

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number: NDA 20997**

**APPROVAL LETTER**



NDA-20-997

Purdue Pharma L.P.  
U. S. Agent for Darwin Discovery Ltd.  
100 Connecticut Avenue  
Norwalk, Connecticut 06850

AUG - 5 1999

Attention: Michele M. Pavlik  
Senior Regulatory Affairs Associate

Dear Ms. Pavlik:

Please refer to your new drug application (NDA) dated April 27, 1998, received April 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Chirocaine (levobupivacaine) Injection, 2.5, 5.0, 7.5 mg/mL.

We acknowledge receipt of your submissions dated March 12, 1999, April 1, 1999, June 4, and 25, 1999. Your submission of June 4, 1999 constituted a complete response to our February 24, 1999 action letter.

This new drug application provides for the use of Chirocaine (levobupivacaine) Injection in adults for surgical anesthesia and pain management.

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 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 enclosed labeling (text for the package insert, immediate container and carton labels). 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 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 20-997." 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 February 24, 1999. These commitments, along with any completion dates agreed upon, are listed below.

Preclinical Studies

1. Direct carotid artery infusion of levobupivacaine with cardiovascular function maintained performed in large mammals (sheep) to evaluate the indirect effect of levobupivacaine on the heart via the CNS.
2. Direct coronary artery infusion of levobupivacaine with CNS function maintained performed in large mammals (sheep) to evaluate the direct effect of levobupivacaine on the heart.
3. Timely completion of a final study report of a cardiovascular resuscitation study in the dog given a convulsive dose of levobupivacaine.
4. Consider the feasibility of performing a developmental toxicity study in a newborn animal model (e.g. neonatal pig or newborn beagle).

Clinical Studies

Pediatric development program to evaluate levobupivacaine in pediatric patients from birth to 16 years of age for anesthesia and pain management. This development plan should primarily include pharmacokinetics and safety data, and efficacy data designed to determine appropriate dosing regimens (including continuous infusions). Please note that this does not constitute a "Written Request" under Section 111 of FDAMA.

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."

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 August 4, 2000. 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.

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](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan.] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

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

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.

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If you have any questions, contact Susmita Samanta, Regulatory Project Manager, at (301) 827-7410.

Sincerely,

CS

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

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20997**

**APPROVABLE LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

FEB 24 1999

NDA 20-997

**PAREXEL**

Rose Tree Corporate Center  
1400 North Providence Road, Suite 2000  
Media, Pennsylvania 19063

Attention: Tracie A. Parker  
Manager, Regulatory Affairs  
U.S. Agent for Darwin Discovery

Dear Ms. Parker:

Please refer to your New Drug Application (NDA) dated April 27, 1998, received April 27, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Chirocaine (levobupivacaine injections) 2.5, 5.0, 7.5 mg/mL.

We acknowledge receipt of your submissions dated July 22, 1998 (2), August 13, 1998, August 25, 1998, August 26, 1998, October 5, 1998, November 24, 1998, December 2, 1998, December 4, 1998, January 8, 1999, January 28, 1999, February 9, 1999, and February 19, 1999.

We have completed the review of this application and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert).

Please submit 20 copies of the final printed labeling, ten of which are 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.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

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 send one copy to the Division Anesthetic, Critical Care, and Addiction Drug Products, HFD-170 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

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. 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.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.



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If you have any questions, contact Susmita Samanta, Project Manager, at (301) 827-7410.

Sincerely,

ISI

Cynthia G. McCormick, M.D.

Director

Division of Anesthetic, Critical Care,  
and Addiction Drug Products, HFD-170

Office of Drug Evaluation III

Center for Drug Evaluation and Research

Enclosure