# CENTER FOR DRUG EVALUATION AND RESEARCH

# APPLICATION NUMBER: 20-533/S-002

# APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-533/S-002

AstraZeneca L.P.
P.O. Box 15437
1800 Concord Pike
Wilmington, DE 19850-5437

NOV - 2 2000

Attention: Lisa Deluca, Ph.D.
Director, Regulatory Affairs

Dear Dr. DeLuca:

Please refer to your supplemental new drug application dated September 24, 1998, received September 28, 1998, submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Naropin (ropivacaine HCl) Injection.

We acknowledge receipt of your submissions dated May 17, June 9, June 23, and July 23, 1999, and May 1, October 16, and November 2, 2000. Your submission of May 1, 2000, constituted a complete response to our September 28, 1999, action letter.

This supplemental new drug application provides for increasing dosage for nerve block anesthesia using Naropin 7.5mg/mL and for extending the duration of treatment for postoperative analgesia using Naropin 2mg/mL.

We have completed the review of this supplemental 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 supplemental 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).

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 supplement NDA 20-533/S-002." Approval of this submission by FDA is not required before the labeling is used.

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 22, 2004. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter. We remind you that the Agency issued a written request for Naropin on March 2, 2000, for pediatric studies to be conducted under the terms of 505A of the Federal Food, Drug and Cosmetic Act. Please note that FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as are required to fulfill the requirements of the pediatric rule. Therefore, it is important that you submit a pediatric plan describing your proposal for meeting your obligations associated with this approval under 21 CFR 314.55.

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 Kimberly Compton, Project Manager, at (301) 827-7432.

Sincerely,

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

Enclosure

/s/
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Cynthia McCormick
11/2/00 06:20:46 PM

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# APPLICATION NUMBER: 20-533/S-002

# APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-533/S-002

AstraZeneca LP
725 Chesterbrook Boulevard
Wayne, Pennsylvania 19087-5677

Attention: Lisa Deluca, Ph.D.
Regulatory Liaison Director

SEP 28 1999

Dear Dr. DeLuca:

Please refer to your supplemental New Drug Application dated september 24, 1998, received September 28, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Naropin (ropivacaine HCl injection) 2.0, 5.0, 7.5 and 10.0 mg/mL.

We acknowledge receipt of your submissions dated May 17, June 9 and 23, and July 22, 1999.

This supplemental New Drug Application provides for the use of Naropin (ropivacaine HCl injection) 2.0, 5.0, 7.5 and 10.0 mg/mL for surgical anesthesia: epidural block for surgery including cesarean section, major nerve block; local infiltration, and acute pain management: epidural continuous infusion or intermittent bolus.

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 draft labeling for the drug. The labeling should be revised as recommended in the enclosed labeling (text for the package insert). Immediate container and carton labels should be changed accordingly.

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.

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.

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.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, contact Susmita Samanta, M.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

121 page(s) of revised draft labeling has been redacted from this portion of the review.