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APPLICATION NUMBER:

203195Orig1s000

PHARMACOLOGY REVIEW(S)

MEMO TO FILE: NDA 203-195

DATE: September 13, 2011

TO: File, NDA 203-195

FROM: Amy C. Nostrandt, D.V.M., Ph.D.
Pharmacologist, DAIP

THROUGH: Wendelyn J. Schmidt, Ph.D.
Pharmacology/Toxicology Supervisor, DAIP

RE: 505(b)(2) application for a new formulation of SUPRAX® Cefixime Capsules, 400 mg

The Applicant, Lupin Limited, has submitted a 505(b)(2) application for a new formulation of SUPRAX® Cefixime Capsules, 400 mg. They currently market the reference listed drug (RLD), SUPRAX® Cefixime Tablets USP, 400 mg (ANDA# A065130, held by LUPIN PHARMS).

The Formulation of the proposed new drug product is shown in the Sponsor's table below:

Ingredients	Quantity mg/ Capsule	Quantity % w/w	Category	Reference to Standards			
(b) (4)							
Active Ingredient							
Cefixime** equivalent to cefixime anhydrous	400.00	56.34	Active	USP			
Other Ingredients							
Mannitol (b) (4)	(b) (4)			USP			
Crospovidone (b) (4)				NF			
Low Substituted Hydroxy Propyl Cellulose (b) (4)				NF			
Colloidal Silicon Dioxide (b) (4)				NF			
Magnesium Stearate (b) (4)				NF			
(b) (4)							
Colloidal Silicon Dioxide (b) (4)				NF			
Magnesium Stearate (b) (4)				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

There do not appear to be any new excipients of toxicological concern. All of the excipients can be found using the FDA Inactive Ingredient Search for Approved Drug Products at the same or higher amounts than in the proposed drug product.

The proposed indication is for the treatment of: uncomplicated urinary tract infections; pharyngitis and tonsillitis; acute bronchitis and acute exacerbations of chronic bronchitis; uncomplicated gonorrhea (cervical/urethral), the same as for the RLD. The proposed dose is 400 mg/day for adults and 8/mg/kg/day for children, also the same as the RLD.

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 obtained by the Applicant via FOI and provided in a previous submission for NDA (b) (4), 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 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.

It is recommended that the proposed label, as well as the referenced label(s), should be updated. The description of the nonclinical reproductive and developmental toxicity data should be revised as follows:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies have been performed in mice and rats at doses up to 400 40 times the human dose and have revealed no evidence of harm to the fetus due to cefixime. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime studies in animals to evaluate carcinogenic potential have not been conducted. Cefixime did not cause point mutations in bacteria or mammalian cells, DNA damage,

or chromosome damage *in vitro* and did not exhibit clastogenic potential *in vivo* in the mouse micronucleus test. In rats, fertility and reproductive performance were not affected by cefixime at doses up to ~~425~~ 25 times the adult therapeutic dose.

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/s/

AMY C NOSTRANDT
10/03/2011

WENDELYN J SCHMIDT
10/03/2011

Comments? Not applicable. The formulation has been modified from a tablet to a capsule without any change to the amount of the active ingredient (400 mg).

- (6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57?

Comments? References to doses in rodent fertility and teratogenicity studies are in terms of multiples of human dose, but these appear to be based on nominal doses in animal studies, not on doses normalized for total body surface area.

- (7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor?

Comments? Not applicable

- (8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route?

Comments? Not applicable

- (9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?

Comments? Not applicable

- (10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics?

Comments? Not applicable

- (11) Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?

Comments? Not applicable; no new original animal study reports were submitted.

- (12) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not.

- (13) If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify:

- (14) Issues that should not be conveyed to the Sponsor:
None

Reviewing Pharmacology Officer

Pharmacology Supervisor

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/s/

AMY C NOSTRANDT
09/23/2011

WENDELYN J SCHMIDT
09/27/2011