CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-011

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-011

AUG 31 2000

Roxane Laboratories, Inc.
P. O. Box 16532
Columbus, Ohio 43216-6532

Attention: Robert Pfeifer, M.S., R.Ph.
Associate Director, Drug Regulatory Affairs

Dear Mr. Pfeifer:

Please refer to your new drug application (NDA) dated September 29, 1998, received September 30, 1998, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Roxicodone (oxycodone hydrochloride) 15mg and 30 mg Tablets.

We acknowledge receipt of your submissions dated October 14 and October 28, 1999, February 28, March 10, April 11, June 23, June 29, July 17, August 1, August 7, August 24, August 29, August 30, and August 31, 2000. Your submission of February 28, 2000, constituted a complete response to our September 23, 1999, action letter.

This new drug application provides for the use of Roxicodone (oxycodone hydrochloride) 15mg and 30 mg Tablets for the management of moderate to severe pain where use of an opioid analgesic is appropriate.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed package insert and the immediate container and carton label submitted on August 31, 2000. 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 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 21-011." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated August 31, 2000. These commitments, along with any completion dates agreed upon, are listed below.

1. Conduct mutagenicity studies for Salmonella typhimurium/E-Coli mamalian-chromosome reverse mutation (with confirmatory assay), mouse lymphoma forward mutation, and *in vivo* mouse micronucleous assays

Final Report Submission	Within 3 months following approval

2. Conduct carcinogenicity studies in either two-year bioassays with two species or one rat two-year bioassay and one alternative model.

Protocol Submission	Within 2 months following approval
Study Start	Within 6 months following approval
Final Report Submission	Within 42 months following approval

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until September 2, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit 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, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Judit Milstein, Regulatory Project Manager, at (301) 827-7440.

Sincerely,

[/S/]

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

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-011

APPROVABLE LETTER(S)

Chamberlin

DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-011

Food and Drug Administration
Rockville MD 20857

Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, Ohio 43216

SEP 23 1999

Attention: Sean Alan F.X. Reade, M.A
Director Regulatory Affairs

Dear Mr. Reade:

Please refer to your new drug application (NDA) dated September 29, 1998, received September 30, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Roxicodone™ (oxycodone hydrochloride) tablets, 15 mg and 30 mg.

We acknowledge receipt of your submissions dated December 1, 1998; December 9, 1998; January 13, 1999; January 14, 1999; February 11, 1999; March 23, 1999; March 30, 1999; April 28, 1999; May 4, 1999; May 24, 1999; June 10, 1999; June 23, 1999; July 21, 1999; August 11, 1999; and September 1, 1999.

We have completed our review of this application, as amended, and it is approvable. Before the application can be approved, however, it will be necessary for you to respond to the following issues:

Clinical Efficacy:

1. There are no data submitted in support of the effectiveness of immediate release 15 and 30 mg oxycodone in this application. There is also no link to any product for which the FDA has made the findings of efficacy.

2. There is no request for a waiver of such studies and no justification provided for the claim that clinical studies are not needed.

Safety:

3. Clinical safety in the higher doses has not been adequately established with the database submitted. There is also no link to any product for which the FDA has made the findings of safety in higher doses. There may be adequate safety data for oxycodone 15 and 30 mg that you can bring to bear on this application. This may include data that you have developed. However, if these data are derived from studies on products other than that to which you have linked your application for purposes of establishing efficacy, an additional biopharmaceutical link must be provided.

4. The safety database as presented, correlating adverse events by tablet size rather than dose does not provide appropriate information about adverse events from which labeling can be written.

Regulatory:

5. This application has relied upon the finding of efficacy of oxycodone and has provided no clinical efficacy data of its own. If you intend to file a bridging study which will enable the Agency to link your product to its finding of efficacy for immediate release oxycodone, this application should be filed as a 505(b)(2) application. If you choose to file a safety study linking your product to an approved product, that would also make your application a 505(b)(2). The necessary documentation for a 505(b)(2) application is lacking.

Labeling:

6. The proposed labeling contains language that is not supported by the studies submitted or by data in the public domain. In addition, it will be necessary for you to submit draft printed labeling as recommended in the enclosed labeling. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be necessary.

To correct these deficiencies the following are necessary:

1. A bridging study or studies will be required from which the Agency can link its prior findings of efficacy for immediate release oxycodone to your product seeking approval. Such a bridging study is generally a biopharmaceutical study demonstrating relative bioavailability to the reference listed product.

2. An adequate rationale will be required for the extension of the dosage form to 15 and 30 mg without having provided clinical studies demonstrating efficacy at higher doses.

3. Information establishing safety at higher doses or a bridging study or studies will be required from which the Agency can link its prior findings of safety for lower doses of oxycodone to the proposed higher doses of oxycodone. Such a bridging study will likely be a biopharmaceutical study demonstrating relative bioavailability to an approved oxycodone product. New clinical safety data using the immediate release (IR) Oxycodone 15 and 30 mg would also be acceptable.

If you have any questions, contact Nancy Chamberlin, Pharm.D., Regulatory Project Manager, at (301) 827-7410.

Sincerely,

[/S/]

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and Addiction
Drug Products, HFD-170
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA 21-011
HFD-170/Div. Files
HFD-170/N. Chamberlin/Moody
HFD-170/McCormick/ Rappaport
HFD-170/ Lee
HFD-170/Geyer/Jean
HFD-170/ Maturu/D'Sa
HFD-170/Ma/Permutt
HFD-870/Kim/Uppoor
HFD-002/ORM
HFD-102/ADRA
HFD-820/DNDC Division Director
HFD-40/ DDMAC
DISTRICT OFFICE

Drafted by: nc/August 26, 1999
Revised: 9-2-99 nc, 9-3-99 nc, 9-14-99 per Cynthia, 9-14-99 per Corinne, 9-17-99 per Cynthia
9-21-99 per Kim, Corinne and Cynthia
Initialed by: C.P. Moody 9-14-99
Final: C. P. Moody 9-21-99
filename: N21011AE.ltr.doc

APPROVABLE (AE)

APPEARS THIS WAY
ON ORIGINAL