-lactam antibiotics. The DS is a prodrug. Its active metabolite, ceftaroline, is said to display a broad antibacterial activity against aerobic and anaerobic gram-positive and gram-negative bacteria.

The drug product (DP) is a sterile powder for injection containing a blend of ceftaroline fosamil and L-arginine. DP strengths per vial are 400 mg and 600 mg of ceftaroline fosamil (anhydrous, (b) (4)). DP is supplied in 20-cc, clear, Type I glass vials closed with (b) (4) rubber injection stoppers and aluminum/lacquered flip cap overseals.

This NDA was developed under IND 71,371 using the DS code names PPI-0903 and TAK-599. Section "1.6 Meetings" in Module 1 contains all IND meeting minutes. The primary reviewer should become familiar with the CMC issues discussed, particularly those related to starting materials.

Seven DMF's are referenced in the NDA for DS and excipient manufacture (Type II), DP sterile processing (Type V), and container closure systems (Type III). Four of these require CMC review. The two Type V DMF's require product quality microbiology review. The DMF for glass does not require review. Module 1 contains Letters of Authorization for all DMFs.

(2) Drug Substance

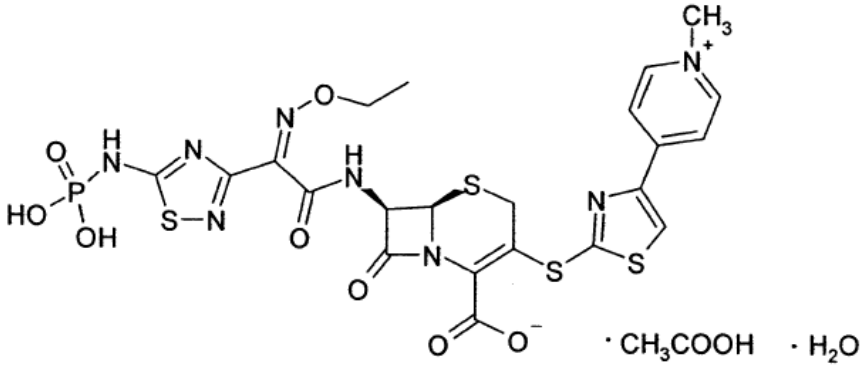

Figure 1: Ceftaroline fosamil acetic acid solvate monohydrate drug substance

Drug substance (DS), ceftaroline fosamil acetic acid solvate monohydrate, is a sterile semi-synthetic powder packaged in (b) (4). The DS is manufactured at ACS Dobfar S.p.A. Adetta Plant, Viale Addetta, 4/12, 20067 Tribiano, Milano, Italy. (b) (4)

The DS CMC information is referenced to ACS Dobfar's Type II DMF #23167. A Letter of Authorization has been provided. This is a new DMF and requires complete CMC review. It should be reviewed early to resolve potential approvability issues, if identified.

The Type III DMF (b) (4) is referenced for the (b) (4). The DMF was found adequate by Quality Microbiology in July 2009. The DMF would need CMC to verify if the deficiencies identified previously have been adequately resolved from a CMC perspective.

(b) (4)

Ceftaroline fosamil is an NME. It is a single stereoisomer with 6R, 7R configuration. DS structure is characterized by elemental analysis, (b) (4), FTIR, NMR, mass spectroscopy and optical rotation. Its solid state is characterized by X-ray powder diffraction and thermal analysis. Important DS properties for the (b) (4) DP manufacture and/or DP performance are (b) (4) Each of these properties is discussed below. The acetic acid solvate monohydrate solvate was selected as it is a crystalline solid with good stability. (b) (4) Cerexa has observed only one polymorph of the acetic acid solvate monohydrate. (b) (4) The drug product is administered as an intravenous solution. DS solubility in water and in 0.1 M Phosphate Buffer pH 7.0 is 4.68 mg/ml (at 25 °C) and 125.8 mg/ml, respectively. The solubility profile shows solubility is above 100 mg/ml approximately between pH 4 and 8. DS is somewhat hygroscopic with a 2.8% water uptake at 25 °C/60% RH. Although this does not appear to be significant, the moisture uptake during DS stability testing should be evaluated as the DS packaging does not appear to include a desiccant.

(b) (4) Their structures are given in the NDA. (b) (4) (b) (4) The proposed (b) (4) level for (b) (4) out of a total impurity specification of (b) (4) does not appear to be unreasonable at first glance, but requires further review for suitability. In addition, the reviewer should also confirm that adequate solubility/particulate matter criteria are met when DP (particularly DP near the end of its shelf-life) is reconstituted and stored as an infusion solution over the infusion solution storage period. Other potentially important issues for evaluation are: (i) Impurity structural alerts. (b) (4)

Drug substance specifications are given in Table 1. Specification tests appear to be reasonable, but the DMF needs to be reviewed for further evaluation.

NDA has batch analysis data for four DS registration batches manufactured in June 2007 These four batches were used to manufacture the DP registration batches. It is unclear why these batches have slightly different scales of manufacture (b) (4) and how they compare to the commercial-scale. All release data are within specification. Impurity profile at batch release shows levels of (b) (4) for (b) (4) and (b) (4) for (b) (4)

Table 1: Proposed drug substance specifications

Test	*Acceptance Criteria*	*Method*
Appearance	Pale yellowish-white to light yellow powder	Visual
Identification A (HPLC)	Positive	By HPLC
Identification B (IR)	Positive	USP < 197K >
Clarity of Solution	≤ Suspension 1	EP 2.2.1
pH	2.0 – 3.0	USP < 791 >
(b) (4)		
Specific Optical Rotation	(b) (4)	Polarimetry
Sulfate Ion		BY IC
Acetic Acid		By IC
Sodium Ion		BY ICP
Heavy Metals		USP < 231 >
Arsenic		BY ICP
Foreign Insoluble Matter		Microscopy
Particulate Matter (b) (4) (b) (4)		USP < 788 >
Particle Size Distribution (b) (4)		USP < 429 >
Assay (anhydrous (b) (4)	(b) (4)	By HPLC
Related Substances (b) (4) (b) (4) (b) (4)		By HPLC
Residual Solvents (b) (4)		By GC
Sterility	Sterile	USP < 71 >
Bacterial Endotoxin	(b) (4)	USP < 85 >

Tests in **bold** are for stability evaluation.

DS stability is not reviewed here as the stability data are in the DMF. An expiration date of 24 months is proposed for DS stored in (b) (4) at 2-8 °C based on 24 months long term (5°C) stability data for the registration batches.

(3) Drug Product

Ceftaroline fosamil for injection, 400 mg/vial and 600 mg/vial are single-dose units of a sterile (b) (4) of ceftaroline fosamil DS and L-arginine. DP is packaged in 20-cc, clear, Type I glass vials. The strength is in terms of anhydrous (b) (4) ceftaroline fosamil.

Bulk DP manufacturing, (b) (4) at ACS Dobfar S.p.A. Adetta plant, 20067 Tribiano, Milano, Italy. Vial filling, testing (release, stability and in-process) and storage of finished DP are at Facta Farmaceutici S.p.A., Nucleo Industriale S. Atto-S. Nicolo a Tordino, 64020 Teramo, Italy. Both sites are ready for inspection. Note that the EES contact (Elizabeth Johnson, OC/DMPQ) was notified on Feb 01, 2010 that both sites should be cephalasporin manufacturing facilities.

The DP composition and bulk DP batch formula are given in Table 2 and 3, respectively. There is no overage. The commercial manufacturing scales for the finished DP are (b) (4) vials using (b) (4) and (b) (4) vials using (b) (4). The selection of the only excipient used, sterile L-arginine, (b) (4) and its compatibility with the DS. L-Arginine is an established excipient and has been used in an approved intravenous parenteral formulation at a maximum daily exposure of (b) (4). Sterile L-arginine manufacture is referenced to (b) (4) Type II DMF (b) (4) titled "Arginine (Sterile Bulk)". This is a new DMF and requires complete CMC review. Critical quality attributes of Arginine to be evaluated during DMF review are (b) (4). Information on the compatibility of DS and arginine is in the NDA.

Table 2: Drug product components and composition

Component	***Quality Standard***	***Function***	***Ceftaroline fosamil: L-arginine Ratio***	***Theoretical Weight***		
				600 mg/vial	*400 mg/vial*	*% w/w*
Ceftaroline fosamil (sterile)	In-house standard[1]	Active		600.0[2]	400.0[2]	(b) (4)
L-arginine (sterile)	In-house standard[3]	(b) (4)	(b) (4)	(b) (4)		
Total Theoretical Weight						100.0

[1] Per specification provided in section 3.2.S.4.1 *Specifications (Ceftaroline fosamil, ACS Dobfar, S.p.A.)*
[2] Equivalent to (b) (4) of ceftaroline fosamil sterile drug substance (acetic acid solvate monohydrate), respectively.
[3] Per specification provided in section 3.2.P.4.1 *Specifications (Ceftaroline fosamil for Injection, 600 mg/vial)*

Table 3: Batch formula for ceftaroline fosamil bulk drug product blend

Ingredient	***Quality Standard***	***% w/w***	***Theoretical Weight***		
			600 mg/vial	*400 mg/vial*	*(kg/batch)*

Ceftaroline fosamil (sterile)	In-house standard[a]	[redacted]	600.0[b]	400.0[b]	[redacted]
L-arginine (sterile)	In-house standard[d]	[redacted]	[redacted]		
[redacted]	EP				
Total theoretical weight		100.0			

a Per specification provided in section 3.2.S.4.1 *Specifications (Ceftaroline fosamil, ACS Dobfar, S.p.A.)*
b Equivalent to [redacted] of ceftaroline fosamil sterile drug substance (acetic acid solvate monohydrate)
c Equivalent to [redacted] of ceftaroline fosamil sterile drug substance (acetic acid solvate monohydrate)
d Per specification provided in section 3.2.P.4.1 *Specifications (Ceftaroline fosamil for Injection, 600 mg/vial)*
e The theoretical amount of L-arginine required to achieve the target pH in solution is [redacted] of ceftaroline fosamil (anhydrous [redacted])
f Mass ratio of [redacted] ceftaroline fosamil sterile (anhydrous [redacted]) : sterile L-arginine

Phase 1 and II studies were performed with ceftaroline fosamil sterile DS packaged in a glass vial, and a separately supplied custom diluent containing 1.9% L-arginine solution with 0.05% sodium sulfite in water for injection.

Bulk DP manufacturing at Dobfar consists of [redacted]

[redacted]

1 Page withheld in full immediately following this page as B4 (CCI/TS)

Table 4: Proposed Drug Product Specification

Test	Acceptance Criteria	Method
Appearance	Pale yellowish-white to light yellow powder	Visual
Identification A (HPLC)	The retention time of the major peak in the sample conforms to the major peak in the standard	By HPLC
Identification B (UV)	The UV spectrum, obtained via photodiode array (PDA) detection of the sample peak in the chromatogram conforms to that of the standard peak	By HPLC
Clarity of Solution	Suspension 1	EP 2.2.1
Constitution Time	NMT (b) (4)	Dissolution Time for one vial in 20mL WFI
pH (30 mg/mL solution)	4.8 . 6.5	USP < 791 >
Percent Label Claim	(b) (4)	By HPLC
Related Substances		By HPLC
(b) (4)		
		By HPLC
Content Uniformity (by Assay)	Complies with current USP Chapter <905> Uniformity of Dosage Units	By HPLC
Container/Closure Integrity	Complies	
Extractable Volume	NLT (b) (4)	
(b) (4)		
Particulate Matter		
NLT (b) (4)	NMT (b) (4)	
NLT (b) (4)	NMT (b) (4)	
Bacterial Endotoxin	Less than (b) (4) EU/mg	
Sterility	Sterile	

Proposed DP specifications are given in Table 4. Total impurity level of (b) (4) is rather high, and increases further to (b) (4) Qualification of all impurities, (b) (4) should be discussed with the Pharmacology Toxicology group.

Cerexa has proposed a shelf life of 24 months for Ceftaroline fosamil for Injection when stored at refrigerated conditions (2-8°C). Stability studies were conducted at 5 °C, 25°C/60% RH, and 40°C/75% RH (6 months data). Long term and accelerated primary

stability data are provided for 1 batch of 400 mg/vial DP (6 months) and 3 batches of 600 mg/vial DP (18 months). Containers were tested in the upright and inverted positions. Both dosages are packaged in the same 20 cc container. Although the headspace is greater for the 400 mg/vial DP, the difference, ~ 2.5%, is minor. A DP photostability study concludes the DP is not photosensitive (DS stress test data is probably in the DMF). No out of specification (OOS) results were observed at the 5 °C and 25°C conditions. Cerexa claims that at 5 and 25 °C, no trends are observed for all tests except for an increase in the level of Open Ring Metabolite and (b) (4) while an OOS result of (b) (4) was obtained for unspecified related substances at the 40°C condition. (b) (4)

Correspondingly, the label claim decreases over stability, but remains within specification. The particulate matter (b) (4) also increases over time, although the level remains low and within specification.

A vial of DP is constituted with 20 ml of sterile water for injection (SWFI), USP. Other diluents tested were not compatible. The constituted solution is transferred to IV bags for administration into patients. Compatible injection solutions are 0.9% sodium chloride 5% dextrose, Lactate Ringer's, 2.5% dextrose and 0.45% sodium chloride. (b) (4)

This appears to be rather unusual. (b) (4) is stated not to be an issue as the product is formulated at a pH of 4.8 – 6.5. However, this could potentially be a problem in infusion solutions around neutral pH. Cerexa should evaluate (b) (4) in each of the infusion solutions used. Several antibiotics of this class have stability problems during diluted infusion solution storage. The stability of the constituted solution and diluted infusion solution needs to be carefully evaluated to determine the appropriate holding time. Hold times proposed are: (b) (4)

B: Critical issues for review

Critical issues listed below are discussed in section A above.

(a) Drug Substance

1. Early review of the ceftaroline fosamil drug substance DMF #23167.
2. Early agreement on the proposed starting materials

(b) Drug Product

1. (b) (4) operations during drug product manufacture

2. (b) (4) operations for bulk (b) (4) and finished drug product (b) (4)
3. Sampling plan/procedures for evaluation of bulk (b) (4) and finished drug product content (b) (4)
4. Stability of constituted and diluted infusion solution
5. Impurity control and qualification

C: Comments for 74-Day Letter

1. Please provide information on drug product stability/impurity profile and any new impurities formed due to the (b) (4) .

Rapti. D. Madurawe
Pharmaceutical Assessment Lead _____ Date

Stephen Miller
Acting Branch Chief _____ Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200327	ORIG-1	CEREXA INC	ceftaroline fosamil for injection

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/s/

RAPTI D MADURAWE
03/01/2010

STEPHEN P MILLER
03/03/2010

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 200-327 **Supplement Number and Type:** **Established/Proper Name: Ceftaroline fosamil**

Applicant: Cerexa Inc. **Letter Date: 30-Dec-09** **Stamp Date: 30-Dec-09**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?		x	Unable to open the drug product stability data sets due to lack of software. IT will correct problem. Meanwhile the company has agreed to provide the data as Excel spreadsheets. Issue resolved.
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?		x	See #6

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**		x	A DMF was not submitted for the starting material (SM) as requested in the preNDA meeting, but additional justification for the proposed SM was provided to the IND prior to NDA submission. This information was will be evaluated for acceptability during NDA review.

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Categorical exclusion requested

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?		x	Section D not applicable as DS is referenced to a DMF
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?			Not applicable
14.	Does the section contain information regarding the characterization of the DS?			Not applicable
15.	Does the section contain controls for the DS?			Not applicable
16.	Has stability data and analysis been provided for the drug substance?			Not applicable
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			Not applicable
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			Not applicable

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?			Pharmaceutical Development section in the NDA contains information on the investigational formulations. Adequacy of the linkage is a review issue.
23.	Have any biowaivers been requested?		x	Not applicable
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?		x	See #3
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		MV provided for DP ID, assay and related substances only.

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	x		Type V DMFs referenced for (b) (4)

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		

DMF #	TYPE (b)	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	V	(b) (4)		Nov 10, 2009	
				May 15, 2009	
	III			May 29, 2009	
	III			Nov 10, 2009	
	II			Nov 10, 2009	
	II			Nov 10, 2009	New DMF submission
	V			Nov 10, 2009	(b) (4)

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		

33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Describe filing issues here or on additional sheets
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?			Please refer to the IQA

Rapti D. Madurawe {See appended electronic signature page}

Name of
Pharmaceutical Assessment Lead or CMC Lead / CMC Reviewer Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Stephen Miller {See appended electronic signature page}

Name of
Branch Chief Date
Division of Pre-Marketing Assessment #
Office of New Drug Quality Assessment

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200327	ORIG-1	CEREXA INC	ceftaroline fosamil for injection

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/s/

RAPTI D MADURAWE
02/18/2010

STEPHEN P MILLER
02/18/2010