

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202091Orig1s000

CHEMISTRY REVIEW(S)

NDA 202091

**Suprax® (cefixime) For Oral
Suspension 500 mg/5mL
Lupin Pharmaceuticals, Inc**

**Lin Qi
ONDQA, Branch V**

For the Division of Anti-Infective Products

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Chemistry Review Data Sheet

1. NDA 202091
2. REVIEW #: 1
3. REVIEW DATE: 1/18/2013
4. REVIEWER: Lin Qi
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original NDA	10/25/10
Amendment	12/10/11
Amendment	2/10/11
Amendment	5/20/11

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission	8/20/2012
Amendment	12/13/2012
Amendments	12/13/2012

7. NAME & ADDRESS OF APPLICANT:

Name: LUPIN PHARMACEUTICALS, INC.

Address: Harborplace Tower,
III South Calvert Street, 21 S1 Floor,
Baltimore, Maryland 21202

Chemistry Review Data Sheet

Representative

Contact person: Pramod Dahibhate
General Manager, Regulatory Affairs

Telephone: 410 576 2000

Fax 410 576 2221

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Suprax® For Oral suspension
- b) Non-Proprietary Name (USAN): Cefixime
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: Type 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: For Oral suspension

12. STRENGTH/POTENCY: 100 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

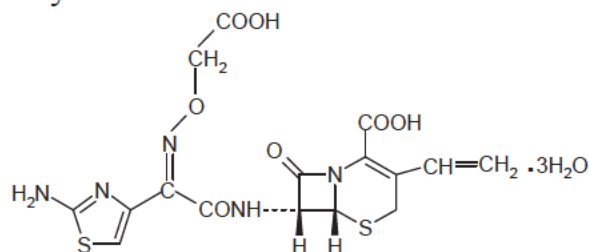
☒ Not a SPOTS product

Chemistry Review Data Sheet

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

USAN: Cefixime USP

(6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid, 7²-(*Z*)-[*O*-(carboxymethyl) oxime] trihydrate.



Molecular weight 507.50
 Molecular Formula $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$
 Chemical Abstract 79350-37-1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE 1	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
15996	II	Lupin Inc.	Cefixime USP	3	Adequate	2/17/2012	Review #12 by Maotang Zhou
(b) (4)	III	(b) (4)		4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

Chemistry Review Data Sheet

			(b) (4)				
(b) (4)	III		(b) (4)	4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	IV			4	Adequate		

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
CMC review	N202091 Original Submission	6/27/2011
Biopharm review	N202091 Original Submission	6/8/2011

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	9/24/2012	R. Safaai-Jazi
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA	EA exclusion waiver found acceptable	2/20/2011	Andrew Yu
Microbiology			

19. ORDER OF REVIEW (OGD Only) N/A

The Chemistry Review for NDA 202-091

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

An “Acceptable” site recommendation from the Office of Compliance has been made. Final labeling is pending team review.

From the CMC perspective, this NDA is recommended for *approval pending team review and acceptance of labeling*.

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

N/A

II. Summary of Chemistry Assessments

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

Drug substance:

The drug substance cefixime USP manufactured by Lupin Pharmaceuticals Inc. is referenced by DMF 15996. The DMF holder is also the NDA applicant. The DMF is current and adequate.

Drug product:

Cefixime for Oral suspension contains 100 mg/mL of drug after reconstitution. The applicant's lower strengths of Cefixime for Oral suspension, 200 mg/5mL and 100mg/5mL, are currently approved as ANDAs. The product is submitted as 505(b)(2) based on the approved RLD. A bioavailability study is submitted with the product in this NDA.

Cefixime for Oral Suspension, 100 mg/mL is off white to cream colored powder, forming an off white to pale yellow suspension with characteristic fruity odor on constitution. It is packed into 3 mL (physician sample), 10 mL, and 20 mL HDPE bottle packs.

Executive Summary Section

The original NDA submission was reviewed by Dr. Andrew Yu. The manufacturing of

(b) (4)

The CMC issues with stability, preservative, dissolution and product quality have been adequately resolved during that review cycle. CMC information requests related to the specifications, fill weights/volumes, and (b) (4) were conveyed to the applicant in the Complete Response letter.

Responses to the aforementioned CMC information requests were provided in the resubmission and evaluated in the current review. A recommendation was sent to the applicant on including the test for Water. The drug product is to be tested for the following: Description, Identification, (HPLC and UV), pH, Water (by KF), Viscosity, Minimum Fill, Fill Weight Variation, Deliverable Volume, Fill Volume variation, Dissolution, Assay, Content of Sodium Benzoate, Related Substances, and Microbial. The revised drug product specification is found acceptable.

Based on the updated stability data, the applicant proposed a shelf life of 12 months for the 3 mL physician sample pack and a shelf life of 24 months for the 10 mL and 20 mL packs.

(b) (4) a combined Package Insert for the subject product and all approved dosage forms and strengths for Suprax is provided, per Division recommendation. Refer to the clinical review for how this strength is intended to be used. The updated labeling is pending team review. CMC labeling comments are included in this review.

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

Cefixime for Oral Suspension, 100 mg/mL is an off white to cream colored powder forming an off-white to pale yellow suspension with characteristic fruity odor on constitution. After reconstituted as directed, each mL of reconstituted suspension contains 100 mg of cefixime as trihydrate. The storage condition is: Prior to reconstitution, store at 20-25°C (68-77°F) See USP controlled room temperature, (b) (4). After reconstitution: The suspension may be kept for 14 days either at room temperature, or under refrigeration, without significant loss of potency. Keep tightly closed. Shake well before using. Discard unused portion after 14 days. Cefixime For Oral administration is intended for the treatment of bacterial infections as described in the package insert. Cefixime For Oral suspension are supplied in HDPE bottles of 10 and 20 mL with (b) (4), NDC 27434-207-02 - 10 mL Bottle and NDC 27434-207-03 - 20 mL Bottle.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

(b) (4) a combined Package
Insert for the subject product and all approved dosage forms and strengths for Suprax is provided, per Division recommendation. Refer to the clinical review for how this strength is intended to be used. The updated labeling is pending team review. CMC labeling comments are included in this review.

This NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made on September 24, 2012. The labeling is pending team review.

Therefore, this NDA is recommended for *approval pending team review and acceptance of labeling*.

III. Administrative**A. Reviewer's Signature**

See Signature in DARRTS.

B. Endorsement Block

ChemistName/Date: Lin Qi/Jan 18, 2013

BranchChiefName/Date: Rapti Madurawe/Jan 18, 2013

ProjectManagerName/Date: Althea Cuff/Jan 18, 2013

C. CC Block

See Signature in DARRTS.

36 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LIN QI
01/18/2013

RAPTI D MADURawe
01/18/2013

Initial Quality Assessment
Branch V
Division of New Drug Quality Assessment II

OND Division:	Division of Anti-Infective Products (DAIP)	
NDA:	202-091 (resubmission)	
Applicant:	Lupin Limited	
Stamp Date:	August 20, 2012	
Proposed Trademark:	Suprax®	
Established Name:	Cefixime for Oral Suspension	
Dosage Form:	Powder for oral suspension	
Route of Administration:	Oral	
Strength:	100 mg/mL (500 mg/5 mL)	
Indication:	Treatment of several infections	
Reviewer:	Qi, Ph.D. (CMC) Mark Seggel, Ph.D. (Biopharmaceutics)	
	YES	NO
Acceptable for filing:	☒	☐
Comments for 74-Day Letter	☐	☒

Background

This is a resubmission of NDA 202-091, for which the CR recommendation was issued on August 26, 2011. CMC Review # 1 (dated June 27, 2011 in DARRTS) included the following recommendation:

“From the ONDQA view point, NDA 202-091 is not recommended for approval as the

(b) (4)

This deficiency, and the outstanding Information Requests listed on page 66 should be satisfactorily addressed in the NDA resubmission. Labeling has not been reviewed in this review cycle and needs to be reviewed in the resubmission.”

Drug Product (deficiencies and additional comments)

The following CMC deficiency was listed on page 66 of the CMC Review # 1:

(b) (4)

In addition, several additional CMC comments listed in the CMC Review # 1 (page 66) were included in the CR letter. One of the comments referred to the product overfill. Several comments referred to the drug product proposed specification and the applicant has addressed them (a copy of the drug product specification is attached below). For example, the upper limit for assay has now been changed to (b) (4). *Comment: The responses to those comments have been provided in this resubmission and they will need a detailed review.*

Labeling

Draft container and carton labels are provided in Module 1. *Comment: The labeling and container labels will need to be reviewed in this review cycle.*

EES Information

The facilities involved in the manufacture of the proposed drug substance and the drug product were entered into EES by Althea Cuff.

Comments/Recommendations

Based on the information submitted, it appears that from the CMC perspective this amendment contains a complete response to deficiencies and comments included in the CR letter dated August 26, 2011. However, the adequacy of the response to deficiencies will be a team decision. Similarly, the adequacy of the responses to the CMC comments will be determined during the review course.

Dorota Matecka
CMC Lead

See DARRTS
Date

Rapti Madurawe
Branch Chief

See DARRTS
Date

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/s/

DOROTA M MATECKA
12/19/2012

RAPTI D MADURawe
12/19/2012

NDA 202-091

**Suprax® (cefixime) For Oral
Suspension 100 mg/mL
Lupin Pharmaceuticals, Inc**

**Andrew Yu PhD
ONDQA, Branch V**

DAIP

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Chemistry Review Data Sheet

1. NDA: 202-091
2. REVIEW #1
3. REVIEW DATE: 3/26/11
4. REVIEWER: Andrew Yu
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original NDA

10/25/10

Amendment

12/10/11

Amendment (IR response & Stability
update)

2/10/11

Amendment (Additional (b)(4) data)

5/20/11(Not reviewed)

Amendment (IR- Biopharm. response)

5/20/11

7. NAME & ADDRESS OF APPLICANT:

:

Name:

LUPIN PHARMACEUTICALS, INC.

Address: Harborplace Tower,
III South Calvert Street, 21 S1 Floor,
Baltimore, Maryland 21202

Representative

Contact person: Pramod Dahibhate
General Manager, Regulatory Affairs

Telephone: 410 576 2000

Fax 410 576 2221

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Suprax® For Oral suspension
- b) Non-Proprietary Name (USAN): Cefixime For Oral suspension
- c) Code Name/# (ONDC only): None
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antibiotic

11. DOSAGE FORM: For Oral suspension

12. STRENGTH/POTENCY: 100 mg/mL

13. ROUTE OF ADMINISTRATION: Buccal

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC

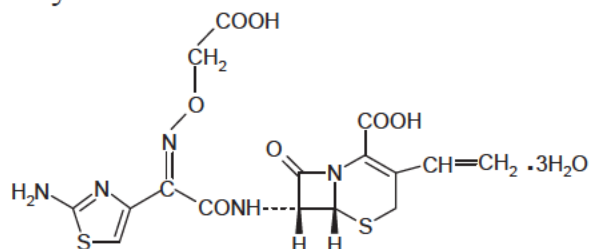
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

☒ Not a SPOTS product

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

USAN: Cefixime USP

(6*R*, 7*R*)-7-[2-(2-Amino-4-thiazolyl)glyoxylamido]-8-oxo-3-vinyl-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylic acid, 7²-(*Z*)-[*O*-(carboxymethyl) oxime] trihydrate.



Molecular weight 507.50
 Molecular Formula $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$
 Chemical Abstract 79350-37-1

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CO DE 1	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
15996	II	Lupin Inc.	Cefixime USP	3	Adequate	17-MAR-2010	Review #10 Signed S. Zuk 07/22/2010
(b) (4)	III	(b) (4)		4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		
	III			4	Adequate		

Chemistry Review Data Sheet

		(b) (4)				
(b) (4)	IV		4	Adequate		

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: NA

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall Acceptable	1 2/20/10	A. Inyard
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA (DMETS)			
EA	EA exclusion waiver found acceptable	2/20/11	Andrew Yu

19. ORDER OF REVIEW (OGD Only) N/A

The Chemistry Review for NDA 202-091

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the ONDQA view point, NDA 202-091 is not recommend for approval as the

(b) (4)

This deficiency, and the outstanding Information Requests listed on page 66 should be satisfactorily addressed in the NDA resubmission. Labeling has not been reviewed in this review cycle and needs to be reviewed in the resubmission.

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

N/A

II. Summary of Chemistry Assessments

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

Drug substance:

The drug substance cefixime USP manufactured by Lupin Pharmaceuticals Inc. is referenced by DMF 15996. The DMF holder is also the NDA applicant. The DMF is current and adequate.

Drug product:

Cefixime For Oral suspension contains 100 mg/mL of drug after reconstitution. The applicant's lower strengths of Cefixime For Oral suspension, 200 mg/5mL and 100mg/5mL are currently approved as ANDAs. The product is submitted as 505(b)(2) based on the approved RLD. A bioavailability study is submitted with the product in this NDA.

(b) (4)

The details of the Review Team teleconference (4/13/11) on

this issue are summarized in Attachment 3 of this review. The resolution of this deficiency would need to consider the drug product formulation concentration.

The manufacturing of the powder For Oral suspension involves (b) (4)

Appropriate in process controls are included to control blend uniformity, moisture, and other process parameters.

The CMC issues with stability, preservative, dissolution and product quality have been adequately responded except for the (b) (4). The deficiencies/IRs communicated to the sponsor and resolved during review are listed in page 66. Based on the stability data provided, some acceptance criteria in the drug product specification need to be tightened for improved quality. CMC IRs related to the specifications and fill weights/volumes were not communicated to the applicant in this review cycle due to the non-approvability of this NDA. Outstanding IRs are listed on page 66 and are to be conveyed to the applicant in the Complete Response letter.

The shelf life of 24 months at USP controlled room temperature is based on three stability batches of long term stability data at 21-24 months and additional stability data at accelerated condition. The stability data provided are adequate to support the shelf life proposed.

Due to the approvability issue, drug product labels and labeling were not reviewed this cycle.

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

Cefixime For Oral Suspension, 100 mg/mL is an off white to cream colored powder forming an off-white to pale yellow suspension with characteristic fruity odor on constitution. After reconstituted as directed, each mL of reconstituted suspension contains 100 mg of cefixime as trihydrate. The storage condition is: Prior to reconstitution, store at 20-25 °C (68-77°F) See USP controlled room temperature, (b) (4). After reconstitution: The suspension may be kept for 14 days either at room temperature, or under refrigeration, without significant loss of potency. Keep tightly closed. Shake well before using. Discard unused portion after 14 days. Cefixime For Oral administration is intended for the treatment of bacterial infections as described in the package insert. Cefixime For Oral suspension are supplied in HDPE bottles of 10 and 20 mL with (b) (4), NDC 27434-207-02 - 10 mL Bottle and NDC 27434-207-03 - 20 mL Bottle.

C. Basis for Approvability or Not-Approval Recommendation

From the CMC view point, the product is not recommended for approval based on unresolved issues regarding th (b) (4)

We concur with DMEPA and Clinical

(b) (4)

Therefore, from the CMC perspective, this NDA is NOT recommended for approval.

III. Administrative

A. Reviewer's Signature

See DARRTS

B. Endorsement Block

See DARRTS

C. CC Block

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/s/

ANDREW B YU
06/27/2011

RAPTI D MADURawe
06/27/2011