DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-378

Forest Laboratories, Inc.
Harborside Financial Center
Plaza III, Suite 602
Jersey City, NJ 07311

Attention: Michael K. Olchaskey, PharmD, RAC
Associate Director, Regulatory Affairs

Dear Dr. Olchaskey:

Please refer to your new drug application (NDA) dated December 19, 2001, received December 20, 2001, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Combunox™ (Oxycodone HCl and Ibuprofen) Tablets, 5mg/400 mg.

We acknowledge receipt of your submissions dated January 10 and 24, February 8, April 30, July 31, August 7, 9 and 30, September 4, and October 23, 2002, February 13 and 14, March 25, May 21, and September 18, 2003, and May 25, June 2 and 7, July 13, August 4, September 21, and November 2 (2), 23 (2) and 24 (2), 2004.

The May 25, 2004, submission constituted a complete response to our October 18, 2002, action letter.

This new drug application provides for the use of Combunox™ (Oxycodone HCl and Ibuprofen) Tablets, 5mg/400 mg for the short term (no more than 7 days) management of acute, moderate to severe pain.

We have completed our review of this application, as amended and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert), and the immediate container and carton labels submitted November 26, 2004. These revisions are terms of the NDA approval. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-378**." Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages 0 to 2 years and deferring pediatric studies for ages 2 to 17 years for this application.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study under PREA for the treatment of acute moderate to severe pain in pediatric patients ages 12 to 17.

   Final Report Submission: November 31, 2007

2. Deferred pediatric study under PREA for the treatment of acute moderate to severe pain in pediatric patients ages 2 to 12.

   Final Report Submission: November 31, 2009.

Submit final study reports to this NDA. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments**".

We remind you of your postmarketing study commitments in your submission dated November 23, 2004. These commitments are listed below.

3. Conduct a Fertility and Early Embryonic Development (Segment I) study in a single species. Please refer to ICH S5A Guideline "Detection of Toxicity to Reproduction for Medicinal Products."

   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by February 2006

4. Conduct a Peri- and Postnatal Development (Segment III) study in a single species. Please refer to ICH Guidance S5B(M) Maintenance of the ICH Guideline on Toxicity to Male Fertility: An Addendum to the Guideline on Detection of Toxicity to Reproduction for Medicinal Products"

   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by May 2006

5. Complete a standard battery of genotoxicity studies of oxycodone hydrochloride or provide data from another source.

   Protocol Submission: by March 2005
   Study Start: by June 2005
   Final Report Submission: by May 2006

We remind you of your agreements to:

1. Continue to work with (b)(4) the Agency to aggressively identify, characterize, and provide adequate specifications for any/all potentially genotoxic (b)(4) (b)(4) products that may be present in the oxycodone drug substance; and

2. Establish the limits for bulk density, tap density and particle size distribution, based on the analysis of at least five additional batches, and to report this in the NDA annual report.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lisa Basham-Cruz, Regulatory Project Manager at (301) 827-7420.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

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

/s/

Bob Rappaport

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