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APPLICATION NUMBER:

202091Orig1s000

OTHER ACTION LETTERS



NDA 202091

COMPLETE RESPONSE

Lupin Pharmaceuticals, Inc.
Attention: Leslie Sands, US Agent
Director, Regulatory Affairs
Harborplace Tower
111 South Calvert Street, 21st Floor
Baltimore, MD 21202

Dear Ms. Sands:

Please refer to your New Drug Application (NDA) dated October 25, 2010, received October 27, 2010, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for SUPRAX Cefixime for Oral Suspension, 100 mg/mL.

We acknowledge receipt of your amendments dated February 10, May 20, May 23, and June 14, 2011.

Your amendment dated May 20, 2011, containing [REDACTED] ^{(b) (4)}, was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. The introduction of the proposed suspension with overlapping numeric strength (100 mg/mL) to a suspension currently marketed (100 mg/5 mL) increases the potential for dosing errors. There may be underdosing (or overdosing) if the 100 mg/mL concentration is confused with the 100 mg/5 mL concentration in the prescribing and dispensing of the product, which poses safety and efficacy concerns. In order to resolve this deficiency, the following measures should be addressed:
 - a. Revise the concentration to read 500 mg/5 mL. This will help to highlight the fact that the 100 mg/mL concentration is more concentrated than the currently marketed concentrations of 100 mg/5 mL or 200 mg/5 mL.
 - b. Revise the container labels and carton labeling so that the labels, labeling, and packaging of this new strength will be visually different from the currently marketed concentrations.

- c. Conduct Human Factors testing to validate that differentiation of the strength and the use of other label enhancements are effective in minimizing the risk of confusion between the Suprax 100 mg/mL concentration and the currently marketed Suprax 100 mg/5 mL and 200 mg/5 mL concentrations.

2. The proposed delivery device

(b) (4)

(b) (4)

PRODUCT QUALITY

The following are requests for information that also need to be addressed:

1. Provide target fill weight with ranges for the powder fill of each configuration of your product.
2. Indicate how the average fill weights are determined (how many units used for determination, frequency of sampling, etc.).
3. Clarify if there is overfill in your product. If so, specify the amount for each configuration.

4. Provide the total volume of the suspension after reconstitution for each configuration of your product at the target maximum and minimum fill weights, respectively. Provide the fill volumes at the target, maximum and minimum fill weights.
5. Clarify the regulatory acceptance criterion (NMT (b)(4) or NMT (b)(4)) for moisture analysis by (b)(4) method for your product.
6. Provide more information on the potential reactivity of sodium benzoate with components in the product.
7. The following changes to your drug product specification are recommended:
 - i. A single acceptance criterion for drug product release and stability.
 - ii. Based on the review of your stability data, the acceptance criterion for total impurity should be tightened from NMT (b)(4)% to NMT (b)(4)%. The acceptance criterion for the cefixime assay should be revised from (b)(4).
 - iii. The upper limit of 120% in the USP is not currently justified based on manufacturing and stability considerations provided for this product.
 - iv. The acceptance criterion for sodium benzoate should be revised from NLT (b)(4) mg/mL to NLT (b)(4) mg/mL based on data from your stability batches.
 - v. Provide an updated specification for your drug product in the NDA reflecting all revisions.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

REGULATORY

A 505(b)(2) application contains “full reports of investigations” of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use. Reliance on an approved ANDA is not acceptable to support your proposed 505(b)(2) application. You need to identify the NDA that was the basis for submission for the ANDA you have incorrectly cited as the listed drug relied upon to support your proposed 505(b)(2) application. You must also provide a patent certification or statement with respect to each patent listed in FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65.

You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Katherine Laessig, M.D.
Deputy Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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

/s/

KATHERINE A LAESSIG
08/26/2011