CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202091Orig1s000

PHARMACOLOGY REVIEW(S)

MEMO TO FILE: NDA 202-091

DATE: April 21, 2011

TO: File, NDA 202-091

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

THROUGH: Wendelyn J. Schmidt, Ph.D.
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RE: 505(b)(2) application for a new formulation of SUPRAX Cefixime for Oral Suspension

The Applicant, Lupin Limited, has submitted a 505(b)(2) application for a new formulation of SUPRAX Cefixime for Oral Suspension. They currently market the reference listed drug (RLD), SUPRAX Cefixime for Oral Suspension, 200 mg/5 mL. The proposed new drug product will contain 100 mg/mL of the active ingredient. The only difference in the formulation, other than the concentration of the drug substance, will be the use of sucralose as a sweetener, (b) (4)

The proposed indication is for the treatment of: uncomplicated urinary tract infections; otitis media; pharyngitis and tonsillitis; (b) (4) 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 the submission, the highest dose used in segment II studies in mice and rats was 3200 mg/kg/day. That dose was stated to be not embrytoxic 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 fertlity 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 approximately16,000 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 (b) (4) 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 (b) (4) 25 times the adult therapeutic dose.

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/s/

AMY C NOSTRANDT
04/27/2011

WENDELYN J SCHMIDT
04/29/2011