CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

18-401 / S-014

APPROVABLE LETTER (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-401/S-014

Reckitt & Colman Pharmaceuticals, Inc.
1909 Huguenot Road
Richmond, VA 23235

Attention: Alan Young
Director, Regulatory Affairs

Dear Mr. Young:

Please refer to your supplemental new drug application dated January 17, 2001, received January 19, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Buprenex (buprenorphine hydrochloride) Injectable.

This supplement proposes revisions in the preclinical sections based on our letter dated July 12, 2000.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

1. In the PRECAUTIONS section, subsection "Drug Interactions" replace your proposed 2nd paragraph with the following:

   CYP3A4 Inhibitors: Since the metabolism of buprenorphine is mediated by the CYP3A4 isozyme, coadministration of drugs that inhibit CYP3A4 activity may cause decreased clearance of buprenorphine. Thus patients coadministered with inhibitors of CYP3A4 such as macrolide antibiotics (e.g., erythromycin), azole antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritanovir) while receiving Buprenex should be carefully monitored and dosage adjustment made if warranted.

   CYP3A4 Inducers: Cytochrome P450 inducers, such as rifampin, carbamazepine, and phenytoin, induce metabolism and as such may cause increased clearance of buprenorphine. Caution is advised when administering Buprenex to patients receiving these medications and if necessary dose adjustments should be considered.

2. In the PRECAUTIONS section, subsection "Carcinogenesis, Mutanogenesis and Impairment of Fertility" replace the word "unadjusted" with "adjusted."

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. 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.

If you have any questions, call Sara Shepherd, Project Manager, at (301) 827-7430.

Sincerely,

{See appended electronic signature page}

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

/s/

Cynthia McCormick
2/15/01 05:18:01 PM