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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

18-225/S-018 & 019
18-226/S-024 & 025

Approvable Letter (S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-225/S-018
NDA 18-226/S-024

Hoffmann-La Roche Inc.
Attention: Mr. Anthony J. Corrado
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Mr. Corrado:

Please refer to your supplemental new drug applications dated April 8, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bumex (bumetanide) 0.05, 1, 2 mg Tablets (NDA 18-225) and Bumex (bumetanide) 0.25 mg/mL Injection (NDA18-226).

These supplements provide for draft labeling revised under the CLINICAL PHARMACOLOGY: Pediatric Pharmacology section as follows:

- The last sentence of the first paragraph "Mean volume of distribution in neonates has been reported to range from 0.26 L/kg to 0.39 L/kg" was moved to the last sentence of the second paragraph.

- The last sentence of the first paragraph was replaced with "Elimination half-life decreased considerably during the first month of life, from a mean of approximately 6 hours at birth to approximately 2.4 hours at 1 month of age."

- The last paragraph was changed from:

To:

In 56 infants aged 4 days to 6 months, Bumex doses ranging from 0.005 mg/kg to 0.1 mg/kg were studied for pharmacodynamic effect. Peak bumetanide excretion rates increased linearly with increasing doses of drug. Maximal diuretic effect was observed at a bumetanide excretion rate of about 7 µg/kg/hr, corresponding to doses of 0.035 to 0.040 mg/kg. Higher doses produced a higher bumetanide excretion rate but no increase in diuretic effect. Urine flow rate peaked during the first hour after drug administration in 80% of patients and by 3 hours in all patients.

Additionally, a reference section was added to the end of the package insert as follows:

The reference section and text citations should be deleted from the package insert.

Minor editorial changes are noted, including, deleting the following from the HOW SUPPLIED section:

a. Tablets, 0.5 mg bottles of 500 (NDC 0004-0125-14)
b. Tablets, 0.5 mg Tel-E-Dose packages of 100 (NDC 0004-0125-49)
c. Tablets, 1 mg Tel-E-Dose packages of 100 (NDC 0004-0121-49)
d. Ampuls (0.25 mg/mL), 2mL, boxes of 10 (NDC0004-1944-06).

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as noted above.

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 (to each application) 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 (to each application), ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs 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 applications, notify us of your intent to file amendments, 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 applications. 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.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309.

Sincerely,

{See appended electronic signature page}

/S/

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Raymond Lipicky
12/18/01 02:44:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-225/S-019
NDA 18-226/S-025

Hoffmann-La Roche Inc.
Attention: Ms. Lynn DeVenezia-Tobias
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. DeVenezia-Tobias:

Please refer to your supplemental new drug applications dated July 18, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bumex (bumetanide) 0.5, 1, 2 mg Tablets (NDA 18-225) and Bumex (bumetanide) 0.25 mg/mL Injection (NDA 18-226).

These supplements provide for draft labeling revised to add the following subsections:

1. **CLINICAL PHARMACOLOGY**/*Geriatric Pharmacology*: In a group of ten geriatric subjects between the ages of 65 and 73 years, total bumetanide clearance was significantly lower (1.8 ± 0.3 mL/min·kg) compared with younger subjects (2.9 ± 0.2 mL/min·kg) after a single oral bumetanide 0.5 mg dose. Maximum plasma concentrations were higher in geriatric subjects (16.9 ± 1.8 ng/mL) compared with younger subjects (10.3 ± 1.5 ng/mL). Urine flow rate and total excretion of sodium and potassium were increased less in the geriatric subjects compared with younger subjects, although potassium excretion and fractional sodium excretion were similar between the two age groups. Nonrenal clearance, bioavailability, and volume of distribution were not significantly different between the two groups.

2. **PRECAUTIONS/Geriatric Use:**

3. **REFERENCE:**

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) revised as requested below:

1. Please omit the *Geriatric Pharmacology* subsection of the **CLINICAL PHARMACOLOGY** section.

2. Please revise the **PRECAUTIONS/Geriatric Use** section as follows:

   Clinical studies of Bumex did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

   This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

3. Please delete the **REFERENCE:** [redacted]

Minor editorial revisions were noted.

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

Please submit the copies of final printed labeling (FPL) electronically (to each application) 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 (to each application), ten of which individually mounted on heavy weight paper or similar material.

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

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If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309.

Sincerely,

/S/

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Raymond Lipicky
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