

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-793

APPROVAL LETTER

NDA 20-793

O.P.R. Development, L.P.
c/o Roxane Laboratories, Inc.
P.O. Box 16532
Columbus, Ohio 43216

Attention: Sean Alan F.X. Reade
Director of Regulatory Affairs

Dear Mr. Reade:

Please refer to your new drug application (NDA) dated August 22, 1997, received August 25, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cafcit (caffeine citrate) Injection.

We acknowledge receipt of your pre-submission dated December 28, 1996.

We also acknowledge receipt of your submissions dated September 12, 25, and 26, October 3, 20, and 23, November 7, 12, and 18, December 12, 1997, February 4, March 5, April 13, May 14, and 18, June 30, October 26, December 10, and 23, 1998, March 22, April 26, and 28, May 20, August 18, 23, and 25, September 16, and 17, 1999.

Your submission of March 22, 1999, constituted a complete response to our February 23, 1998, action letter.

This new drug application provides for the use of Cafcit (caffeine citrate) Injection for the short term treatment of apnea of prematurity in infants between 28 and <33 weeks gestational age.

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 enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling with the changes enclosed (package insert submitted September 20, 1999, immediate container and carton labels submitted September 20, 1999). Marketing the product with FPL that is not identical to the approved labeling may render the product misbranded and an unapproved new drug.

Please submit 20 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. For administrative purposes, this submission should be designated "FPL for approved NDA 20-793." 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 submissions dated December 23, 1998, and September 17, 1999. These commitments, along with any completion dates agreed upon, are listed below.

1. Commit to submit updated stability data beyond - months on three primary batches (Lot Nos. 989051, 989052, 989053) as they become available.
2. Commit to conduct an additional clinical trial of Cafcit to further elucidate the therapeutic plasma concentration range of Cafcit in premature infants with apnea of prematurity, by July 22, 2002. Submission to the Agency of further evaluation and analysis of plasma concentrations of caffeine and clinical outcomes in the already completed clinical study (Study OPR-001) may, if found acceptable by the Division, address this issue in lieu of an additional clinical study.
3. Commit to conducting a study to evaluate the pharmacokinetics of Cafcit in preterm neonates with renal impairment by July 22, 2002.

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 314.82(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."

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-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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.

NDA 20-793

Page 3

Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

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

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, contact Mr. J. Lindsay Cobbs, R.Ph., Regulatory Project Manager, at (301) 827-1051.

Sincerely,

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**APPEARS THIS WAY
ON ORIGINAL**