CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203195Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	203195
Drug	Cefixime
Brand Name	Suprax®
Formulation; Strength	400 mg capsule
Indication	Treatment of Uncomplicated Urinary Tract Infection (UTI), Pharyngitis & Tonsillitis, Acute Bronchitis & Acute Exacerbation of Chronic Bronchitis (AEBC), Uncomplicated Gonorrhea (cervical/urethral)
Applicant	Lupin Pharmaceuticals Inc.
Reviewer	Assadollah Noory, Ph.D.
Secondary Reviewer	Kimberly Bergman, Pharm.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Anti-infective Products
Stamp Date	June 28, 2011

Table of Contents

1. EXECUTIVE SUMMARY

Under the provisions of 505(b)(2), Lupin Pharmaceuticals Inc. is seeking approval for their product Suprax® (cefixime 400 mg) capsule for the treatment of uncomplicated UTI, pharyngitis, tonsillitis, acute bronchitis, AECB, and uncomplicated gonorrhea (cervical/urethral). In support of the approval, the applicant submitted one bioequivalence study assessing the performance of their product Suprax® (cefixime 400 mg) capsule versus Suprax® (cefixime 400 mg) tablet reference product under fasting and fed conditions. Lupin Pharmaceuticals Inc. has marketed Suprax® cefixime 400 mg tablets USP since its approval on February 12, 2004 (ANDA# 65-130), Suprax® cefixime 100 mg/5 mL for oral suspension USP (ANDA# 65-129), and Suprax® cefixime 200 mg/5 mL for oral suspension USP (ANDA # 65-355).

1.1. Recommendation

The Office of Clinical Pharmacology completed the review of the clinical pharmacology portion of this NDA and finds that the sponsor has adequately addressed the clinical pharmacology aspects required for the approval of this NDA. Therefore, the Office of Clinical Pharmacology recommends the approval of the capsule formulation of Suprax®, NDA 203-195.

1.2. Phase IV Commitments

There is no phase 4 requirement.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings:

This application for cefixime 400 mg capsule includes one bioequivalence study report. Study LBC-10-044 was conducted under fasting conditions to assess the bioavailability of the capsule relative to the tablet (reference product); the capsule was also given with food to assess the effect of food on the capsule relative to the fasting conditions. The study was a randomized, open-label, balanced, analyst-blind, three-treatment, three-period, three-sequence, single-dose, crossover bioequivalence study assessing the bioequivalence between Suprax® capsule containing 400 mg cefixime by Lupin Inc. and Suprax® tablet (cefixime 400 mg,) by Lupin Inc. in healthy adult subjects.

Single-Dose Fasting and Fed Bioequivalence Study (LBC-10-044)

Thirty-one subjects completed this three-way crossover bioequivalence study. Plasma PK parameter estimates (arithmetic mean ± SD and geometric least square mean (GLSM)), point estimates as ratio of test over reference and fed over fasted, expressed as percent, and the 90% confidence intervals (CI) for cefixime following administration of single doses of the tablet (reference) and capsule (test) under fasting and fed conditions are presented in the following tables.

Summary Statistics for Capsule vs. Tablet under fasting conditions, (N= 31)

Parameter	Capsule (mean +/- SD),	GLSM	Tablet (mean +/- SD)	GLSM	Point Estimate & 90% C. I.	
C_{max} (ng/mL)	4882.10-+ 1460.92	4652.87	5447.79 + 1227.35	5279.78	88.13	82.31 – 94.36
AUC_{0-t} (ng•h/mL)	43071.17 + 17249.13	39656.23	47120.63 + 15465.85	44462.93	89.19	82.28 – 96.68
$AUC_{0-\infty}$ (ng•h/mL)*	45331.91 + 17622.97	41853.81	48999.85 + 16178.00	46292.47	90.41	83.85 – 97.48
Treatments						
Test	Suprax® (cefixime 400 mg) capsules, batch number MCB9001A, expiration September 2011; Lupin, India					
Reference	Suprax® (Cefixime 400 mg) Tablets USP, manufactured by Lupin Limited Mumbai, India for Lupin Pharmaceuticals, Inc., 111 South Calvert Street, Baltimore, Maryland 21202 USA; batch number MTD8011B, expiration date August 2010					
* - N=30						

Summary Statistics for capsule, Fed vs. Fasted, (N= 31)

Parameter	Food (mean +/- SD), GLSM		Fasted (mean +/- SD), GLSM		Point Estimate & 90% C. I.	
C_{max} (ng/mL)	3563.08 + 1072.19	3427.32	4882.10-+ 1460.92	4652.87	73.66	68.79 - 78.88
AUC_{0-t} (ng•h/mL)	35337.68 + 13595.74	33099.76	43071.17 + 17249.13	39656.23	83.47	76.98 - 90.49
$AUC_{0-\infty}$ (ng•h/mL)*	38128.18 + 14369.79	35978.14	45331.91 + 17622.97	41853.81	85.96	78.85 - 91.55
Treatment: Suprax® (cefixime capsules 400 mg), batch number MCB9001A, expiration September 2011, Lupin, India						
* - N=30						

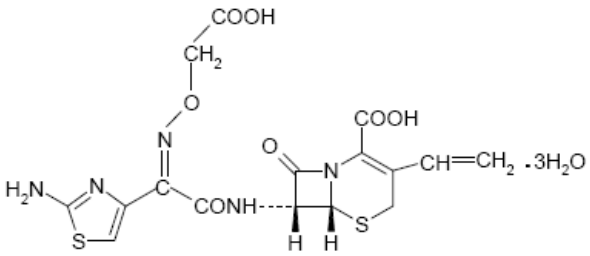
The 90% confidence limits for cefixime are within 80% - 125% for AUC and C_{max} indicating that the capsule is bioequivalent to tablet under fasting conditions. The results of study LBC-10-044 indicate

that the Suprax® capsule provides acceptable exposure compared to Suprax® tablet under fasting conditions. However, food reduced cefixime exposure by 15% based on AUC and 25% based on C_{max}. Also there is an increase in time to maximum concentration (T_{max}) from 5.06 hours to 6.45 hours (approximately 27%).

2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

Suprax® (cefixime) is a semisynthetic, cephalosporin antibiotic for oral administration. Chemically, it is (*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.
The chemical formula of cefixime is $C_{16}H_{15}N_5O_7S_2 \cdot 3H_2O$ with a molecular weight of 507.50 as the trihydrate.



Structural Formula

Cefixime inhibits cell-wall synthesis, thereby providing bactericidal action. Cefixime is highly stable in the presence of beta-lactamase enzymes.

Suprax® is available for oral administration as 400 mg film coated tablets and as powder for oral suspension; when reconstituted the suspension provides either 100 mg/5 mL or 200 mg/5 mL of cefixime as trihydrate.

2.2. General Clinical Pharmacology

The bioavailability of Suprax® oral tablet and suspension is about 40%-50% following oral administration with or without food; however, time to maximum concentration is increases approximately by 45 minutes when administered with food. Serum protein binding is concentration independent with a bound fraction of approximately 65%. Approximately 50% of the absorbed dose is excreted unchanged in the urine in 24 hours. For additional clinical pharmacology information on the tablet and suspension formulations refer to the FDA Approved Labeling for Suprax® Cefixime Tablets USP, 400 mg and Cefixime for Oral Suspension USP, 100 mg/ 5mL and 200 mg /5 mL.

2.3. Intrinsic Factors

Not applicable.

2.4. Extrinsic Factors

Not applicable.

2.5. General Biopharmaceutics

2.5.1. What is the in vivo relationship of the proposed formulation to the currently marketed formulation in terms of comparative exposures under fasting and fed states?

The study was an open label, balanced, randomized, three-sequence, three-treatment, three-period, single-dose, crossover oral bioequivalence study under both fasting and fed conditions. Subjects received treatments A (reference tablet), treatment B (test capsule), and treatment C (test capsule after meal). For the tablet versus capsule comparison, the 90% confidence intervals for cefixime are within 80% - 125% for AUC and C_{max} indicating that the capsule is bioequivalent to the tablet under fasting conditions. The results of study LBC-10-044 indicate that the cefixime 400 mg capsule provides acceptable exposure compared to tablet under fasting conditions; however, food reduces cefixime exposure by 15% based on AUC and 25% based on C_{max}. The following tables contain the summary results of this study.

Geometric least squares means, ratios, and 90% CI for cefixime (treatment B vs A)

PK Parameter	N	Geometric Least Square Means		B/A Ratio (%)	90% Confidence Interval	
		Capsule (B)	Tablet (A)		LCL	UCL
C_{max} (ng/mL)	31	4652.87	5279.78	88.13	82.31	94.36
AUC_{0-t} (ng*h/mL)	31	39656.23	4446.93	89.19	82.28	96.68
$AUC_{0-\infty}$ (ng*h/mL)	30	41853.81	46292.47	90.41	83.85	97.48

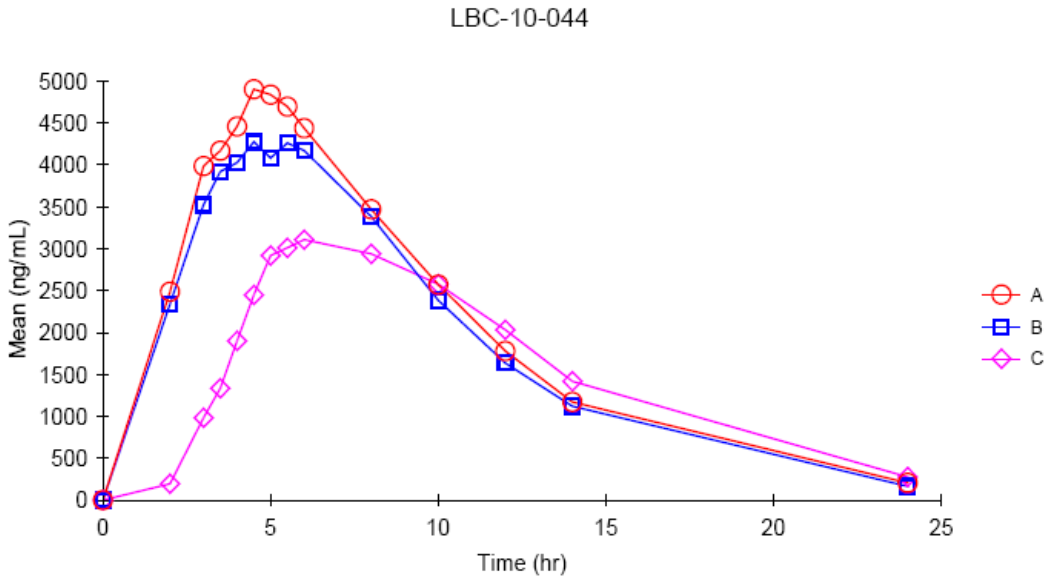
LCL, lower confidence limit; UCL, upper confidence limit

Geometric least squares means, ratios, and 90% CI for capsule (treatment C vs B)

PK Parameter	N	Geometric Least Square Means		C/B Ratio (%)	90% Confidence Interval	
		Fed (C)	Fasting (B)		LCL	UCL
C_{max} (ng/mL)	31	3427.32	4652.87	73.66	68.79	78.88
AUC_{0-t} (ng*h/mL)	31	33099.76	39656.23	83.47	76.98	90.49
$AUC_{0-\infty}$ (ng*h/mL)	30	35978.14	41853.81	85.96	78.85	91.55

LCL, lower confidence limit; UCL, upper confidence limit

The following figure shows the area under the mean plasma concentration as a function of time for the three treatments.



A = reference tablet
B = test capsule
C = test capsule after meal

Reference ID: 3124453

2.6. Bioanalytical Section

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

The concentrations of cefixime in human plasma are determined by using ultra performance liquid chromatography (UPLC/MS/MS) method.

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

Greater than 50% of the administered dose is recovered in urine unchanged in 24 hours, thus, it is acceptable to assess the parent for pharmacokinetics measurements.

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?

Protein binding of cefixime is 65%; it is acceptable to measure the total concentration of cefixime for this 505(b)(2) application.

2.6.4. What bioanalytical method is used to assess concentrations?

An ultra performance liquid chromatography with mass spectrometry (UPLC/MS/MS) method is used to determine the cefixime concentrations in plasma.

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 calibration curve ranged from 100.16 ng/mL to 8008.76 ng/mL for cefixime. This range is acceptable for determination of cefixime concentrations for the study in this application. The correlation coefficient (r) ranged from 0.997 to 0.999 with weighing factor of $1/x^2$ for the calibration curve.

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

The lower and upper limits of quantitation are 100.16 ng/mL to 8008.67 ng/mL for cefixime respectively.

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

The accuracy ranged from 96.03% to 101.98%; and the precision (%CV) ranged from 1.91% to 6.23% for cefixime.

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

The long-term stability of cefixime in plasma at -75□C for 99 days ranged from 90.30% to 106.51%; after 4 freeze thaw cycle the stability of cefixime ranged from 97.31% to 105.60%; the autosampler stability for cefixime ranged from 97.69% to 98.85%.

2.6.4.5. What are the QC samples?

The concentrations of cefixime in the QC samples were 100.38, 296.12, 3254.05, 6026.03 ng/mL. The intra-batch accuracy ranged from 87.14% to 95.36% with precision of 2.48% to 8.29%; the inter-batch accuracy ranged from 92.58% to 98.49% with precision of 2.86% to 8.51%.

Reference ID: 3124453

3. LABELING RECOMMENDATIONS

The following sections of the labeling should be modified as follows (recommendations appear in underlined/bold/strike-through type):

(b) (4)

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

4. APPENDICES

4.1. Individual Study Review

4.1.1. Study LBC-10-044

Title:
An Open Label, Balanced, Randomized, Single-Dose, Three-Treatment, Three-Sequence, Three-Period Crossover Oral Bioequivalence Study of Reference product (Treatment A) Suprax® (Cefixime 400 mg) Tablets, manufactured by Lupin Limited Mumbai 400098, India for Lupin Pharmaceuticals, Inc. 111 South Calvert Street Baltimore, Maryland 21202 USA, and Test Product (Treatment B) Cefixime Capsules 400 mg manufactured by Lupin Limited, India, under Fasting Conditions and Food Effect Study of Test Product Cefixime Capsules 400 mg Manufactured by Lupin Limited, India Administered under Fasting (Treatment B) and Fed (Treatment C) Conditions in Healthy, Adult, Human Male Subjects.

Dosing Dates:

Study initiation date: June 21, 2010
Study completion date: July 7, 2010

Treatments:

Test:

Suprax® (Cefixime Capsules 400 mg), batch number MCB9001A, expiration September 2011 by Lupin Limited, Mandideep, India

References:

Suprax® (Cefixime 400 mg) Tablets USP, manufactured by Lupin Limited Mumbai 400098, India manufactured for Lupin Pharmaceuticals, Inc., 111 South Calvert Street Baltimore, Maryland 21202 USA; batch number MTD8011B, expiration August 2010; Lupin Limited, Mumbai-400098, India Lupin Pharma, Baltimore, Maryland 21202, USA

Objective:
To assess the bioequivalence between Suprax® cefixime capsule 400 mg (test product) and Suprax® cefixime 400 mg tablet (reference product) under fasting conditions; to assess the food effect on the pharmacokinetics of cefixime capsule 400 mg (test product); and to monitor the safety of subjects.

Study Design:
The study was an open label, balanced, randomized, three-treatment, three-sequence, three-period, single-dose, crossover oral bioequivalence study in healthy adult male subjects under fasting and fed (the effect of food on the test product) conditions. The three treatments were as follows: treatment A was tablet administered under fasting conditions (the reference), treatment B was capsule administered under fasting conditions (the test), and treatment C was capsule administered under fed conditions (the test). Subjects were confined at the clinical facility from at least 11.00 hours prior to dosing to at least 24 hours post dose. Study medications were administered with 240 mL of water at

Reference ID: 3124453

ambient temperature. Subjects received treatment C 30 minutes following a high-fat, high-calorie breakfast. The wash out period was seven days. The following table shows the meal composition for treatment C.

Composition of Meal Used under fed condition (Treatment C)		
Composition	**Percent of total Kcal**	**Kcal**
Fat	52.62	526.05
Carbohydrate	27.10	270.92
Protein	20.29	202.84
Total	**100.01**	**999.67**

Reviewer Comment: The composition of the meal used in this study is similar to the meal recommended in the Food-Effect guidance.

Study Population:
Thirty-one of the thirty-six male subjects enrolled in this study completed the study. Two subjects were withdrawn from the study due to fever before drug administration. Two subjects did not report to the facility for period two. And one subject tested positive for blood alcohol at period two. The following table contains subjects' demographics.

Demographic details of subjects who dosed in the study (N=36)					
Parameter	**Mean**	**SD**	**Min**	**Max**	**CV%**
Age (years)	25	4.9	18	37	19.60
Height (cm)	167	4.9	157	176	2.93
Weight (Kg)	60.4	6.33	51.2	74.5	10.48
BMI (Kg/m^2)	21.5	2.04	18.6	24.9	9.49
Demographic details of subjects who completed the study (N=31) and included for Statistical analysis					
Age (years)	25	4.9	18	37	19.60
Height (cm)	168	5.2	157	176	3.10
Weight (Kg)	60.0	6.39	51.2	74.5	10.65
BMI (Kg/m^2)	21.4	1.94	18.6	24.9	9.07

Sample Collection for Pharmacokinetic Measurements:
Blood samples (5 mL each) were collected at the following specified times during each Period for the determination of concentrations of cefixime in plasma: prior to dosing (zero hour) and at 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 8.0, 10.0, 12.0, 14.0, and 24 hours post dosing.

Reference ID: 3124453

Bioanalytical Assay Performance:
A validated UPLC/MS/MS bioanalytical method was used for determination of cefixime concentrations in human plasma. The summary of bioanalytical assay performance during analysis of study samples is shown in the following table.

Parameters	Cefixime		
Range (ng/mL)		(b) (4)	
	Low	Mid	High
Nominal Conc. (ng/mL)	296.73	3260.79	6393.71
QC Conc. (ng/mL)	301.62	3230.63	6048.69
Precision (%)	13.26	10.26	10.30
Accuracy (%)	101.65	99.08	94.60

Pharmacokinetic and Statistical Analysis:
WinNonlin version 5.2 was used for determination of pharmacokinetic parameters values for cefixime. SAS® software for Windows release 9.1.3 was used for the statistical analysis of this bioequivalence study. The GLM procedure with model being the sequence, subject within the sequence, period, and treatment was used for the analysis. The values for pharmacokinetic parameters are shown in the following three tables.

Descriptive Statistics of Pharmacokinetic Parameters of Cefixime for Reference Product (A) administered under fasting conditions

PK parameter (Units)	N	Mean	SD	Min	Median	Max	CV%	Geometric Mean
t_{max} (hr)	31	4.79	1.283	3.00	4.50	10.00	26.78	4.65
C_{max} (ng/mL)	31	5447.794	1227.3454	3131.480	5544.770	7885.790	22.53	5311.233
AUC_{0-t} (ng*hr/mL)	31	47120.631	15465.8542	21184.880	46825.990	87474.008	32.82	44686.107
†$AUC_{0-\infty}$ (ng*hr/mL)	30	48999.850	16177.9973	23066.148	49653.126	93372.826	33.02	46519.403
†K_{el} (hr^{-1})	30	0.189	0.0275	0.134	0.185	0.250	14.59	0.187
†$t_{½}$ (hr)	30	3.75	0.554	2.77	3.75	5.16	14.77	3.71
†$AUC_{\_\%Extrap\_obs}$ (%)	30	3.365	2.4426	1.227	2.456	9.736	72.60	2.751

Descriptive Statistics of Pharmacokinetic Parameters of Cefixime for Test Product (B) administered under fasting conditions

PK parameter (Units)	N	Mean	SD	Min	Median	Max	CV%	Geometric Mean
t_{max} (hr)	31	5.06	0.955	3.50	5.00	8.00	18.86	4.98
C_{max} (ng/mL)	31	4882.104	1460.9179	2224.690	4908.690	7886.180	29.92	4659.696
AUC_{0-t} (ng*hr/mL)	31	43071.173	17249.1306	16797.733	44042.493	94144.150	40.05	39690.005
†$AUC_{0-\infty}$ (ng*hr/mL)	30	45331.911	17622.9713	19094.141	44843.184	99274.543	38.88	42011.173
†K_{el} (hr^{-1})	30	0.198	0.0392	0.139	0.192	0.309	19.77	0.195
†$t_{½}$ (hr)	30	3.61	0.631	2.24	3.61	4.98	17.47	3.56
†$AUC_{\_\%Extrap\_obs}$ (%)	30	4.257	3.9750	0.996	2.781	18.614	93.37	3.165

Descriptive Statistics of Pharmacokinetic Parameters of Cefixime for Test formulation (C) - Administered under fed conditions

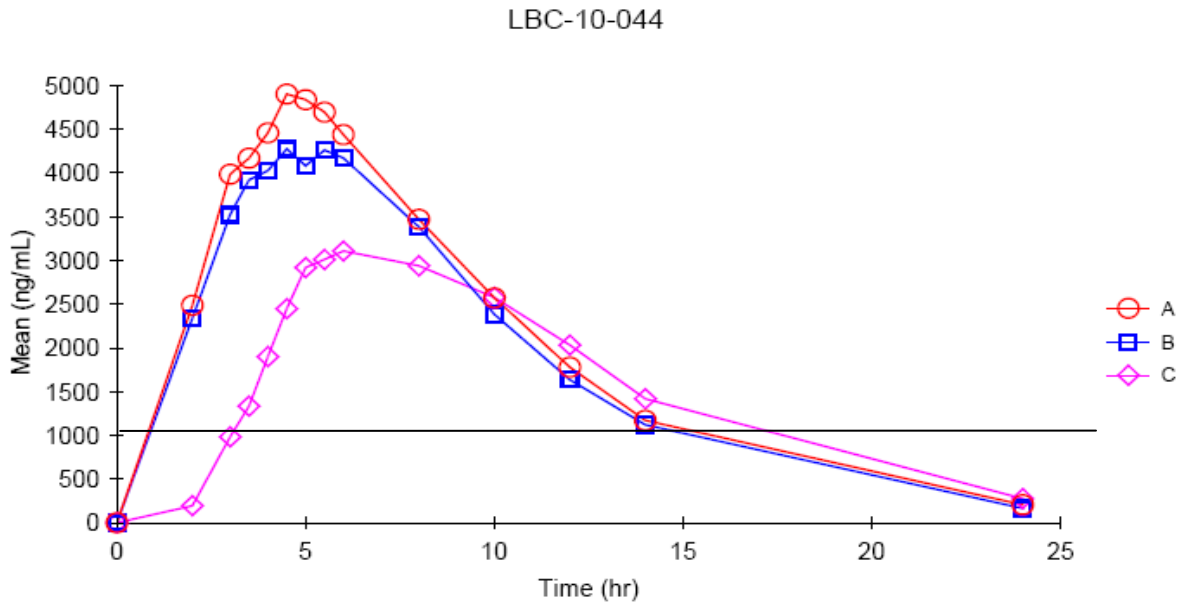
PK parameter (Units)	N	Mean	SD	Min	Median	Max	CV%	Geometric Mean
t_{max} (hr)	31	6.45	1.881	4.50	6.00	12.00	29.16	6.23
C_{max} (ng/mL)	31	3563.075	1072.1934	1910.200	3475.870	6696.570	30.09	3414.857
AUC_{0-t} (ng*hr/mL)	31	35337.677	13595.7402	13740.328	36380.930	78877.183	38.47	32978.819
†$AUC_{0-\infty}$ (ng*hr/mL)	30	38128.183	14369.7893	18024.870	37720.795	87978.412	37.69	35880.056
†K_{el} (hr^{-1})	30	0.178	0.0410	0.114	0.177	0.312	23.02	0.174
†$t_{½}$ (hr)	30	4.08	0.877	2.22	3.91	6.10	21.50	3.99
†$AUC_{\_\%Extrap\_obs}$ (%)	30	5.316	3.0325	1.846	4.224	11.810	57.04	4.579

† For subject no. 24, value of $AUC_{\_\%Extrap\_obs}$ found to be more than 20%, hence excluded

N-Number of Observations

Reference ID: 3124453

The following figure shows the area under the mean plasma concentration as a function of time for the three treatments.



A – Tablet B – Capsule under fasting conditions C – Capsule under fed conditions

Line represents microbiological breakpoint of 1 µg/mL.

The statistical analysis for bioequivalence i.e. geometric least squares mean, the point estimates (ratio of test vs. the reference expressed as percent), and 90% confidence intervals are shown in the following two tables.

Geometric least squares means, ratios, and 90% CI for cefixime (treatment B vs A)

PK Parameter	N	Geometric Least Square Means		B/A Ratio (%)	90% Confidence Interval	
		Capsule (B)	Tablet (A)		LCL	UCL
C_{max} (ng/mL)	31	4652.87	5279.78	88.13	82.31	94.36
AUC_{0-t} (ng*h/mL)	31	39656.23	4446.93	89.19	82.28	96.68
$AUC_{0-\infty}$ (ng*h/mL)	30	41853.81	46292.47	90.41	83.85	97.48

Geometric least squares means, ratios, and 90% CI for capsule (treatment C vs B)

PK Parameter	N	Geometric Least Square Means		C/B Ratio (%)	90% Confidence Interval	
		Fed (C)	Fasting (B)		LCL	UCL
C_{max} (ng/mL)	31	3427.32	4652.87	73.66	68.79	78.88
AUC_{0-t} (ng*h/mL)	31	33099.76	39656.23	83.47	76.98	90.49
$AUC_{0-\infty}$ (ng*h/mL)	30	35978.14	41853.81	85.96	78.85	91.55

The 90% confidence limits for cefixime are within 80% - 125% for AUC and C_{max} under fasting conditions indicating that cefixime capsule by Lupin Inc. is bioequivalent to Suprax® tablet. There is approximately 15% reduction in exposure based on AUC and 25% based on C_{max} when Suprax® capsule was administered with food. There is an increase in time to maximum concentration (T_{max}) from 5.06 hours to 6.45 hours, approximately 27% increase.

Reference ID: 3124453

The following information request was sent to the sponsor on March 6, 2012:
Cefixime capsule is bioequivalent to Suprax® tablet and provides similar exposure as the Suprax® tablet under fasting conditions. However, the capsule formulation is not bioequivalent to the tablet when administered with food; there is approximately a 15% reduction in exposure based on AUC and 25% reduction based on C_{max}. The impact of this reduction in exposure on efficacy when the capsule is given with food is unknown. Administration of the capsule without regards to food is proposed, however, a justification for this proposal to administer the capsule without regards to food was not provided. Please provide a justification for the proposal to administer the capsule without regard to food.

The following response from the sponsor was received on April 20, 2012:
We would like to bring to agency's kind notice that, according to the insert labeling of Suprax® Cefixime Tablets USP, 400 mg, a single 400 mg tablet under fasted conditions produces an average peak concentration of approximately 3.7 mcg/mL (range 1.3 to 7.7 mcg/mL). The C_{max} of the 400 mg capsule under fed conditions was 3.6 mcg/mL (range 1.9 to 6.7 mcg/mL) [as per study report LBC-10-044, page 15]. The C_{max} and range of the capsules under fed conditions are therefore similar to the reported values in the Suprax labeling under fasted conditions and therefore within the clinical therapeutic range. Hence, administration of the capsule without regard to food is proposed.

Reviewer Comment: The cross-study comparison of Cmax as proposed by the sponsor is not an ideal approach for establishing bioequivalence as the sponsor is suggesting. As the results of study LBC-10-044 show the Cmax for capsule under fasting and fed conditions are 4.9 µg and 3.6 µg respectively which is a much better estimate as it is derived from one study population receiving the same treatment under two different conditions.

Time Above MIC:
The sponsor did not provide any pharmacodynamic assessment for time above MIC in support of administration of capsule without regards to food. Therefore, the clinical pharmacology reviewer attempted to address the question as to whether differences in overall exposure affect the time above MIC (T>MIC), the PK/PD parameter associated with efficacy for Suprax®. The reviewer calculated approximate estimates for T> MIC for each subject and treatment in Study LBC-10-044. A statistical comparison of T>MIC for subjects receiving cefixime capsule 400 mg under fasted and fed conditions is presented in the following table. The results show similar estimated T>MIC values following the two modes of administration. Thus, it is recommended the capsule be administered without regard to food intake.

T-test comparing the % time above MIC following administration of capsule under the fasting and fed conditions

Fasted				With Food		
Subject	T>MIC (h)	%T>MIC		Subject	T>MIC (h)	%T>MIC
1	(b) (4)			1		(b) (4)
2				2		
5				5		
6				6		
7				7		
8				8		
10				10		
11				11		
12				12		
13				13		
14				14		
15				15		
16				16		
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27				27		
28				28		
29				29		
30				30		
31				31		
32				32		
34				34		
35				35		
Mean		42.88				41.80
SD		9.01				9.80
Min		25.00				25.00
Max		50.00				83.33
T-test:	p-Value = 0.5732		Not Significant			

Safety and Tolerability:
There were four moderate and five mild adverse events reported during the study. There were no serious adverse events. The test and reference products were tolerated well by the study subjects.

Reference ID: 3124453

Protocol Deviations:
Several delays were noted in blood sampling in all treatment periods. These deviations ranged from 0.2% to 5% from the protocol. These protocol deviations do not impact the overall interpretation of study results.

Conclusion:
The 90% confidence limits for cefixime are within 80% - 125% for AUC and C_{max} under fasting conditions indicating that cefixime capsule by Lupin Pharmaceuticals Inc. is bioequivalent to Suprax® tablet. Suprax® capsule provides similar exposure as the Suprax® tablet under fasting conditions. There is approximately a 15% reduction in exposure based on AUC and 25% reduction based on C_{max} when Suprax® capsule is administered with food. Although the applicant did not provide sufficient information in the application to support the administration of Suprax® capsule without regard to food, the results of the analysis of percent time above MIC by this reviewer supports the administration of capsule without regards to food.

OSI inspection:
The memorandum from OSI dated April 9, 2012 indicates that the review of EIR from the clinical and analytical sites of study LBC-10-044 concluded that the data from this study are acceptable for the Agency's review.

Clinical Center:
Lupin Bioresearch Center,
(b) (4)
Survey No. 146/2/1B,
Pashan, pune-411021 India

Analytical site:
Bioanalytical Research Department,
Lupin Bioresearch Center,
(b) (4)
Survey No. 146/2/1B,
Pashan, pune-411021 India

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/s/

ASSADOLLAH NOORY
05/01/2012

KIMBERLY L BERGMAN
05/01/2012

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	203-195/N-000
Submission Date:	06/28/11 and 02/08/12
Brand Name:	Suprax
Generic Name:	Cefixime
Formulation:	Immediate release (IR) capsule
Strength:	400 mg (one strength)
Applicant:	Lupin
Type of submission:	505(b)(2) NDA
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Lederle's Suprax (Cefixime) IR 400 mg tablet was approved under NDA 050-621 on 04/28/89, but later its marketing was discontinued. Lupin's Suprax (Cefixime) 400 mg IR tablet under NDA 065-130 is the reference listed drug (RLD) now. Suprax 400 mg IR tablet is indicated for uncomplicated urinary tract infections, pharyngitis and tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis, and uncomplicated gonorrhea (cervical/urethral).

CURRENT SUBMISSION

On 06/28/11, Lupin submitted 505(b)(2) NDA 203-195 for Suprax (Cefixime) IR (b) (4) 400 mg capsules, but the review clock did not start until 08/01/11, when the user fee was paid. In support of the 505(b)(2) application, Lupin submitted one bioequivalence (BE) study (No. LBC10044) comparing Suprax 400 mg IR capsule with the RLD, Suprax 400 mg IR tablet. Currently, Lupin is seeking approval for Suprax 400 mg capsule strength only.

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution development report, the proposed dissolution method (submitted on 06/28/11), and the revised dissolution acceptance criterion (dated 02/08/12) for Suprax 400 mg IR capsule supporting the approval of this NDA.

Reference ID: 3096818

RECOMMENDATION

The proposed dissolution method and the revised dissolution criterion as shown below are acceptable.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Dissolution Medium	Acceptance Criterion
Type I (Basket)	100 rpm	900mL	37°C ± 0.5°C	0.05 M phosphate buffer, pH 7.2	Q = (b)(4)% at 45 min

From the Biopharmaceutics perspective, 505(b)(2) NDA for Suprax (Cefixime) IR 400 mg capsules is recommended for approval.

Tien-Mien Chen, Ph.D.
ONDQA Biopharmaceutics Reviewer

03/02/11
Date

Angelica Dorantes, Ph.D.
ONDQA Biopharmaceutics Team Leader

03/02/11
Date

CC: *DARRTS/NDA 203-195*

Reference ID: 3096818

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Cefixime is a semi-synthetic, cephalosporin antibiotic for oral administration. Lederle's Suprax (Cefixime) 400 mg IR tablet was approved under NDA050-621 on 04/28/89, but later it was discontinued for the market. Lupin's Suprax (Cefixime) 400 mg IR tablet approved under NDA 065-130 is the RLD now. Monograph for cefixime drug substance as well as that of the Tablet is available in USP. Suprax 400 mg IR tablet is indicated for uncomplicated urinary tract infections, pharyngitis and tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis, and uncomplicated gonorrhea (cervical/urethral).

CURRENT SUBMISSION

On 06/28/11, Lupin submitted 505(b)(2) NDA 203-195 for Suprax (Cefixime) (b) (4) 400 mg IR capsules, but the review clock did not start until 08/01/11, when the user fee was paid. In support of the 505(b)(2) application, Lupin submitted only one bioequivalence (BE) study (No. LBC10044) comparing Suprax 400 mg IR capsule with the RLD, Suprax 400 mg IR tablet. However, Lupin is currently seeking approval for Suprax 400 mg IR capsule strength only.

The above BE study report is under review by the Office of Clinical Pharmacology. The information on the manufacturing of Suprax 400 mg IR capsule is under review by the ONDQA CMC Reviewer.

BIOPHARMACEUTICS REVIEW

The ONDQA-Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution development report, the proposed dissolution method, and the revised dissolution acceptance criterion for the new dosage form, Suprax (Cefixime) 400 mg IR capsules.

FORMULATION COMPARISONS

The proposed description and composition of Lupin's Suprax 400 mg IR capsule is shown below.

Table 1. Description and Composition of Suprax 400 mg IR Capsules

Ingredients	Quantity mg/ Capsule	Quantity % w/w	Category	Reference to Standards
[redacted]				(b) (4)
Active Ingredient				
Cefixime** equivalent to cefixime anhydrous	400.00	56.34	Active	USP
Other Ingredients				
Mannitol [redacted]	[redacted]	[redacted]	[redacted]	USP
Crospovidone [redacted]				NF
Low Substituted Hydroxy Propyl Cellulose [redacted]				NF
Colloidal Silicon Dioxide [redacted]				NF
Magnesium Stearate [redacted]				NF
[redacted]				
Colloidal Silicon Dioxide [redacted]				NF
Magnesium Stearate [redacted]				NF
Theoretical Fill Weight				--
CAPSULE FILLING				
Size "00EL" capsules with dark brown cap and dark brown body imprinted with "LU" on cap and "U43" on body in white ink				IH

IH – In House

DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

The initially proposed dissolution method and dissolution acceptance criteria are summarized below:

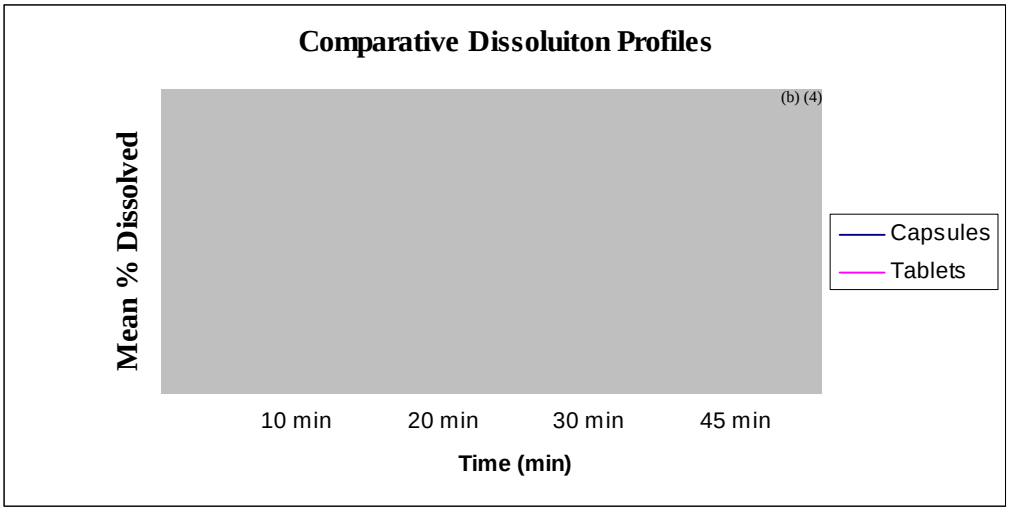
Apparatus: **USP Type I (Basket) with 100 RPM**
Medium: **0.05 M Phosphate buffer, pH 7.2,**
Volume: **900 mL,**
Temperature: **37°C ± 0.5°C**
Sampling Points: **10, 20, 30, and 45 minutes**
Acceptance Criterion: **Q = [redacted] % at 45 minutes**

Mean comparative dissolution data and profiles between the tablet and capsule biobatches are shown below.

Table 2. Mean Comparative Dissolution Data between Suprax IR Tablet and Capsule 400 mg Biobatches (n=12 articles/batch)

Dissolution Time	10 Min	20 Min	30 Min	45 Min
Capsule Batch No. MCB9001A	(b) (4)			
Tablet Batch No. MTD8011B				

Figure 1. Mean Comparative Dissolution Profiles Between Suprax IR Tablet and IR Capsule 400 mg Biobatches (n=12 articles/batch)



Additional long-term stability dissolution data are also provided below.

Table 3. Mean Long-Term Stability Data for Suprax 400 mg IR Capsule Primary Batches (Under 25 ± 2ºC & 60 ± 5% RH)

Batch No.	Initial (Month Zero)	3 Months	6 Months	9 Months	12 Months	18 Months
MCB9001A*	(b) (4)					
MCB9002A						
MCB9003A						

*. Biobatch: MCB9001A (size: (b) (4) capsules) used in the BE Study LBC-10-044.

The revision/modification to the capsule IR formulation was tailoring the BE study results during the formulation development. The proposed dissolution method for Suprax 400 mg capsule IR formulation using USP Apparatus 1 (Basket) with a speed of 100 rpm is found acceptable. The proposed dissolution acceptance criterion, of Q= (b) (4) % at 45 min; however, needed to be (b) (4) of cefixime dissolved at 45 min (Tables 2 and 3).

On 01/31/12, a Biopharmaceutics information request was sent to the Applicant asking to (b) (4) the acceptance criterion to Q= (b) (4) % at 45 min. The applicant responded on 02/08/11 and counter proposed Q= (b) (4) % at 45 min. After a thorough review, it was determined that the applicant's newly proposed dissolution acceptance criterion, Q= (b) (4) % at 45 min, for the Suprax 400 mg IR capsule was acceptable.

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Reference ID: 3096818

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/s/

TIEN MIEN CHEN
03/05/2012

ANGELICA DORANTES
03/05/2012

CLINICAL Pharmacology: 45-Day Meeting Checklist
505(b)(2) application
NDA 203195
Sponsor: Lupin Ltd.
Drug: SUPRAX® Cefixime Tablets USP (400mg)
Letter Date: June 28, 2011
PDUFA Goal Date: June 1, 2012

On **initial** review of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?			x	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?			x	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and			x	

	undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?				
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Assadollah Noory, Ph. D.

Reviewing Clinical Pharmacologist Date: 9/12/11

Dakshina Chilukuri, Ph. D.

Team Leader Date:

Reference ID: 3013878

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/s/

ASSADOLLAH NOORY
09/12/2011

DAKSHINA M CHILUKURI
09/14/2011