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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

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

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

Dear Ms. DeVenezia-Tobias:

Please refer to your supplemental new drug applications, dated April 8, 1999 (18-225/S-018 & 18-226/S-024) and July 18, 2000 (18-225/S-019 & 18-226/S-025), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bumex (bumetanide) 0.25, 1 and 2 mg Tablets (NDA 18-225), and Bumex (bumetanide) 0.25 mg/mL Injection (NDA 18-226).

We acknowledge receipt of your submissions dated January 4 (4), April 4 (4), and July 15, 2002 (4). Your submissions dated July 15, 2002 constitute a complete response to our December 14, 2001 (18-225/S-019 & 18-226/S-025) and December 18, 2001 (18-225/S-018 & 18-226/S-024) action letters.

These supplemental new drug applications provide for final printed labeling revised as follows:

NDA 18-225/S-018 (Bumex Tablets)
NDA 18-226/S-024 (Bumex Injection)

CLINICAL PHARMACOLOGY/ Pediatric Pharmacology

- 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 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 mcg/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.

NDA 18-225/S-019 (Bumex Tablets)

The following sections have been added:

- **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.

- **PRECAUTIONS/Geriatric Use**
  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.

In addition the following editorial changes are noted:

- The word "ampuls" was changed to "vials" in the **MISCIBILITY AND PARENTERAL SOLUTIONS** section.

- The following have been deleted from the **HOW SUPPLIED** section:

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

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the final printed labeling submitted July 15, 2002. Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional"

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, please call:

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

Sincerely,

/s/

{See appended electronic signature page}

Douglas C. Throckmorton M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doug Throckmorton
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