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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

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Date	April 24, 2012
From	Kimberly L. Bergman, Pharm.D.
Subject	Cross Discipline Team Leader Review
NDA #	203-195
Applicant	Lupin Pharmaceuticals, Inc.
Date of Submission	June 28, 2011
PDUFA Goal Date	June 1, 2012
Proprietary Name / Established (USAN) names	SUPRAX® (Cefixime)
Dosage forms / Strength	Cefixime capsules, 400 mg
Proposed Indication(s)	For the treatment of uncomplicated urinary tract infections; pharyngitis and tonsillitis; acute bronchitis and acute exacerbations of chronic bronchitis; uncomplicated gonorrhea (cervical/urethral)
Recommended:	Approval

1. Introduction

Lupin Pharmaceuticals, Inc. submitted the 505(b)(2) application for SUPRAX® Cefixime Capsules USP, 400 mg. The reference listed drug (RLD) to support the safety and efficacy of the product is SUPRAX® Cefixime Tablets USP, 400 mg, approved in 2004 under ANDA #A065130 from the same applicant. Cefixime has been previously approved for oral administration in four tablet strengths (100, 150, 200 and 400 mg) and two suspension concentrations (200 mg/5mL and 100 mg/5 mL).

In support of this 505(b)(2) application, the Applicant conducted a bioavailability/bioequivalence (BA/BE) study (Study LBC-10-044) to bridge the proposed formulation with the RLD. Study LBC-10-044 was an open label, balanced, randomized, single-dose, three-treatment, three-sequence, three-period crossover oral study to assess the bioequivalence of cefixime capsules 400 mg with respect to cefixime 400 mg tablets, under fasting conditions and food effect study of cefixime capsules 400 mg under fasting and fed conditions in healthy, adult, subjects.

This CDTL review summarizes the findings of the various discipline reviews.

2. Background

Cefixime is a semi-synthetic, cephalosporin antibiotic for oral administration and is an active ingredient in previously FDA-approved products with extensive marketing history. 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. Cefixime products are indicated in the treatment of the following infections when caused by susceptible strains of designated microorganisms: uncomplicated urinary tract infections; otitis media; pharyngitis and tonsillitis; acute bronchitis and acute exacerbations of chronic bronchitis; and uncomplicated gonorrhea (cervical/urethral).

Cefixime has been marketed in the U.S. for many years, initially by Lederle Laboratories. The original NDAs for SUPRAX® (oral tablet) (NDA 50-621) and SUPRAX® (cefixime for oral suspension) (NDA 50-622) were both approved on April 28, 1989. The NDA for SUPRAX® Cefixime for Oral Suspension, USP, 200 mg/5 mL (NDA 65-355) was approved on April 10, 2007. Cefixime is currently manufactured by Lupin Limited worldwide. Lupin Limited has marketed SUPRAX® since the approval of SUPRAX® Cefixime Tablets USP, 400 mg on February 12, 2004 (ANDA# A065130). Subsequently, Lupin received approval for SUPRAX® Cefixime for Oral Suspension USP, 100 mg/5 mL, (approved on February 23, 2004; ANDA# A065129), and

SUPRAX® Cefixime for Oral Suspension USP, 200 mg/5 mL (approved on April 10, 2007; ANDA# A065355). Lupin is utilizing the 505(b)(2) pathway for the SUPRAX® Cefixime Capsules USP, 400 mg because the proposed formulation of cefixime is a new formulation for a previously approved product and the applicant is relying on (1) one BA/BE study conducted by Lupin, (2) FDA's previous findings of safety and efficacy for the RLD, and (3) safety and efficacy data from the published literature for cefixime. The RLD to support the safety and efficacy of the proposed product is SUPRAX® Cefixime Tablets USP, 400 mg. The proposed dose schedule for Lupin's cefixime 400 mg capsules for adults is the same as SUPRAX® tablets (400 mg daily).

3. CMC/Device

Drug Substance

The drug substance Cefixime USP manufactured by Lupin Limited, Madhya Pradesh, India is supported by DMF 15996 (currently held by the applicant). The DMF is current and adequate.

Drug Product

SUPRAX® (cefixime) Capsules, 400 mg are size "00EL" capsules with dark brown cap and dark brown body imprinted with "LU" on cap and "U43" on body in white ink containing white to yellowish white granular powder. All of the excipients in the new formulation are of USP/NF grade and can be found using FDA's Inactive Ingredients Guide (IIG) Search for approved drug products at the same or higher amounts than the proposed drug product. The capsule shells meet acceptance specifications. The drug product will be manufactured by Lupin Limited, Madhya Pradesh, India. A (b)(4) method is selected due to the (b)(4) property of the drug substance. The drug product specifications include description, identification, water content, dissolution, uniformity of dosage units, degradation products and assay, and microbial limits. The acceptance criteria are comparable to those of other FDA- approved cefixime formulations manufactured by the same applicant. The specifications have been (b)(4) according to FDA's recommendation during the NDA review and are deemed appropriate as revised.

Manufacturing and Stability

The manufacturing, testing and stability study of drug product i.e. SUPRAX® Cefixime Capsules, 400 mg is carried out in the Lupin Limited, Mandideep, India facility. (b)(4)

The stability studies of the exhibit batches of drug product, Cefixime Capsules, 400 mg are conducted at 25°C /60% RH and 40°C /75% RH for the long term and accelerated storage conditions, respectively. The exhibit batches were packaged in two container closure systems which are the same as those proposed for the commercial product. At the time of the NDA submission, the applicant provided 18 months data from the long term storage conditions and 6 months data from the accelerated storage conditions. All test results submitted, up to 18 month data, met the acceptance criteria. There are no out of specification results and no apparent trends in the stability data. Based on the stability data available (accelerated and long term conditions), the applicant proposed an expiration-dating period of 24 months for SUPRAX® Cefixime Capsules, 400 mg, and a storage

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condition: “Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].” Based on the CMC reviewer evaluation, comparing to the intended commercial batch size of (b) (4) capsules/batch, the stability batch size of (b) (4) capsules/batch is acceptable. The applicant’s stability protocol is in compliance with ICH guidelines. The proposed impurity limits are well within the limits which were approved in ANDA 65-130/S-001 (Cefixime Tablets USP, 400 mg) by the Office of Generic Drugs (OGD) on August 31, 2007. Based on the available stability data, the proposed shelf life and storage conditions are acceptable.

Biopharmaceutics Assessment

The Biopharmaceutics review 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 February 8, 2012) for SUPRAX® 400 mg IR capsule supporting the approval of this NDA. The initially proposed dissolution method and dissolution acceptance criteria are summarized as follows:

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 = (b) (4) % at 45 minutes

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. On January 31, 2012, an information request was sent to the applicant proposing a (b) (4) acceptance criterion (Q = (b) (4) % at 45 min). The applicant responded on February 8, 2012 and counter-proposed Q = (b) (4) % at 45 min. The Biopharmaceutics reviewer 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.

In summary, the CMC information as provided in the NDA is adequate to assure the identity, strength, purity, and quality of the drug product. In addition, an “Acceptable” site recommendation from the Office of Compliance has been made. Therefore, from the CMC perspective, this NDA is recommended for approval. As CDTL reviewer, I concur with this assessment. Refer to the CMC reviews by Drs. Zhou (dated April 17, 2012) and Chen (dated March 5, 2012) for further information.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology review focused on data from reproductive/developmental studies and its presentation in the proposed labeling. Proposed labeling is consistent with that of the RLD, however dose multiples for extrapolation from reproductive/developmental studies performed in rats and mice do not appear to be based on doses normalized for total body surface area (TBSA). According to the summary basis of approval for NDA 50-621, the highest dose used in segment II studies in mice and rats was 3200 mg/kg/day. That dose was stated to be not embryotoxic or teratogenic in both species. The NOAEL dose for effects on fertility was stated in the FDA review to be 1000 mg/kg/day in rats. The dose multiples in the proposed label appear to have been derived by dividing these nominal doses by a human dose of 8 mg/kg/day, arriving at dose multiples of 400 for developmental and reproductive toxicity studies and 125 for the fertility study.

The Nonclinical reviewer recommends that dose multiples for extrapolation from nonclinical studies to clinical doses should be updated to the current standard; i.e. based on doses normalized for TBSA. The NOAEL in segment II studies in mice and rats would be equivalent to human doses (HED) of 267 mg/kg and 533 mg/kg, respectively. For a 60 kg patient, the lower of those would be approximately 16,000 mg/day or 40 times the adult dose, not 400 times the dose as currently stated in the label. Similarly, the NOAEL dose for effects on fertility in rats would be equivalent to a human dose of 167 mg/kg/day, or 10,000 mg/day for a 60 kg patient. The dose multiple in this case would be 25, not 125 as currently stated in the label.

In summary, it is recommended that the proposed label, as well as the referenced label(s), be updated and the description of the nonclinical reproductive and developmental toxicity data be revised. As CDTL reviewer, I agree with this recommendation. This recommendation should be addressed in a future review cycle, as labeling will not be reviewed during the current cycle due to issuance of a Complete Response. Refer to the Nonclinical Pharmacology/Toxicology Memo to File by Dr. Nostrandt dated October 3, 2011 for further information.

5. Clinical Pharmacology

In support of this 505(b)(2) application, the applicant submitted one bioequivalence study assessing the performance of SUPRAX® cefixime 400 mg capsule (test) versus SUPRAX® cefixime 400 mg tablet (reference) and the effect of food on capsule bioavailability (Study LBC-10-044). The study was a randomized, open-label, balanced, analyst-blind, three-treatment, three-period, three-sequence, single-dose, crossover bioavailability/bioequivalence (BA/BE) in healthy adult subjects. The primary pharmacokinetic objectives of this study were to assess the bioequivalence between SUPRAX® cefixime capsule 400 mg and SUPRAX® cefixime 400 mg tablet under fasting conditions and to assess the food effect on the pharmacokinetics of cefixime capsule 400 mg. Statistical comparisons of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ for the capsule versus tablet formulations are summarized in Table 5.1. Statistical comparisons of C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$ for the capsule administered under fed and fasted conditions are summarized in Table 5.2. 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 versus the RLD tablet formulation. However, food reduces cefixime exposure by 15% based on AUC and 25% based on C_{max} following administration of the capsule formulation. To assess the potential clinical relevance of these differences in exposure, the Clinical Pharmacology Reviewer estimated time above MIC ($T > MIC$) values for each subject after receiving the cefixime capsule in both the fed and fasted states and compared the two treatments. A statistical comparison of $T > MIC$ for subjects receiving cefixime capsule 400 mg under fed and fasted conditions demonstrated similar estimated $T > MIC$ values following the two modes of administration (mean \pm SD: fed, $41.80 \pm 9.80\%$; fasted, $42.88 \pm 9.01\%$; $p = 0.5732$). Thus, it is recommended the capsule be administered without regard to food intake. The Clinical Pharmacology information provided by the applicant in the NDA submission was deemed acceptable by the Clinical Pharmacology Reviewer. As CDTL reviewer, I concur with this assessment. Refer to the Clinical Pharmacology review by A. Noory dated May 1, 2012 for further information.

Table 5.1 Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Comparison of Cefixime Exposure – Capsule Versus Tablet

Parameter	Capsule (mean \pm SD)	GLSM	Tablet (mean \pm SD)	GLSM	Point Estimate (90% CI)
C_{max} (ng/mL)	4882.10 \pm 1460.92	4652.87	5447.79 \pm 1227.35	5279.78	88.13 (82.31 – 94.36)
AUC_{0-t} (ng•h/mL)	43071.17 \pm 17249.13	39656.23	47120.63 \pm 15465.85	44462.93	89.19 (82.28 – 96.68)
$AUC_{0-\infty}$ (ng•h/mL)*	45331.91 \pm 17622.97	41853.81	48999.85 \pm 16178.00	46292.47	90.41 (83.85 – 97.48)

Table 5.2 Geometric Least Squares Mean, Ratios, and 90% Confidence Interval for Comparison of Cefixime Exposure – Capsule Fed Versus Capsule Fasted

Parameter	Fed (mean ± SD)	GLSM	Fasted (mean ± SD)	GLSM	Point Estimate (90% CI)
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-∞} (ng•h/mL)*	38128.18 ± 14369.79	35978.14	45331.91 ± 17622.97	41853.81	85.96 (78.85 - 91.55)

* N = 30

6. Clinical Microbiology

No new clinical microbiology data were submitted with this application. The Microbiology reviewer recommends that the microbiology section of the label be revised to reflect the current CLSI guidelines. As CDTL reviewer, I concur with this assessment. Refer to the proposed labeling recommendations in Section 12 and the Microbiology review by Dr. Goodwin dated April 16, 2012 for further information.

7. Clinical/Statistical- Efficacy

No new clinical efficacy data were submitted with this application. The applicant is relying on the previous findings of efficacy for the reference listed drug, SUPRAX®. The applicant included a review of published studies that contain both efficacy and safety data to support the application, which was the focus of the Clinical Reviewer’s review. Fourteen (14) studies were identified in the published literature demonstrating the efficacy of cefixime in different bacterial infections such as urinary tract infections (UTI), respiratory tract infections (RTI), and uncomplicated gonorrhea. Tabular summaries of these studies are presented Tables 7.1 through 7.3. In addition, the applicant submitted review articles and other supportive data from the literature (i.e. for indications such as acute otitis media).

Table 7.1 Summary of Clinical Efficacy Studies for Cefixime in Treatment of Urinary Tract Infection (UTI) from Published Literature

Author	Study Design	Study Population	Bacteria ^a	Treatment Groups
(Ho, 2001)	Randomized, prospective, open-label trial	45 patients with complicated UTI Age = 24 – 87 y Sex = 23 M/ 22 F	<i>E. coli</i> (> 80%)	Cefixime oral capsules 200 mg bid for 10 – 14 days (N = 22) Ceftibuten oral capsules 200 mg bid for 10 – 14 days (N = 23)
(Ludwig, 1998) ^b	Clinical Phase 4, open-label, multinational, nonrandomized trial	85 adults with UTI Age = NR Sex = NR	<i>E. coli</i> <i>K. pneumonia</i> <i>P. mirabilis</i>	Cefixime 400 mg qd orally for 3 – 7 days (N = 85)
(Raz, 1994)	Double-blind, randomized study	106 female patients with uncomplicated cystitis Age = 16 – 88 y Sex = All females	<i>E. coli</i> <i>K. pneumonia</i>	Cefixime 400 mg qd orally for 3 days (N = 54) Ofloxacin 200 mg bid orally for 3 days (N = 52)
(Asbach, 1991)	Placebo-controlled, prospective, randomized, double-blind clinical trial	80 female outpatients with acute cystitis Age = 18 – 35 y Sex = All females	<i>E. coli</i> <i>P. mirabilis</i>	Cefixime 400 mg single dose orally (N = 20) Cotrimoxazole 160/800 mg single dose orally (N = 20) Ofloxacin 200 mg single dose orally (N = 20) Placebo (N = 20)

^aMost commonly isolated bacteria from the UTI patients in the given study

^bThis study also had patients with RTI which had different bacteria profile and different treatment protocol (Table 2.7.3-6)

bid = twice a day; F = female; M = male; mo = months; NR = not reported; qd = once a day; y = years

Table 7.2 Summary of Clinical Efficacy Studies for Cefixime in Treatment of Respiratory Tract Infection (RTI) from Published Literature

Author	Study Design	Study Population	Bacteria*	Treatment Groups
(Lorenz, 1998)	Multicentre, double-blind, randomized clinical trial	222 patients with AECB 5-day group: Age = 56 ±14.3 y Sex = 53 M/ 55 F 10-day group: Age = 54 ±12.3 y Sex = 57 M/ 52 F	<i>H. influenzae</i> <i>S. aureus</i> <i>S. pneumoniae</i>	5 days group: Cefixime 400 mg qd for 5 days and placebo qd for a further 5 days (N = 108) 10 days group: Cefixime 400 mg qd for 10 days (N = 109)
(Salvareza, 1998)	Randomized open-label study	60 adults with CAP Age = 18 – 60 y Sex = 39 M/ 21 F	<i>S. pneumoniae</i> (43%)	Cefixime 400 mg qd for 8 – 10 days (N = 30) Roxithromycin 300 mg qd for 8 – 10 days (N = 30)
(Matthews, 1993)	Multicentre, non-comparative clinical trial	118 adult patients with acute sinusitis or acute exacerbation of chronic sinusitis Age = 20 – 83 y Sex = 53 M/ 65 F	<i>H. influenzae</i> α -hemolytic streptococci <i>S. pneumoniae</i>	Cefixime 400 mg tablet qd for 10 - 14 days (N = 106)
(Neu, 1993)	Multicentre, double-blind, randomized clinical trial	213 patients with LRTIs (bacterial pneumonia or AECB or asthmatic bronchitis) Age = All age groups Sex = 118 M/ 95 F	<i>H. influenzae</i> <i>M. catarrhalis</i> <i>S. pneumoniae</i>	Cefixime 400 mg qd orally for 7 – 14 days (N = 110) Clarithromycin 500 mg bid orally for 7 – 14 days (N = 103)
(Verghese, 1990)	Randomized study	86 patients with AECB Mean Age = 63 y Sex = All males	<i>H. influenzae</i> <i>B. catarrhalis</i> <i>S. pneumoniae</i>	Cefixime 400 mg qd orally for 14 days (N = 48) Cephalexin 250 mg qid orally for 14 days (N = 38)
(Kiani, 1988)	Two randomized, double-blind, 2-treatment, multicentre studies: 1 for LRTI and another for URTI	244 patients with LRTI and 316 patients with URTI Age = ≥13 y Sex = Both males and females	<u>LRTI patients:</u> <i>S. pneumoniae</i> <i>H. influenzae</i> <i>E. coli</i> <u>URTI patients:</u> Group A, β -hemolytic <i>Streptococcus</i> <i>H. influenzae</i>	<u>LRTI Study:</u> Cefixime 400 mg qd orally for 14 days (N = 122) or Amoxicillin 500 mg tid orally for 14 days (N = 122) <u>URTI Study:</u> Cefixime 400 mg qd orally for 10 days (N = 160) or Amoxicillin 250 mg tid orally for 10 days (N = 156)

*Most commonly isolated bacteria from the RTI patients in the given study

AECB = acute exacerbation of chronic bronchitis; bid = twice a day; CAP = community-acquired pneumonia; F = female; LRTI: lower respiratory tract infections; M = male; NR = not reported; qd = once a day; qid = 4 times a day; tid = 3 times a day; URTI: upper respiratory tract infections; y = years

Table 7.3 Summary of Clinical Efficacy Studies for Cefixime in Treatment of Uncomplicated Gonorrhea from Published Literature

Author	Study Design	Study Population	Bacteria	Treatment Groups
(Hook, III, 1997)	Randomized open-label study	351 male patients with uncomplicated gonorrhea Age = ≥16 y Sex = All males	<i>N. gonorrhoea</i>	Cefixime 400 mg single oral dose (N = 150) Grepafloxacin 400 mg single oral dose (N = 149)
(Miller, 1997)	Retrospective review of clinic records	102 pregnant woman with gonorrhea Age = 14 – 37 y Sex = All females	<i>N. gonorrhoea</i>	Cefixime 400 mg single oral dose (N = 102)
(Megran, 1990)	Randomized study	170 men with uncomplicated gonorrhea Age = ≥18 y Sex = All males	<i>N. gonorrhoea</i>	Cefixime 800 mg (four 200 mg capsules) single oral dose (N = 99) Amoxicillin 3.0 gm and probenecid 1 gm single oral dose (N = 47)

y = years

An overall summary of efficacy results from these studies from published literature is presented in Table 7.4.

Table 7.4 Overall Summary of Clinical Efficacy Findings for Cefixime from Published Literature

Indication	Dose Form	Study Designs	Number of Cefixime-treated Patients	Cefixime Dose Range	Efficacy Conclusions
Urinary Tract Infections (UTI)	Oral Tablets or Capsules or Suspension	Randomized, prospective; Clinical Phase 4, open-label, nonrandomized; Placebo-controlled, prospective, randomized, double-blind trials	244: children and adults; both males and females	8 mg/kg/day or 200 mg bid or 400 mg qd or 400 mg single dose	Clinical cure in 77.3% – 92% of cefixime-treated patients; Bacteriological cure in 63.6% – 83% of cefixime-treated patients
Respiratory Tract Infections (RTI)	Oral Tablets or Suspension	Double-blind randomized; Randomized open-label; Clinical Phase 4, open-label, nonrandomized trials	960: children and adults; both males and females	8 mg/kg qd or 200 mg bid or 400 mg qd	Clinical cure in 49% – 100% of cefixime-treated patients; Clinical cure or improvement in 90% – 100% of cefixime-treated patients; Bacteriological cure in 54% – 100% of cefixime-treated patients; Radiographic clearing or improvement in 66% – 70% of cefixime-treated patients
Uncomplicated Gonorrhea	Oral Tablets or Capsules	Randomized trials; Retrospective review of clinic records	351: ≥14 y; both males and females	400 mg single dose or 800 mg single dose	Clinical cure in 99% of cefixime-treated patients; Bacteriological cure in 95.2% – 99% of cefixime-treated patients

bid = twice a day; qd = once a day; y = years

According to the applicant’s analysis and conclusions from this literature review, in conjunction with previous findings of efficacy for the reference listed drug:

- Six clinical studies (244 patients receiving cefixime) from published literature showed that cefixime is effective in treating UTI;
- One clinical study discussed in the SBA (401 patients receiving cefixime) and seven clinical studies (960 patients receiving cefixime) from published literature showed that cefixime is effective in treating RTI; and
- Three clinical studies (351 patients receiving cefixime) from published literature showed that cefixime is effective in treating uncomplicated gonorrhea.

Based on the Clinical Reviewer’s assessment of the submitted literature reports, the information presented in the current submission is consistent with the previous findings of efficacy demonstrated for the RLD, SUPRAX®. As CDTL reviewer, I concur with this assessment. Additionally, the review division proposed removal of the acute bronchitis claim in the label, and the applicant agreed. The proposed indications for SUPRAX® cefixime

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capsules, 400 mg were based on FDA's previous findings of safety and efficacy for cefixime oral products. The labeled indications include uncomplicated urinary tract infections, otitis media, pharyngitis and tonsillitis, acute exacerbations of chronic bronchitis, and uncomplicated gonorrhea. The labeling for acute exacerbation of chronic bronchitis (AECB) also included a claim for treatment of acute bronchitis. As described in the literature, acute bronchitis is typically a viral infection, and there is no evidence that antibacterial treatment is efficacious for this condition. Therefore, the acute bronchitis claim has been removed. Refer to the Clinical review by Dr. Moledina dated May 10, 2012 for further information.

8. Safety

Clinical Safety Review

The applicant is relying on the previous findings of safety for the RLD, SUPRAX®, with supportive data from the aforementioned literature reports. The applicant included a review of published studies that contain both efficacy and safety data to support the application, which was the focus of the Clinical Safety review. Eleven studies from the published literature provide safety information for cefixime. Three other studies are referenced that provide information only on exposure of cefixime (no safety data reported). A review of the published literature for studies showing safety data for cefixime identified the following:

- Two randomized clinical studies evaluating cefixime for UTI
- Six clinical studies (4 randomized and 1 non-comparative) evaluating cefixime for RTI
- Three clinical studies (2 randomized and 1 retrospective review) evaluating cefixime for uncomplicated gonorrhea

The studies included a total of 1508 patients who were exposed to administration of cefixime; of which, 1203 participated in randomized clinical trials. Studies from the published literature included patients from 16 to 88 years of age. Patients presented with UTI, RTI, or gonorrhea at study entry. Overall, reports in the published literature demonstrate that the gastrointestinal events are the most common adverse events (AEs), which is consistent with the AE profile of the approved cefixime product. Some studies have reported few clinically significant adverse laboratory changes with cefixime treatments, which did not require remedial treatment or discontinuation of therapy. One death was reported in the published literature, in which a patient exposed to cefixime died during the study from an extended carcinoma of the gall bladder and sigma that was undiagnosed at study entry. The safety profile of cefixime was deemed acceptable by the Clinical Reviewer, as the adverse events are mild and self-limited and are consistent with the previous findings of safety. I concur with the Clinical Reviewer's assessment of safety. Refer to the Clinical review by Dr. Moledina dated May 10, 2012 for further information.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

No regulatory issues are outstanding for this application.

12. Labeling

The applicant has modified the approved labeling for the RLD SUPRAX® Cefixime Tablets USP, 400 mg to include the proposed capsule formulation, and the proposed label is in physician's labeling rule (PLR) format. Upon review, the Agency recommended a merged label to include the RLD SUPRAX® Cefixime tablets, the proposed SUPRAX® Cefixime Capsule and SUPRAX® Cefixime for oral suspension USP (200 mg/5mL and 100 mg/5 mL).

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I concur with the assessments made by the review team and recommend approval of this 505(b)(2) application.

- Risk Benefit Assessment

Cefixime is currently marketed by the applicant as SUPRAX® 400 mg tablets (ANDA #065130), SUPRAX® 200 mg/5 mL oral suspension (ANDA 065355), and SUPRAX® 100 mg/5 mL oral suspension (ANDA 065129) for the treatment of bacterial infections such as UTI, AOM, RTI, and uncomplicated gonorrhea. The adult dose is 400 mg cefixime daily (administered as a single dose or in two divided doses BID). The information presented in the current submission is consistent with the previous findings of efficacy and safety for the reference listed drug, SUPRAX®. The proposed capsule formulation met the bioequivalence criteria with respect to the rate and extent of absorption of cefixime versus the RLD tablet formulation, therefore the risk-benefit profile is expected to be similar to the RLD.

- Recommendation for Post-marketing Risk Management Activities

Not applicable.

- Recommendation for other Postmarketing Study Commitments

Not applicable.

- Recommended Comments to Applicant

Not applicable.

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05/10/2012