CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202091Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA#	202-091
Product	Suprax® (cefixime)
Submission Date(s)	17AUG2012
Submission Number	SDN010/SN0007
Submission Type	Class 2 Resubmission (including labeling updates)
Applicant	Lupin Pharmaceuticals, Inc.
Primary Reviewer	Zhixia Yan, Ph.D.
Secondary Reviewer	Kimberly L. Bergman, Pharm.D.
OCP Division	DCP4
Medical Division	DAIP

CLINICAL PHARMACOLOGY REVIEW

Background

On October 25, 2010, Lupin Pharmaceuticals, Inc. submitted the 505(b)(2) application for Suprax® (cefixime) for Oral Suspension, 100 mg/mL. Cefixime has been approved for oral administration in four tablet forms (100, 150, 200 and 400 mg) and two suspension forms (200 mg/5mL and 100 mg/5 mL). The proposed cefixime 100 mg/mL product was developed to offer a treatment option for children, and also adults who have difficulty swallowing oral tablets, as the proposed formulation is more concentrated than the currently available suspension formulations.The Agency issued a Complete Response (CR) letter (dated August 26, 2011) based on the finding that the risks for potential medication errors outweighed the benefits of treatment with the 100 mg/mL strength of cefixime oral suspension.

In this Class 2 resubmission (dated August 17, 2012), the Sponsor has addressed the deficiencies raised in the Agency's CR letter, and agreed to revise the concentration of the drug product to read as "500 mg/5ml" to prevent potential dosing errors. No new clinical pharmacology information was submitted. The focus of this clinical pharmacology review is on the labeling for Suprax® (cefixime) which has been updated based on the recently approved combined insert labeling of Suprax® (cefixime) Tablets USP, 400 mg; Capsules, 400 mg; Oral Suspension USP, 100 mg/5 mL, 200 mg/5 mL [NDA #203195; Suprax®(cefixime) Capsules, 400 mg approved on June 1, 2012].

Recommendation

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 4 has reviewed the submission and it is acceptable from a clinical pharmacology perspective. There are no clinical pharmacology labeling recommendations to convey to the sponsor.

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/s/

ZHIXIA YAN
01/08/2013

KIMBERLY L BERGMAN
01/08/2013

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-091	**Reviewer:** Mark R. Seggel	
Submission Date:	25-OCT-2010		
Division:	DAIOP / HFD-520	**Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Lupin Ltd.	**Supervisor:** Patrick J. Marroum, Ph.D.	
Trade Name:	Suprax	**Date Assigned:**	-
Generic Name:	Cefixime for Oral Suspension	**Date of Review:**	31-MAY-2011
Indication:	(b) (4)	**Type of Submission:** Original new drug application for new strength of powder for oral suspension; 505(b)(2), RLD is Suprax Cefixime for Oral Suspension, USP, 200 mg/5 mL (ANDA 65-355).	
Formulation / strengths	Powder for Oral Suspension, 100 mg/mL		
Route of Administration	Oral		

SUMMARY: Suprax Cefixime for Oral Suspension is currently available from Lupin in two concentrations, 200 mg/5 mL (the RLD) and 100 mg/5 mL. The applicant has proposed a third, more concentrated formulation of 100 mg/mL (after reconstitution). [Note that the clinical utility of this product has been questioned by the review team.] Bioequivalence of the new 100 mg/mL and the RLD has been demonstrated (see Clinical Pharmacology review).

The dissolution test is identical to the tests approved for the lower concentration products, except that for the 200 mg/5 mL product a sample containing the equivalent of 200 mg cefixime is introduced into each vessel while for the 100 mg/mL and 100 mg/5 mL suspensions the equivalent of only 100 mg cefixime is transferred to each vessel. USP Apparatus Type 2 is used at 50 rpm; the medium consists of 900-mL 0.05M potassium phosphate buffer of pH 7.2.

The proposed acceptance criterion for the new product was NLT (b) (4) (Q) dissolved after 30 minutes while the acceptance criterion for the approved products is NLT (b) (4) (Q) at 30 minutes. At our request and for consistency, the applicant revised the acceptance criterion to NLT (b) (4) (Q) at 30 minutes.

The current USP monograph for Cefixime for Oral Suspension does not include a dissolution test. It should be noted that under the established test conditions, all cefixime suspensions are rapidly dissolved (greater than (b) (4) in the first 10 minutes; dissolution is complete within 30 minutes). The established test therefore appears to have limited value as a quality control tool.

RECOMMENDATION: The dissolution test and acceptance criterion for the proposed 100 mg/mL suspension are comparable to those approved for the 200 mg/5 mL suspension (RLD) and for the 100 mg/5 mL product. It is, therefore, recommended that this NDA, as amended, be approved.

Signature
Mark R. Seggel
Reviewer
Office of New Drugs Quality Assessment

Signature
Patrick J. Marroum, Ph.D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: A.Dorantes, A.Yu, R.Madurawe, K.Hyon

Review Notes

Submissions Reviewed:

eCTD Sequence	Submission Type	Date
0000	Original Application	10/25/2010
0002	Amendment	2/10/2011
0004	Amendment	5/23/2011

Drug Substance Solubility:

Cefixime is slightly soluble in water and highly soluble in pH 7.5 phosphate buffer:

Solvent	Solubility (mg/mL)
Water	0.84 (slightly soluble)
pH 1.2 (0.1 N HCl)	3.18
pH 4.5 (Acetate Buffer)	8.28
pH 6.5 (Phosphate Buffer)	6.34
pH 7.5 (Phosphate Buffer)	12.34 (highly soluble)

(from eCTD 3.2.P.2.2)

Drug Product Formulation:

Application	NDA 202-091	ANDA 65-355	ANDA 65-129
Product	100 mg/mL	200 mg/5 mL (40 mg/mL)	100 mg/5 mL (20 mg/mL)
Components	(b) (4)		
Cefixime [1]			
Xanthan Gum			
Sodium Benzoate			
Strawberry Flavor			
Colloidal Silicon Dioxide			
Sucralose			
Sucrose			
Total Weight			
Cefixime [2]			

[1] Equivalent to Cefixime Anhydrous (with 5% overage)
[2] 1.5 % extra quantity (1.5 mg per unit dose) of Cefixime added to compensate the losses during processing i.e., milling.

API particle size distribution (b) (4)) NLT (b) (4) particles should be (b) (4)

Suprax® Cefixime for Oral Suspension, 100 mg/mL is packed into 3 mL, 10 mL and 20 mL HDPE bottle packs.

Pharmaceutical Development Report (eCTD 3.2.P.2.2):

Section 3.2.P.2.2 of the application provides an overview of the development of the new, 100 mg/mL, formulation, including lab scale optimization, in vitro performance as determining by

dissolution testing, and a pilot BE study. Starting with the formulation of the RLD, eight batches of 100 mg/mL powder for oral suspension were evaluated. These varied in formulation and/or manufacturing process details. Dissolution profiles of the developmental formulations were compared to 200 mg/5 mL RLD batch 7010A. A pilot bioequivalence study was conducted with the RLD and batch 008 (the final formulation and process); bioequivalence was demonstrated.

Dissolution profiles for batches 006, 007 and 008, along with the RLD, are shown below for reference. Data from a ninth, scale-up, batch were not provided.

(b) (4)

With regard to the dissolution profile of the RLD, the applicant notes that, "the dissolution profile of Suprax® Cefixime for Oral Suspension, 200 mg/5 mL exhibited more than 75 % of Cefixime released within 30 minutes in the USP official media."

Comments: While the dissolution data presented in the Pharmaceutical Development report suggests that dissolution of the RLD and of the new formulation is 80-90% at 30 minutes, data presented elsewhere in this NDA (see below), and in recent annual reports to the ANDAs for the RLD and 100 mg/5 mL product, indicate that dissolution is always complete by 30 minutes. It is unclear what differences in products or dissolution test methodology could account for the apparent discrepancy.

Dissolution Method Development (eCTD 3.2.P.2.2):

The applicant states that "In-vitro Dissolution Methodology was adopted as per Office of Generic Drugs (OGD) recommendations and USP monograph. The product is official in USP, the comparative dissolution testing for routine quality control and stability testing is done using the following USP method."

Comments: It should be noted that the USP monograph for Cefixime for Oral Suspension does not include a test for dissolution. However, the dissolution test medium (see below) is consistent with the dissolution medium specified for Cefixime Tablets, USP, and with the established ANDA methods for the 200 mg/5 mL and 100 mg/5 mL products.

Summary of Biopharmaceutics Studies (eCTD Section 2.7.1):

Two bioavailability / bioequivalence studies were conducted to establish a clinical bridge to the RLD Suprax Cefixime for Oral Suspension, 200 mg/5 mL. Suprax Cefixime for Oral Suspension, 100 mg/mL was shown to be bioequivalent to Suprax Cefixime for Oral Suspension, 200 mg/5 mL when both were given at a dose of 200 mg cefixime to healthy adults under fasted (Study 312-07) and fed (Study 313-07) conditions.

Comments: See Clinical Pharmacology review (01-JUN-2011) for an assessment of the pharmacokinetic studies submitted in support of the new concentrated formulation. The reviewer concluded that new product met the bioequivalence criteria with respect to rate and extent of absorption.

Comparative Dissolution Profiles (eCTD Section 2.7.1):

The results from the comparative dissolution studies (dissolution profiles of three lots of the test product and of the RLD) are shown below. No significant differences were noted.

Dissolution Test and Acceptance Criterion:

Test Conditions: USP Apparatus Type 2, 50 rpm, 900ml, 0.05M potassium phosphate buffer of pH 7.2.

Sample: Reconstituted suspension equivalent to 100 mg cefixime.

Acceptance Criterion (Proposed): NLT (b) (4)% (Q) of the Labeled amount of Cefixime ($C_{16}H_{15}N_5O_7S_2$) dissolved in 30 minutes.

Acceptance Criterion (Revised): NLT (b) (4)% (Q) of the Labeled amount of Cefixime ($C_{16}H_{15}N_5O_7S_2$) dissolved in 30 minutes.

Comments: The dissolution test requirement for both the 200 mg/5 mL RLD and 100 mg/5 mL product is NLT (b) (4) (Q) at 30 minutes. The dissolution test acceptance criterion for the 100 mg/mL product was, at our request, revised for consistency with the approved products.

The concentrations of the dissolved products are compared in the following table.

Application	Strength	Concentration after Reconstitution per Label	Cefixime DS Weight for Dissolution Test	Final Concentration in 900 mL Dissolution Test Medium
ANDA 65129	100 mg / 5 mL	20 mg/mL	100 mg	0.11 mg/mL
ANDA 65355 (rld)	200 mg / 5 mL	40 mg/mL	200 mg	0.22 mg/mL
NDA 202091	100 mg / 1 mL	100 mg/mL	100 mg	0.11 mg/mL
ANDA 65130	400 mg / Tablet	-	400 mg	0.45 mg/mL
Solubility of cefixime in the dissolution medium				9.257 mg/mL

Justification of Specification: The justification is simply stated as, "USP".

Comments: As there currently is no USP test for dissolution of cefixime [for oral] suspension, the applicant's justification is meaningless.

Drug Product Stability:

Note: As the application provided no other analysis of dissolution data, results from stability batches were compiled below by the reviewer.

Representative Stability Data at 25°C/60% RH

Batch/ Packaging	Stability Timepoint	% Dissolved at 10 minutes	% Dissolved at 20 minutes	% Dissolved at 30 minutes
7001A, 3-mL bottle	Initial			(b) (4)
	24 months			
9001A, 3-mL bottle	Initial			
	3 months			
	12 months			
	21 months			
9002A, 3-mL bottle	Initial			
	3 months			
	21 months			
7001B, 10-mL bottle	Initial			
	9 months			
	24 months			
9001B 10-mL bottle	Initial			
	9 months			
	21 months			
9002B,	Initial			

10-mL bottle	9 months	(b) (4)		
	21 months			
7001C, 20-mL bottle	Initial			
	9 months			
	24 months			
9001C, 20-mL bottle	Initial			
	21 months			
9002C, 20 mL bottle	Initial			
	9 months			
	21 months			

Representative Stability Data at 40°C/75% RH

Batch/ Packaging	Stability Timepoint	% Dissolved at 10 minutes	% Dissolved at 20 minutes	% Dissolved at 30 minutes
7001A, 3-mL bottle	Initial		(b) (4)	
	3 months			
	6 months			
9001A, 3-mL bottle	Initial			
	3 months			
	6 months *			
9002A, 3-mL bottle	Initial			
	3 months			
	6 months			
7001B, 10-mL bottle	Initial			
	3 months			
	6 months			
9001B 10-mL bottle	Initial			
	3 months			
	6 months			
9002B, 10-mL bottle	Initial			
	3 months			
	6 months			
7001C, 20-mL bottle	Initial			
	3 months			
	6 months			
9001C, 20-mL bottle	Initial			
	3 months			
	6 months			
9002C, 20-mL bottle	Initial			
	3 months			
	6 months			

* yet fails assay (81.4% LC)

Comments: These data suggest that an acceptance criterion of NLT (b) (4)% at 20 minutes (or even 10 minutes) would be appropriate. Alternatively different test conditions may have provided a more discriminatory test. However, given the comparability of the formulation to the approved cefixime for oral suspension products, developing a new test or alternative acceptance criterion at this time appears unwarranted.

Appendix 1. Dissolution Tests for Cefixime Dosage Forms

FDA Dissolution Methods Webpage

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Cefixime	Tablet			Refer to USP *			12/23/2010
Cefixime	Tablet ** (Chewable)	II (Paddle)	25	Phosphate Buffer, pH 7.2	900	10, 15, 20, 30, and 45	12/23/2010
Cefixime	Suspension	II (Paddle)	50	0.05 M Phosphate buffer, pH 7.2	900	10, 20, 30 and 45	04/09/2007

* Cefixime Tablets, USP
Dissolution 711--
Medium: 0.05 M potassium phosphate buffer, pH 7.2, prepared by dissolving 6.8 g of monobasic potassium phosphate in 1000 mL of water and adjusting with 1 N sodium hydroxide to a pH of 7.2; 900 mL.
Apparatus 1: 100 rpm.
Time: 45 minutes.
Procedure-- Determine the amount of cefixime ($C_{16}H_{15}N_5O_7S_2$) dissolved from UV absorbances at the wavelength of maximum absorbance at about 288 nm of filtered portions of the solution under test, suitably diluted with Dissolution Medium if necessary, in comparison with a Standard solution having a known concentration of USP Cefixime RS in the same medium. [note-An amount of methanol not to exceed 0.1% of the total volume of the Standard solution may be used to bring the Reference Standard into solution prior to dilution with Dissolution Medium, and the solution may be sonicated to assure complete dissolution of the Reference Standard.]
Tolerances-- Not less than (b)(4)% (Q) of the labeled amount of cefixime ($C_{16}H_{15}N_5O_7S_2$) is dissolved in 45 minutes.

** Chewable tablets 100, 150 and 200 mg are available from Lupin (ANDA 65-380).

Appendix 2. Information Requests

03-JAN-2011 Information Request (Response submitted in Amendment 2/10/2011):

The approved Suprax suspension products provide 200 mg/5 mL and 100 mg/5 mL. The approved dissolution requirement for both is NLT (b)(4)% (Q) dissolved after 30 minutes. For the new product, you are proposing NLT (b)(4)% (Q) after 30 minutes (in one place you also mention NLT (b)(4)% Q after (b)(4) minutes). Please provide your justification for Q of (b)5% (include the dissolution data supporting the proposed specification-time point and specification value).

Response: The approved Suprax suspension products provide 200 mg/5 mL and 100 mg/5 mL. The approved dissolution requirement for both is NLT (b)(4)% (Q) dissolved after 30 minutes. For the new product, you are proposing NLT (b)(4)% (Q) after 30 minutes (in one place you also mention NLT (b)(4)% Q after (b)(4) minutes). Please provide your justification for Q of (b)(4)% (include the dissolution data supporting the proposed specification-time point and specification value). It may kindly be noted that, we have revised our dissolution testing specification as "NLT (b)(4)% (Q) of the labeled amount of Cefixime is dissolved in 30 minutes" in-line with the approved Suprax suspension products 100 mg/5 mL and 200 mg/5 mL. Further, we regret for the inadvertent error that we had mentioned "NLT (b)(4)% (Q) after (b)(4) minutes" under section "m-3-2-p-2-2-drug-product" submitted in the original NDA. However, we have corrected it to read as "NLT (b)(4)% (Q) after 30 minutes" (as per the above mentioned revised proposed specification) and the revised document is provided as Formulation Development under section "m-3-2- p-2-2-drug-product."

"The revised finished product specifications, test procedures and updated stability data are included as below: Revised Documents Section Revised Finished Product Specification m3-2-P-5-1-specifications Revised Finished Product Test Procedure m3-2-P-5-2-analytical-procedures Updated Stability Data m3-2-p-8-3-stability-data"

05-APR-2011 Information Request (Responses submitted in Amendment 5/23/2011)

1. Provide the solubility of cefixime in the dissolution medium.

2. In section m3-2-p-5-2 analytical procedures, page 5, Preparation of Test Solution, you state that, "From each bottle, weigh and transfer slowly an amount of constituted suspension equivalent to 100 mg of Cefixime in a dissolution vessel containing dissolution medium with the help of syringe." However, in the validation report (dissolutionval-cefiximedrops, page 4, Test preparation), you state that, "Weigh and transfer an amount of constituted suspension equivalent to 500 mg of Cefixime in a dissolution vessel containing dissolution medium." Please clarify this discrepancy and justify the sample weight selected for regulatory purposes.

3. In addition, please indicate the weight of cefixime transferred to the dissolution vessels for the regulatory dissolution tests for the previously approved 200 mg/5 mL and 100 mg/4 mL {should read 5 mL} cefixime suspension products.

Ressponse:

Product	**Weight of Cefixime transferred to the dissolution vessels**
Suprax Cefixime for Oral Suspension USP, 100 mg/5 mL	Constituted suspension equivalent to 100 mg of cefixime (about 5.9 g accurately weighed suspension in syringe)
Suprax Cefixime for Oral Suspension USP, 200 mg/5 mL	Constituted suspension equivalent to 200 mg of cefixime (about 5.9 g accurately weighed suspension in syringe)
Suprax Cefixime for Oral Suspension, 100 mg/1 mL	'an amount of constituted suspension equivalent to 100 mg of cefixime to be transferred into stated dissolution medium' *[this will require ca. 1.1-1.4 gm. of reconstituted suspension]*

4. Please identify the sample weights used in the study comparing the 100 mg/mL to 200 mg/5 mL suspensions as described in 2.7.1.2.1.

100 mg/mL: ca. 1.1 - 1.4 gm. suspension *[equivalent to 100 mg of cefixime]*
200 mg/5 mL: ca. 5.8 - 6.4 gm. suspension [equivalent to 200 mg of cefixime]

Comments: The request should have been specifically for the weight of cefixime. It was the weight of cefixime that was of interest, not the weight of the suspension. Shouldn't the weight of cefixime added to each dissolution vessel be the same, regardless of the concentration of the reconstituted suspension?

Appendix 3. BE/BA Investigational Products

Fed Study 313-07
Investigational Products

Reference Product-A
SUPRAX (Cefixime for Oral Suspension, USP 200 mg / 5 mL) (50 mL Pack) Manufactured for Lupin Phama, Baltimore, Maryland 21 202, United States. Lot No. MSB 7014B

Test Product-B
SUPRAX (Cefixime for Oral Suspension 100 mg / mL) (20 mL Pack) Manufactured by Lupin Limited, Mandideep, India. Batch No. MSC 7001 C

Fasting Study 312-07
Investigational Products

Reference Product-A
SUPRAX (Cefixime 200 mg / 5mL - For Oral Suspension USP) Manufactured for-Lupin Pharma Baltimore, Maryland21202, United States. Lot No. MSB7014B

Test Product-B
SUPRAX (Cefixime 100 mg / mL - For Oral Suspension) Manufactured by- Lupin Limited, India.
Batch No. MSC7001C

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/s/

MARK R SEGGEL
06/08/2011

ANGELICA DORANTES
06/08/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	202-091
Submission Date(s):	October 25, 2010
Brand Name	Suprax® Cefixime for oral suspension, 100 mg/mL
Generic Name	Cefixime
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Kimberly Bergman, Pharm.D.
OCP Division	DCP4
OND Division	DAIOP
Applicant	Lupin Pharmaceutical Inc.
Relevant IND(s)	NA
Submission Type; Code	505(b)(2); New formulation, standard review (3S)
Formulation; Strength(s)	Oral suspension, 100 mg/mL
Indication	For the treatment of uncomplicated urinary tract infections; otitis media; pharyngitis and tonsillitis; (b) (4) acute exacerbations of chronic bronchitis; uncomplicated gonorrhea (cervical/urethral).

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1. EXECUTIVE SUMMARY

The Applicant, Lupin Pharmaceutical Inc, submitted the 505(b)(2) application for Suprax® Cefixime for Oral Suspension, 100 mg/mL. The reference listed Drug (RLD) to support the safety and efficacy of the product is Suprax® Cefixime for Oral Suspension USP, 200 mg/5mL, approved in 2007 under ANDA #A065355 by the same Applicant.

Cefixime has been approved for oral administration in four tablet forms (100, 150, 200 and 400 mg) and two suspension forms (200 mg/5mL and 100 mg/5 mL). The cefixime 100 mg/mL product has been developed to offer treatment option for children, and also adults who have difficulty swallowing oral tablets, as the proposed formulation is more concentrated than the currently available suspension formulations.

In support of the NDA, the Applicant conducted two bioequivalence (BE) studies (#312-07 & #313-07) to bridge the proposed formulation with the RLD. These two studies are Phase 1, open label, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover oral BE studies under fasted and fed conditions, respectively. In addition, the Applicant also submitted an in vitro dissolution study comparing the dissolution profiles between the test formulation and RLD.

1.1. Recommendation

The Clinical Pharmacology information provided by the Applicant in this submission is acceptable.

1.2. Phase IV Commitments

None.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The Applicant submitted pharmacokinetic studies seeking approval of the proposed formulation (cefixime 100 mg/mL oral suspension) by demonstrating bioequivalence to their own RLD product. Results from Studies #312-07 and #313-07 (**Table 1**) adequately assessed the PK of cefixime following single oral administration of the test formulation in comparison to the RLD under fed and fasted conditions. The test product met the bioequivalence criteria with respect to the rate and extent of absorption (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) of cefixime under both fed and fasted conditions (**Table 2**). As expected, a lower bioavailability of cefixime was observed when subjects were fed (#313-07) versus fasted (#312-07).

Table 1: Studies Evaluating the Bioequivalence of Cefixime 100 mg/mL Oral Suspension (Test) and Suprax Cefixime 200 mg/5 mL Oral Suspension (Reference)

Study Number Location	Study Design	Dose Groups and Number of Subjects	Sex and Age Range (Years)
312-07 5.3.1.2.1	Phase 1, open-label, balanced, randomized, 2-treatment, 2-period, 2-sequence, single dose, 2-way crossover BE study	Test (fasted): 2 mL Suprax (cefixime 100 mg/mL for Oral Suspension) (N = 24) Reference (fasted):5 mL Suprax (cefixime 200 mg/5 mL for Oral Suspension USP) (N = 24)	Male 20 – 32 years
313-07 5.3.1.2.2	Phase 1, open-label, balanced, randomized, 2-treatment, 2-period, 2-sequence, single dose, 2-way crossover BE study	Test (fed): 2 mL Suprax (cefixime 100 mg/mL for Oral Suspension) (N = 24) Reference (fed):5 mL Suprax (cefixime 200 mg/5 mL for Oral Suspension USP) (N = 24)	Male 20 – 40 years

BE = bioequivalence

Table 2: Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Cefixime under Fasted and Fed Conditions.

Fasted:

Parameters (Units)	ln-transformed data			
	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	B: Cefixime 100 mg/mL (fasted)	A: Cefixime 200 mg/5 mL (fasted)	Ratio (B / A)%	
C_{max} (µg/mL)	3.636	3.283	110.8	104.23 – 117.71%
AUC_{0-t} (µg*h/mL)	29.736	26.702	111.4	103.97 – 119.29%
$AUC_{0-\infty}$ (µg*h/mL)	30.210	27.284	110.7	103.59 – 118.36%

Source: Study 312-07 Final Report

Fed:

Parameters (Units)	(ln-transformed) Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	B: Cefixime 100 mg/mL (fed)	A: Cefixime 200 mg/5 mL (fed)	Ratio (B / A)%	
C_{max} (µg/mL)	1.773	1.892	93.7	84.48 - 103.88%
AUC_{0-t} (µg*h/mL)	14.531	15.375	94.5	85.58 - 104.38%
$AUC_{0-\infty}$ (µg*h/mL)	15.088	15.897	94.9	86.22 - 104.48%

Source: Study 313-07 Final Report

Yongheng Zhang, Ph.D.
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Concurrence:

Kimberly L. Bergman, Pharm.D.
Team Leader
Division of Clinical Pharmacology 4
Office of Clinical Pharmacology

cc:
Division File: NDA 202-091
HFD-520 (CSO/Hyon)
HFD-520 (MO/Pohlman)
HFD-520 (Chambers)
HFD-880 (Lazor)

2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

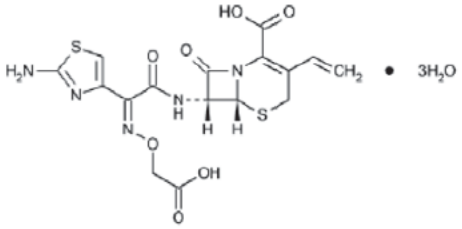
Cefixime is a white to light yellow crystalline powder, soluble in methanol and propylene glycol; slightly soluble in alcohol, acetone and glycerin; practically insoluble in ether, ethyl acetate, hexane and water.

Structural Formula: $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$

Molecular Weight: 507.50 Dalton

CAS Index Name: 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl) [(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-,trihydrate [6R -[6α ,7β (Z)]]-. (6R, 7R)-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

Chemical Structure:



Drug Product:
The drug product is formulated in a suspension form with the composition shown in **Table 2.1.1-1**. It is 2.5-fold more concentrated than the RLD (100mg/ mL vs. 200 mg/5mL).

Table 2.1.1-1: Composition of Drug Product

Ingredients	UNIT QTY. (mg/mL)	Percentage (% w/w)	Category	Reference to Standards
Cefixime* (b) (4)			(b) (4)	USP
Xanthan Gun (b) (4)				NF
Sodium Benzoate				NF
Strawberry Flavour (b) (4) (b) (4)				IH
Colloidal Silicon Dioxide (b) (4) (b)				NF
Sucralos (b) (4)				NF
Sucrose** (b) (4)				NF
Total Weight				
Cefixime*** (b) (4)				USP

IH – In House

Reviewer's comments: *Because the test suspension is in a more concentrated form and dosing is weight-based for pediatric patients, it is believed that the test suspension formulation is more prone to measurement errors than the currently available suspension formulations. Refer to Section 2.1.3.*

2.1.2. What is the proposed mechanism of drug action and therapeutic indication?

Cefixime is a semi-synthetic, cephalosporin antibiotic for oral administration. As with other cephalosporins, bactericidal action of cefixime results from inhibition of cell-wall synthesis. Cefixime is highly stable in the presence of beta-lactamase enzymes. As a result, many organisms resistant to penicillins and some cephalosporins due to the presence of beta-lactamases, may be susceptible to cefixime.

Cefixime products are indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms: uncomplicated urinary tract infections; otitis media; pharyngitis and tonsillitis; (b) (4) acute exacerbations of chronic bronchitis; uncomplicated gonorrhea (cervical/urethral).

2.1.3. What are the proposed dosage(s) and route(s) of administration?

For adults, the recommended dose of cefixime is 400 mg daily. This may be given as a 400 mg tablet daily or as 200 mg tablet every 12 hours. For the treatment of uncomplicated cervical/urethral gonococcal infections, a single oral dose of 400 mg is recommended.

For children, the recommended dose is 8 mg/kg/day of the suspension. This may be administered as a single daily dose or may be given in two divided doses, as 4 mg/kg every 12 hours. Children weighing more than (b) (4) kg or older than 12 years should be treated with the recommended adult dose. Pediatric dosage calculations by weight are presented in **Table 2.1.3-1**.

Otitis media should be treated with the suspension. Clinical studies of otitis media were conducted with the suspension, and the suspension results in higher peak blood levels than the tablet when administered at the same dose. Therefore, the tablet should not be substituted for the suspension in the treatment of otitis media.

(b) (4)

Reviewer's comments: *Because the proposed drug product is in a concentrated form (100mg/mL), significant difference in body weight for pediatric patients only requires a small change in dosing volume for those with low body weight. For example, a 50% increase in body weight from* (b) (4) *only requires* (b) (4) *ml increase in dosing volume. At the time of the*

review, the applicant has noi (b) (4) [redacted] *Refer to the Medical Officer's review and the Division of Medication Error Prevention and Analysis (DMEPA) review for further discussion of this dosing issue.*

2.2. General Clinical Pharmacology

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In support of the 505(b)(2)NDA, the Applicant conducted two bioequivalence (BE) studies (#312-07 & #313-07) to bridge the proposed formulation with the RLD. These two studies are Phase 1, open label, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover oral BE studies under fasted and fed conditions, respectively. In addition, the Applicant also submitted the in vitro dissolution study comparing the dissolution profiles between the test formulation and RLD. This in vitro study is reviewed by the Office of New Drug Quality Assurance Biopharmaceutics reviewer.

2.2.2. What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

The primary variable for comparison in two BE studies was the pharmacokinetics of cefixime following administration of the proposed and RLD formulations, specifically C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. Efficacy endpoints were not formally evaluated in this study.

2.2.3. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The sponsor used an adequately validated liquid chromatography with UV method to quantitate concentrations of cefixime in human plasma. (*Refer to Section 2.6*).

2.2.4. Exposure-response

The characteristics of exposure-response relationships for efficacy and safety of cefixime have been previously described. Refer to the approved cefixime product labeling revised on 03/29/2004 for NDA 50621.

2.2.5 What are the PK characteristics of cefixime? Is the proposed formulation bioequivalent to the RLD?

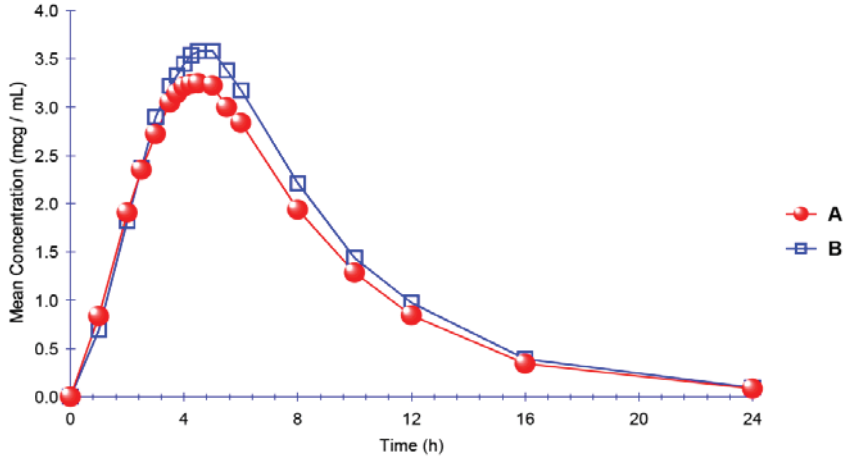
The proposed formulation met the bioequivalence criteria with respect to the rate and extent of absorption (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) of cefixime under both fed and fasted conditions.

The two BE Studies #312-07 and #313-07 are Phase 1, open label, randomized, two-treatment, two-period, two-sequence, single dose, two-way crossover oral studies under fasted and fed conditions, respectively.

The mean plasma concentration-time profiles for cefixime following single oral administration of the reference and test product in healthy, male subjects under fasted and fed conditions were presented in **Figure 2.2.5-1**. The mean pharmacokinetic parameters of cefixime for Suprax cefixime 100 mg/mL and 200 mg/5 mL were summarized in **Table 2.2.5-1**.

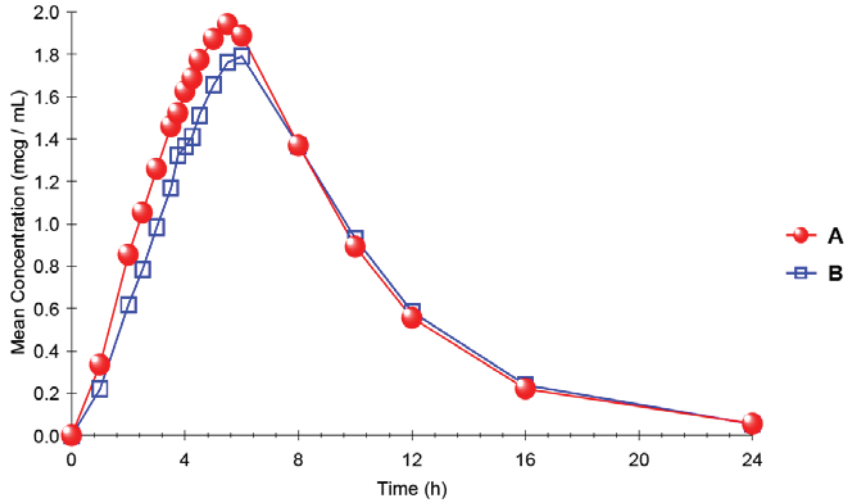
The 90% confidence intervals for the geometric mean test-to-reference for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were shown in **Table 2.2.5-2**. They were within the bioequivalence acceptance range of 80 to 125%. As expected, a lower bioavailability of cefixime was observed when subjects were fed (#313-07) versus fasted (#312-07).

Fasted



A = cefixime 200 mg/5 mL (fasted); B = cefixime 100 mg/mL (fasted)
Source: Study 312-07 Final Report

Fed



A = cefixime 200 mg/5 mL (fed); B = cefixime 100 mg/mL (fed)
Source: Study 313-07 Final Report

Figure 2.2.5-1: Mean Plasma Concentration-time profiles for Cefixime After Administration of Cefixime 200 mg/5 mL and Cefixime 100 mg/mL to Healthy, Adult, Human Subjects Under Fasted and Fed Conditions

Table 2.2.5-1: Mean Pharmacokinetic Parameters for Cefixime Under Fasted and Fed Conditions (n=24)

Fasted:

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Cefixime 200 mg/5 mL (fasted)	Cefixime 100 mg/mL (fasted)
T_{max} (h)[a]	4.500	4.500
C_{max} (µg/mL)	3.368 ± 0.7575	3.696 ± 0.6598
AUC_{0-t} (µg*h/mL)	27.493 ± 6.4355	30.211 ± 5.4185
$AUC_{0-\infty}$ (µg*h/mL)	28.045 ± 6.4460	30.694 ± 5.5275
λ_z (1/h)	0.197 ± 0.0228	0.201 ± 0.0162
$t_{½}$ (h)	3.559 ± 0.4442	3.479 ± 0.2911
AUC_% Extrap_obs (%)	2.125 ± 1.4124	1.568 ± 0.5697

[a]T_{max} is represented in median value.
Source: Study 312-07 Final Report

Fed:

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Cefixime 200 mg/5 mL (fed)	Cefixime 100 mg/mL (fed)
T_{max} (h)[a]	5.500	6.000
C_{max} (µg/mL)	1.990 ± 0.6189	1.837 ± 0.4964
AUC_{0-t} (µg*h/mL)	16.365 ± 5.7052	15.335 ± 5.0503
$AUC_{0-\infty}$ (µg*h/mL)	16.868 ± 5.7441	15.864 ± 5.0646
λ_z (1/h)	0.209 ± 0.0398	0.206 ± 0.0346
$t_{½}$ (h)	3.416 ± 0.5962	3.461 ± 0.5794
AUC_% Extrap_obs (%)	3.273 ± 1.5220	3.673 ± 1.9651

[a]T_{max} is represented in median value.
Source: Study 313-07 Final Report

Table 2.2.5-2: Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Cefixime under Fasted and Fed Conditions.

Fasted:

Parameters (Units)	ln-transformed data			
	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	B: Cefixime 100 mg/mL (fasted)	A: Cefixime 200 mg/5 mL (fasted)	Ratio (B / A)%	
C_{max} (µg/mL)	3.636	3.283	110.8	104.23 – 117.71%
AUC_{0-t} (µg*h/mL)	29.736	26.702	111.4	103.97 – 119.29%
$AUC_{0-\infty}$ (µg*h/mL)	30.210	27.284	110.7	103.59 – 118.36%

Source: Study 312-07 Final Report

Fed:

Parameters (Units)	(ln-transformed) Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	B: Cefixime 100 mg/mL (fed)	A: Cefixime 200 mg/5 mL (fed)	Ratio (B / A)%	
C_{max} (µg/mL)	1.773	1.892	93.7	84.48 - 103.88%
AUC_{0-t} (µg*h/mL)	14.531	15.375	94.5	85.58 - 104.38%
$AUC_{0-\infty}$ (µg*h/mL)	15.088	15.897	94.9	86.22 - 104.48%

Source: Study 313-07 Final Report

2.3. Intrinsic Factors

The impact of intrinsic factors on cefixime exposure following oral administration have been preciously described. Refer to the approved cefixime product labeling revised on 03/29/2004 for NDA 50621.

2.4. Extrinsic Factors

The impact of extrinsic factors on cefixime exposure following oral administration have been preciously described. Refer to the approved cefixime product labeling revised on 03/29/2004 for NDA 50621.

2.5. General Biopharmaceutics

Refer to Section *2.2.5* for the BE assessment between the proposed formulation and RLD. Also refer to the review by the Office of New Drug Quality Assurance Biopharmaceutics reviewer for the comparison on the dissolution profiles between the test formulation and RLD.

2.6. Analytical Section

2.6.1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The sponsor used liquid chromatography with UV-VIS detector to quantitate cefixime concentrations in human plasma.

2.6.2. Which metabolites have been selected for analysis and why?

No metabolite was selected for analysis. Since metabolites of cefixime have not been identified in vivo, it is appropriate to assess only the parent compound.

2.6.3. For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The reported concentrations of cefixime in human plasma represented total concentrations. Cefixime plasma protein binding is concentration independent at approximately 65%. Measurement of total concentrations is appropriate for this 505(b)(2) application.

2.6.4. What bioanalytical methods are used to assess concentrations?

Refer to *Section 2.6.1.* for further information.

2.6.4.1. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The standard curve in plasma ranged from 0.053 μg/mL to 8.0 μg/mL for cefixime. This range was adequate relating to the requirement for the BE studies in this application. The linear regression of the curves for peak area ratios *versus* concentration was weighted $1/x^2$ for the standard curve.

2.6.4.2. What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The lower and upper limits of quantitation were 0.053 µg/mL to 8.0 µg/mL for cefixime, respectively.

2.6.4.3. What are the accuracy, precision, and selectivity at these limits?

The accuracy (%RE) and precision (%CV) ranges for cefixime were -9.1% to 5.8% and 1.4% to 9.0%, respectively.

Selectivity was demonstrated by the lack of interference by potential endogenous interfering substances in eight distinct lots of human plasma.

2.6.4.4. What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Cefixime was shown to be stable in plasma at -22°C for 202 days; after 3 freeze thaw cycle; in reconstituted sample on auto sampler at room temperature for 33 hours.

2.6.4.5. What is the QC sample plan?

The concentrations of the QC samples consisted of 0.156, 1.926, 3.853, 6.880 µg/mL for cefixime. Between-run and within-run accuracy and precision were evaluated using replicates (n=5) from each of these concentrations.

3. LABELING RECOMMENDATIONS

Not applicable.

4. APPENDICES

4.1. Individual Study Review

4.1.1. Human Bioequivalence PK Study

Study Number: 312-07 & 313-07
AN OPEN-LABEL, BALANCED, RANDOMIZED, TWO-TREATMENT, TWO-PERIOD, TWO-SEQUENCE, SINGLE DOSE, TWO-WAY CROSSOVER BIOEQUIVALENCE STUDY OF TWO FORMULATIONS OF CEFIXIME ORAL SUSPENSION 200 mg, IN HEALTHY, ADULT, HUMAN MALE SUBJECTS UNDER FED OR FASTED CONDITIONS (Phase 1)

Dates: 17 December, 2007 to December 28, 2007
Analytical site: (b) (4) Gujarat, India

OBJECTIVES:

To compare the bioavailability and characterize the pharmacokinetic profile of the sponsor's formulation (Oral Suspension containing Suprax equivalent to 100 mg/mL of Cefixime) with respect to the innovator product (SUPRAX® for Oral Suspension containing Cefixime equivalent to 200 mg/5 mL of Cefixime) in healthy, adult, human subjects under fasted or fed conditions and to assess the bioequivalence.

FORMULATION & ADMINISTRATION

Reference Product: SUPRAX® (Cefixime 200 mg/5mL for oral suspension USP, Lot No. MSB7014B). Each dose of 200 mg with 5 mL administered.

Test Formulation: SUPRAX (Cefixime 100 mg/mL for oral suspension, Batch No. MSC7001C). Each dose of 200 mg with 2mL administered.

STUDY DESIGN:

See **Table 1**.

Fasted study:
This was a two period, single oral dose cross-over study. Equal allocation of treatment sequence was as per the randomization schedule. After an overnight fast for at least 10 hours, subjects (n=24) were administered with the study medication (either the reference product 200 mg in 5 mL or the test formulation 200 mg in 2 mL) in sitting posture with 240 mL of drinking water. Blood samples for analyses were collected before dosing and at pre-defined time-points 1, 2, 2.5, 3, 3.5, 3.75, 4, 4.25, 4.5, 5, 5.5, 6, 8, 10, 12, 16 and 24 hours post dose. The two doses were separated by a washout period of 9 days.

Fed study:
Similar to the above, except that subjects fasted overnight for at least 10 hours prior to serving of the high fat and high calorie-vegetarian breakfast which they consumed within 30 minutes in each period, and the two doses were separated by a washout period of 7 days.

Table 1: Studies Evaluating the Bioequivalence of Cefixime 100 mg/mL Oral Suspension (Test) and Suprax Cefixime 200 mg/5 mL Oral Suspension (Reference)

Study Number Location	Study Design	Dose Groups and Number of Subjects	Sex and Age Range (Years)
312-07 5.3.1.2.1	Phase 1, open-label, balanced, randomized, 2-treatment, 2-period, 2-sequence, single dose, 2-way crossover BE study	Test (fasted): 2 mL Suprax (cefixime 100 mg/mL for Oral Suspension) (N = 24) Reference (fasted):5 mL Suprax (cefixime 200 mg/5 mL for Oral Suspension USP) (N = 24)	Male 20 – 32 years
313-07 5.3.1.2.2	Phase 1, open-label, balanced, randomized, 2-treatment, 2-period, 2-sequence, single dose, 2-way crossover BE study	Test (fed): 2 mL Suprax (cefixime 100 mg/mL for Oral Suspension) (N = 24) Reference (fed):5 mL Suprax (cefixime 200 mg/5 mL for Oral Suspension USP) (N = 24)	Male 20 – 40 years

BE = bioequivalence

ASSAY METHODOLOGY:

Plasma samples were assayed for cefixime by a validated HPLC method using a UV-VIS detector. The analyte was extracted from the plasma using a [redacted] (b) (4) method. The retention times for cefixime and [redacted] (b) (4) (internal standard) was around 15.0 and 17.5 minute, respectively.

Criterion	Cefixime	Comments
Conc. range, µg/mL	0.053 – 8.000	satisfactory
LLOQ, µg/mL	0.052	satisfactory
Linearity, r^2	>0.98	satisfactory
Accuracy, % RE (fasting conditions)	-3.0 – 5.8 (-6.2 – 5.6) [a] -5.9 – 4.6 (-9.1 – 5.2) [b]	satisfactory
Precision, % CV (fasting conditions)	1.8 – 7.8(1.9 – 9.0) [a] 1.6 – 5.1(1.4 – 5.5) [b]	satisfactory
Recovery	Low, medium, and high QCs: 33.8±1.9%, 47.1±1.5%, 54.6±1.1%, respectively	satisfactory
Specificity	Interference by endogenous compounds and common co-administered drugs evaluated	satisfactory
Stability	Stable in plasma at -22°C for 202 days; after 3 freeze thaw cycle; in reconstituted sample on auto sampler at room temperature for 33 hours.	satisfactory

[a], QC samples at 0.156, 1.926, 3.853, 6.880 µg/mL; [b], eight calibration standards.
Reference: Study report No. MV-104-05

DATA ANALYSIS

The pharmacokinetic parameters were calculated from the drug concentration-time profile by non-compartmental model using WinNonlin Version 5.0.1 (Pharsight Corporation, USA) for Cefixime. Statistical comparison of the pharmacokinetic parameters of the two formulations was

carried out using PROC GLM of SAS® release 9.1.3 (SAS Institute Inc., USA) to assess the bioequivalence of Cefixime.

RESULTS:

Study population
All 24 subjects in each study, who entered the study, were randomized and completed the study according to protocol. There were no discontinuations of treatment in this trial. A summary of demographic and baseline characteristics for the study population is presented in **Table 2**.

Table 2: Demographic Characteristics
Fasted study

Parameter (Units)	Mean ± SD	
	n= 24 (Dosed Subjects)	n= 24 (Subjects completed clinical phases of the study)
Age (years)	23.9± 3.87	23.9± 3.87
Weight (kg)	61.66 ± 7.156	61.66 ± 7.156
Height (cm)	168.90 ± 6.772	168.90 ± 6.772
BMI (kg / m^2)	21.43 ± 2.009	21.43 ± 2.009

Fed study

Parameter (Units)	Mean ± SD
	n=24 (Subjects who were dosed and completed all the phases of the study)
Age (years)	24.8 ± 5.23
Weight (kg)	60.28 ± 6.388
Height (cm)	166.93 ± 6.167
BMI (kg / m^2)	21.628 ±1.9762

Plasma Pharmacokinetics
Fasted
Individual and mean plasma concentration-time profiles for cefixime following single oral administration of the reference and test product in healthy, male subjects under fasted conditions are presented in **Figures 1**(individual) and **2** (mean). The mean pharmacokinetic parameters of cefixime for Suprax cefixime 100 mg/mL and 200 mg/5 mL are summarized in **Table 3**.

The 90% confidence intervals for the geometric mean test-to-reference for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ are shown in **Table 4**. They were within the bioequivalence acceptance range of 80 to 125%.

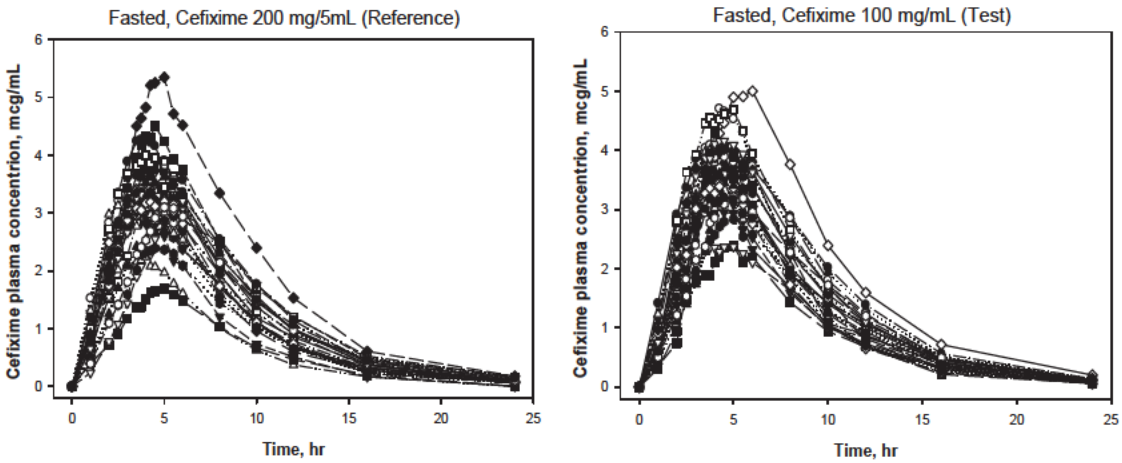
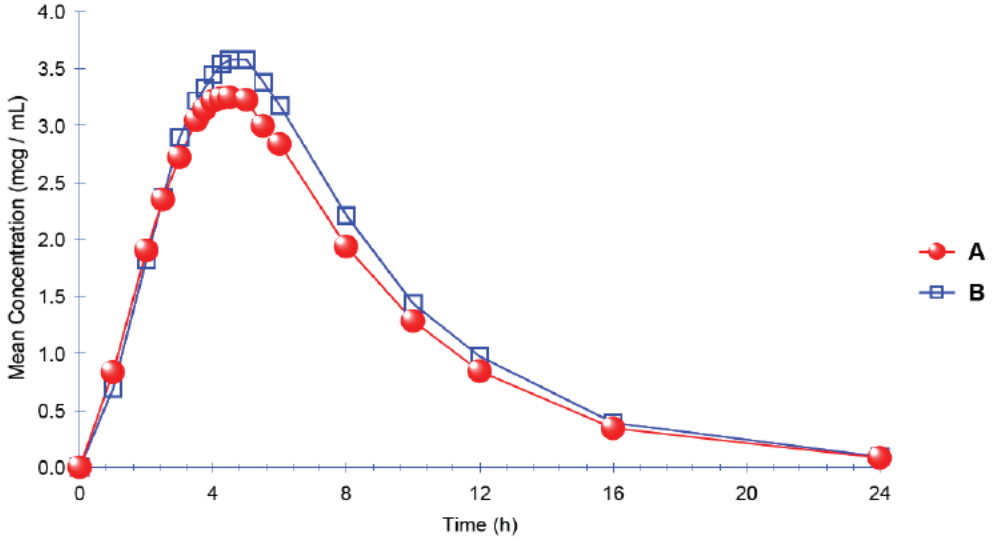


Figure 1: Individual Plasma Concentration-Time profiles for Cefixime After Single Oral Administration of the Reference (Cefixime 200 mg/5mL) and the Test formulation (Cefixime 100 mg/mL) in Healthy, Male Subjects under Fasted Condition (N=24)



A = cefixime 200 mg/5 mL (fasted); B = cefixime 100 mg/mL (fasted)
Source: Study 312-07 Final Report

Figure 2: Mean Plasma Concentration-time profiles for Cefixime After Administration of Cefixime 200 mg/5 mL and Cefixime 100 mg/mL to Healthy, Adult, Human Subjects Under Fasted Condition

Table 3: Mean Pharmacokinetic Parameters for Cefixime Under Fasted Condition (N=24)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Cefixime 200 mg/5 mL (fasted)	Cefixime 100 mg/mL (fasted)
T_{max} (h)[a]	4.500	4.500
C_{max} (µg/mL)	3.368 ± 0.7575	3.696 ± 0.6598
AUC_{0-t} (µg*h/mL)	27.493 ± 6.4355	30.211 ± 5.4185
$AUC_{0-\infty}$ (µg*h/mL)	28.045 ± 6.4460	30.694 ± 5.5275
λ_z (1/h)	0.197 ± 0.0228	0.201 ± 0.0162
$t_{½}$ (h)	3.559 ± 0.4442	3.479 ± 0.2911
AUC_%Extrap_obs (%)	2.125 ± 1.4124	1.568 ± 0.5697

[a] T_{max} is represented in median value.
Source: Study 312-07 Final Report

Table 4: Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Cefixime Under Fasted Condition

Parameters (Units)	ln-transformed data			
	Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	B: Cefixime 100 mg/mL (fasted)	A: Cefixime 200 mg/5 mL (fasted)	Ratio (B / A)%	
C_{max} (µg/mL)	3.636	3.283	110.8	104.23 – 117.71%
AUC_{0-t} (µg*h/mL)	29.736	26.702	111.4	103.97 – 119.29%
$AUC_{0-\infty}$ (µg*h/mL)	30.210	27.284	110.7	103.59 – 118.36%

Source: Study 312-07 Final Report

Fed

Individual and mean plasma concentration-time profiles for cefixime following single oral administration of the reference and test product in healthy, male subjects under fed condition were presented in **Figures 3** (individual) and **4** (mean). The mean pharmacokinetic parameters of cefixime for Suprax cefixime 100 mg/mL and 200 mg/5 mL were summarized in **Table 5**.

The 90% confidence intervals for the geometric mean test-to-reference for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were shown in **Table 6**. They were within the bioequivalence acceptance range of 80 to 125%.

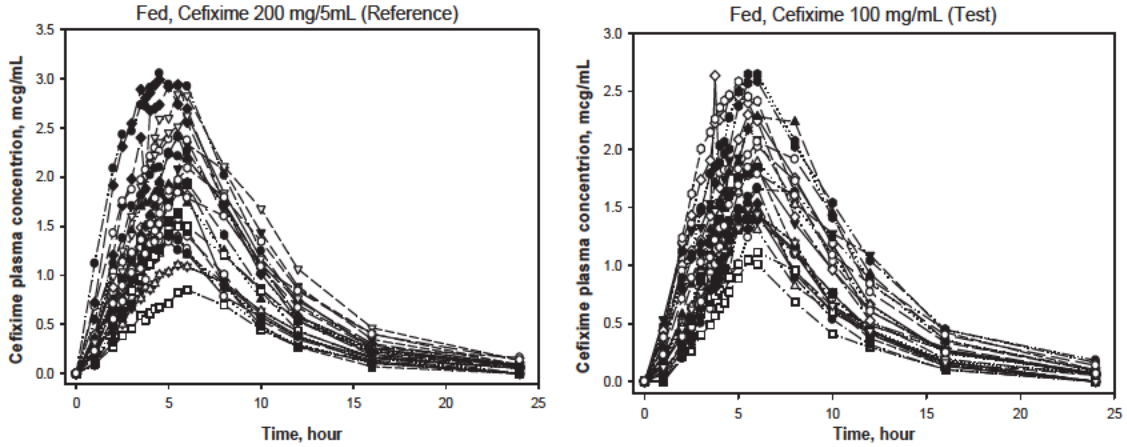
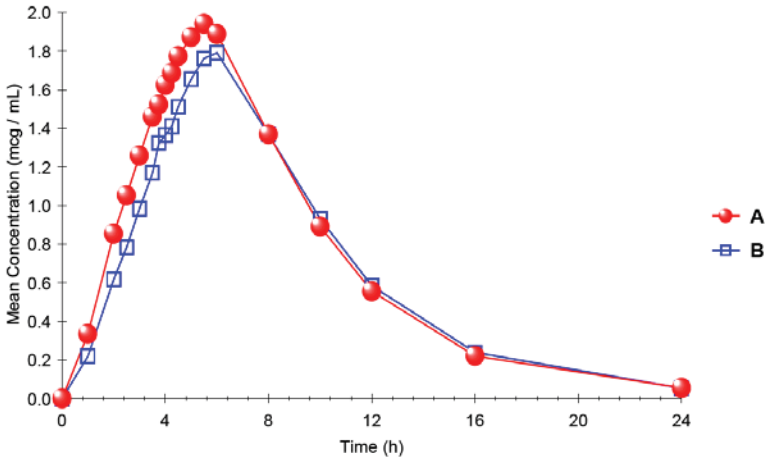


Figure 3: Individual Plasma Concentration-Time profiles for Cefixime After Single Oral Administration of the Reference (Cefixime 200 mg/5mL) and the Test formulation (Cefixime 100 mg/mL) in Healthy, Male Subjects under Fed Condition (N=24)



A = cefixime 200 mg/5 mL (fed); B = cefixime 100 mg/mL (fed)
Source: Study 313-07 Final Report

Figure 4: Mean Plasma Concentration-time profiles for Cefixime After Administration of Cefixime 200 mg/5 mL and Cefixime 100 mg/mL to Healthy, Adult, Human Subjects Under Fed Condition

Table 5: Mean Pharmacokinetic Parameters for Cefixime Under Fed Condition (N=24)

Parameters (Units)	Mean ± SD (Un-transformed data)	
	Cefixime 200 mg/5 mL (fed)	Cefixime 100 mg/mL (fed)
T_{max} (h)[a]	5.500	6.000
C_{max} (µg/mL)	1.990 ± 0.6189	1.837 ± 0.4964
AUC_{0-t} (µg*h/mL)	16.365 ± 5.7052	15.335 ± 5.0503
$AUC_{0-\infty}$ (µg*h/mL)	16.868 ± 5.7441	15.864 ± 5.0646
λ_z (1/h)	0.209 ± 0.0398	0.206 ± 0.0346
$t_{½}$ (h)	3.416 ± 0.5962	3.461 ± 0.5794
AUC_% Extrap_obs (%)	3.273 ± 1.5220	3.673 ± 1.9651

[a]T_{max} is represented in median value.
Source: Study 313-07 Final Report

Table 6: Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Cefixime Under Fed Condition

Parameters (Units)	(ln-transformed) Geometric Least Squares Mean			90% Confidence Interval (Parametric)
	B: Cefixime 100 mg/mL (fed)	A: Cefixime 200 mg/5 mL (fed)	Ratio (B / A)%	
C_{max} (µg/mL)	1.773	1.892	93.7	84.48 - 103.88%
AUC_{0-t} (µg*h/mL)	14.531	15.375	94.5	85.58 - 104.38%
$AUC_{0-\infty}$ (µg*h/mL)	15.088	15.897	94.9	86.22 - 104.48%

Source: Study 313-07 Final Report

SPONSORS CONCLUSIONS:

The test product (cefixime 100 mg/mL oral suspension) met the bioequivalence criteria with respect to the rate and extent of absorption (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) of cefixime in both the fed and fasted BE studies. As expected, a lower bioavailability of cefixime was observed when subjects were fed (Study 313-07) versus fasted (312-07).

REVIEWER'S ASSESSMENT & RECOMMENDATION:

Results from Studies 312-07 & 313-07 adequately assessed the pharmacokinetics of cefixime following single oral administration of the tested formulation in comparison to the reference formulation under fed and fasted conditions. The sponsor's conclusion regarding the bioequivalence between the two formulations of cefixime is valid.

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

/s/

YONGHENG ZHANG
05/31/2011

KIMBERLY L BERGMAN
06/01/2011