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# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*

**21-378**

| | |
|---|---|
| ***Trade Name:*** | Combunox |
| ***Generic Name:*** | Oxycodone HCL and Ibuprofen Tablets |
| ***Sponsor:*** | Forest Laboratories, Inc. |
| ***Approval Date:*** | November 26, 2004 |
| ***Indications:*** | 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. |

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*APPLICATION NUMBER:*

# 21-378

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## Reviews / Information Included in this NDA Review.

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| **Approval Letter** | **X** |
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| **Medical Review(s)** | **X** |
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| **EA/FONSI** | |
| **Pharmacology Review(s)** | **X** |
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| **Administrative Document(s) and Correspondence** | **X** |

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-378**

# APPROVAL LETTER(S)

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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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-378**

## APPROVABLE LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-378

Forest Laboratories
Harborside Financial Center
Plaza Three, Suite 602
Jersey City, NJ 07311

Attention: Andrew Friedman, R.Ph.
Manager, Regulatory Affairs

Dear Mr. Friedman:

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 oxycodone HCl/ibuprofen 5/400 mg tablets.

We acknowledge receipt of your submissions dated January 10, February 8, April 30, May 17, July 31, August 7, 9, and 30, and September 4, 2002.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following deficiencies.

1. You have not provided sufficient evidence for the effectiveness of the oxycodone HCl 5-mg and ibuprofen 400-mg tablet for the treatment of acute, moderate-to-severe pain in the manner of proposed use. Although statistical differences in total pain relief and pain intensity from baseline between the combination drug product and ibuprofen alone are noted in the two single dose trials, the studies were not designed adequately to evaluate the effectiveness of this combination drug in the manner of intended use. The effect provided by the combination tablet was not sustained through the entire 6-hour dosing interval described in the proposed label. The dosing interval should be informed by pharmacokinetic profile of the components of this drug product and confirmed by the demonstration of efficacy in a multiple dose clinical trial.

   Perform an adequate and well-controlled multiple-dose study demonstrating the efficacy of the oxycodone HCl 5-mg and ibuprofen 400-mg tablet given every 6 hours demonstrating the effectiveness of multiple doses of oxycodone HCl/ibuprofen, for the proposed acute pain indication for up to 3 weeks. You are strongly encouraged to consult this Division regarding the design of these studies before they are initiated.

2. You have not adequately evaluated the safety of oxycodone HCl 5 mg and ibuprofen 400 mg tablets in the population for this drug product and in the setting that reflects how it is likely to be used in practice. Perform clinical study (studies) lasting a minimum of 3 months, demonstrating the safety of the oxycodone HCl 5-mg and ibuprofen 400-mg tablet in a population of patients with acute and chronic pain.

3. Your pediatric development program has not adequately addressed development of this drug product in pediatric patients from ages 2 years-16 years. Submit such a pediatric development program, or provide adequate justification for why this is not possible.

4. You have used an unapproved drug product, Roxicodone™ 5 mg, as the reference listed product for your 505(b)2 application. The Agency has not made a finding of safety and efficacy for this product at this dose and therefore this reference does not support your application. Perform a relative bioavailability study and provide the data that will allow the Agency to link your product to an approved oxycodone product.

5. Conduct Segment I (Fertility) and Segment III (peri- and post-natal development) studies as a requirement for this NDA. Depending on the timing of the resubmission, you may provide justification of these as a Phase 4 commitment.

6. Provide assessment in two species of the carcinogenic potential of this drug product unless you can demonstrate post-marketing data from similar combination drug products containing oxycodone that the drug product will not be used chronically.

7. Provide appropriate patent certification to support reference to labeled nonclinical information regarding other marketed products.

8. The following deficiencies pertain to the acceptance specifications for oxycodone HCl. Submit revised specifications as recommended below.

   a. Limit the acceptance criteria of individual drug substance impurities other than — to NMT — or provide nonclinical toxicologic qualification (3-month toxicity study using adequate levels of the impurities in an appropriate species). We recommend that you consult with the agency in the design of these studies.

   b. Submit adequate qualification of the potentially genotoxic — impurity — — either via demonstration that it is a human metabolite or via two in vitro genotoxicity testing studies (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay). If no qualification is submitted, or if it is determined to be genotoxic, limit it (e.g., — — to —

   c. If — is determined to be genotoxic, or if no genotoxicity testing is submitted for it, submit adequate qualification of the other potential — — impurities either via demonstration that they are significant human metabolites or via genotoxicity testing (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay); or, if no qualification is submitted, or the impurity is determined to be genotoxic, limit the impurity (e.g., via in-process controls or drug substance acceptance criteria) to "— —

   d. Revise the limits on other impurities from "Unidentified impurities (each): NMT — to "Individual unspecified drug-related impurity: NMT —

e. Revise the wording "Total impurities: NMT to "Total impurities (sum of individual reportable drug-related impurities > : NMT

f. Revise the acceptance criteria for oxycodone hydrochloride assay to tighten the range to or provide appropriate justification (including supporting data) for the currently proposed acceptance criteria. Mere reference to USP monograph is not adequate.

g. Provide certificates of analysis for the oxycodone HCl batches used in the manufacture of clinical batches of the drug product.

9. The following deficiencies relate to the acceptance specifications for Provide revised specifications as recommended.

10. The following comments relate to the excipients used in the manufacture of the drug product. Provide adequate responses to the listed deficiencies.

a. Provide the following additional specifications for sodium starch glycolate and also provide Forest's representative certificate of analyses.

i. Bulk density
ii. Tap density
iii. Particle size distribution

b. Provide Forest's test results for microcrystalline cellulose.

c. Provide revised certificates of analysis for stearic acid and calcium stearate stating that if these excipients are derived from animal sources, they comply with the Agency's guidance on bovine spongiform encephalopathy (BSE).

11. The following comments pertain to the drug product manufacture and drug product specifications.

    a. Provide revised in-process tests for the manufacture of oxycodone/ibuprofen tablets by including — testing of oxycodone HCl.

    b. Provide a description of the in-process controls during packaging operations such as specifications (test, test method, acceptance criteria) for —

    c. Provide a specification for — (or as in-process test) and during stability testing.

    d. Tighten the dissolution specification for both oxycodone and ibuprofen, e.g. Q = — at 30 minutes.

    e. Provide a specification, including upper and lower limits for the — in the drug product supported by the stability batch data.

    f. The validation of the HPLC test methods for impurities in oxycodone and ibuprofen are not satisfactory as the detection limits (DL), and quantitation limits (QL) are not provided. In general the quantitation limits should be at least equal to the ICH reporting threshold of 0.05%. Submit the requested data to the NDA.

    g. Provide an investigation of — as a degradation product in the drug product. If present, provide an acceptance criteria of — , or adequate qualification either via demonstration that it is a human metabolite or via two in vitro genotoxicity studies (one point mutation assay and one cytogenetic assay with the isolated impurity tested up to the limit doses for each assay). If the chemical is unqualified or mutagenic, appropriate steps will be necessary to limit its level e.g. to —

    h. The — — are not likely — They are more likely to be — impurities. Provide supporting data to show that these — are degradation products — or — impurities.

12. The following comments relate to other critical aspects of CMC: packaging, stability, environmental assessment, labeling, and the referenced DMFs.

    a. Provide justification why the — blister configuration used in the primary stability studies is deemed representative of the 4 X 25 configuration proposed for marketing.

    b. ——technical document states that the —— — Provide copies of packaging SOPs that incorporate these recommendations.

c. We reserve comments on the proposed expiration dating period and the post-approval stability protocol at this time. Submit updated stability data along with statistical analysis including 95% confidence intervals around the regression plots. The data should also be submitted as SAS transport files.

d. Provide the stability protocol in the format described in the Agency's draft stability guidance.

e. Provide detailed calculation including the projected sales in the next five years and the projected EIC (environmental introduction concentration) and appropriate CFR provisions in the environmental assessment in support of your claim for categorical exclusion.

f. Revise the chemical name of oxycodone HCl in the description section of the labeling to be consistent with the chemical name described in the USP25 monograph on oxycodone HCl.

g. Revise the description section of the labeling to include Opadry® II White, Y-22-7719 coloring agent, — , and povidone.

h. Provide the address of the manufacturer in the package insert.

i. DMFs — were reviewed and found to be inadequate to support your application. The holders of the DMFs have been notified of the deficiencies by letters on October 18, 2002.

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 non-clinical and clinical studies 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 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 study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study 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 a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

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, contact Lisa E. Basham-Cruz, Regulatory Project Manager, at (301) 827-7420.

Sincerely,

*{See appended electronic signature page}*

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

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/s/

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Cynthia McCormick
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