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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Administrative Documents

RHPM Review of Final Printed Labeling
NDA 18-225/ S-018 & S-019
NDA 18-226/ S-024 & S-025

Date of Submissions:	April 8, 1999 (18-225/S-018 & 18-226/S-024) July 18, 2000 (18-225/S-019 & 18-226/S-025)
FPL Submitted:	April 4, 2002 (BF) not accepted as AF because sponsor deleted the Miscibility and Parenteral section of the labeling. July 15, 2002 (AF)
Dates of Review:	April 22, 2002, May 24 & October 11, 2002
Most recent FPL:	September 1997
Applicant Name:	Hoffmann-La Roche Inc.
Product Names:	
NDA 18-225/S-018 18-225/S-019	Bumex® (bumetanide) 0.5, 1, and 2 mg Tablets
NDA 18-226/S-024 18-226/S-025	Bumex® (bumetanide) 0.25 mg/mL Injection

Evaluation:

NDA 18-225/S-018 & NDA 18-226/S-024 (Pediatric labeling)

The text in the **CLINICAL PHARMACOLOGY/ Pediatric Pharmacology** section of the FPL is identical to the proposed language in the approvable letter for the draft pediatric labeling dated December 18, 2001.

NDA 18-225/S-019 & NDA 18-226/S-025 (Geriatric labeling)

The text in the **CLINICAL PHARMACOLOGY/ Geriatric Pharmacology** section of the FPL is identical to the language in the proposed draft labeling dated July 18, 2000.

The approvable letter dated December 14, 2001 requests this section should be omitted. In an undated memo, Dr. Lipicky stated that the sponsor could insert the **CLINICAL PHARMACOLOGY/ Geriatric Pharmacology** section exactly as they propose in the draft labeling dated July 18, 2000. See Memo to the File by Daryl Allis, P.M., dated February 27, 2002.

The text in the **PRECAUTIONS/ Geriatric Use** section of the FPL is identical to the proposed language in the approvable letter for the geriatric draft labeling dated December 14, 2001.

In addition, the Miscibility and Parenteral Solutions section was revised by replacing "ampules" with "vials" as follows:

> The compatibility tests of Bumex injection (0.25 mg/mL, 2-mL vials) with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution in both glass and plasticized PVC (Viaflex) containers have shown no significant absorption effect with wither containers, nor a measurable loss of potency doe to degradation of the drug. However, solutions should be freshly prepared and used within 24 hours.

The sponsor discontinued manufacturing the ampules (noted in the Annual Report dated May 2, 2000) and, currently manufactures the vials only; therefore, reference to ampules is deleted from the labeling and the word vials is used instead. This change is acceptable with Dr. Srinivasachar, Team Leader, Chemistry.

The sponsor submitted revised FPL dated July 15, 2002, with revisions noted above.

Recommendation:

An approval letter should issue for these supplements as set forth under 21 CFR 314.70 (b) (3) (i) [Labeling: Any change in labeling except one described in paragraphs (c) (2) or (d) of this section].

Daryl Allis, M.S., F.N.P.
Regulatory Health Project Manager

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/s/

Daryl L. Allis
10/28/02 03:41:04 PM
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RHPM Review of Draft Labeling
NDA 18-225/s018 and 18-226/s024

Date of Submissions: April 8, 1999
Dates of Review: June 26, 2001, November 26, 2001
Most recent FPL: September 1997

Applicant Name: Hoffmann-La Roche Inc.
Product Names:
NDA 18-225/S-018: Bumex® (bumetanide) 0.5, 1, and 2 mg Tablets

NDA 18-226/S-024: Bumex® (bumetanide) 0.25 mg/mL Injection

Evaluation:

These supplements provide for draft labeling revised by incorporating additional information to the **CLINICAL PHARMACOLOGY/** *Pediatric Pharmacology* section as follows:

CLINICAL PHARMACOLOGY/ *Pediatric Pharmacology:* Elimination of Bumex appears to be considerably slower in neonatal patients compared with adults, possibly because of immature renal and hepatobiliary function in this population. Small pharmacokinetics studies of intravenous Bumex in preterm and full-term neonates with respiratory disorders have reported an apparent half-life of approximately 6 hours, with a range up to 15 hours and a serum clearance ranging from 0.2 to 1.1 mL/min/kg. In a population of neonates receiving Bumex for volume overload, mean serum clearance rates were 2.17 mL/min/kg in patients less than 2 months of age and 3.8 mL/min/kg in patients aged 2 to 6 months. Mean serum half-life of bumetanide was 2.5 hours and 1.5 hours in patients aged less than 2 months and those aged 2 to 6 months, respectively. 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.[1]

In preterm ~~and~~ neonates, mean serum concentrations following a single 0.05 mg/kg dose ranged from 126 mcg/L at 1 hour to 57 mcg/L at 8 hours. In another study, mean serum concentrations following a single 0.05 mg/kg dose were 338 ng/mL at 30 minutes and 176 ng/mL after 4 hours. A single dose of 0.1 mg/kg produced mean serum levels of 314 ng/mL at 1 hour, and 195 ng/mL at 6 hours. Mean volume of distribution in neonates and infants has been reported to range from 0.26 L/kg to 0.39 L/kg.[2]

The degree of protein binding of bumetanide in cord sera from healthy neonates was approximately 97%, suggesting the potential for bilirubin displacement. A study using pooled sera from critically ill neonates found that bumetanide at concentrations of 0.5 to 50 µg/mL, but not 0.25 µg/mL, caused a linear increase in unbound bilirubin concentrations.

In 56~~36~~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.[3]

A reference section was added as follows:

References:

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

In addition, the following minor text and editorial revisions were noted:

1. The last sentence of the first paragraph of the **CLINICAL PHARMACOLOGY** / *Pediatric Pharmacology* section was moved to the last sentence of the second paragraph and the data were changed from, [redacted] " **to** "0.26 L/kg to **0.39** L/kg."
2. The word "and" was deleted from the first sentence of the ninth paragraph of the **CLINICAL PHARMACOLOGY** section of the labeling as requested in the approval letter for Final Printed Labeling dated, February 10, 1998.
3. The labeling insert codes and revision date were revised.
4. As described in the Annual Report (Y-021) dated, May 2, 2000, the following have been deleted from the **HOW SUPPLIED** section:
   a. Tablets, 0.5 mg bottle 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).

Recommendation:

Dr. Lipicky reviewed the supplemental new drug applications and the medical and bio-pharmaceutical reviews completed by the Division of Cardio-Renal Drug Products. The revised pediatric draft labeling proposed by the sponsor is acceptable to the Division. An approvable letter should issue for these supplements as set forth under 21 CFR 314.70 (b) (3) (i) [Labeling: Any change in labeling except one described in paragraphs (c) (2) or (d) of this section]. The sponsor may submit Final Printed Labeling to include the changes described in the approvable letters for the pending pediatric (SLR-018 & SLR-024) and geriatric (SLR-019 & SLR-025) labeling supplements for NDAs 18-225 and 18-226 [Bumex® (bumetanide)].

/S/

Daryl Allis, M.S., F.N.P.
Regulatory Health Project Manager

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/s/

Daryl L. Allis
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RHPM Review of Draft Labeling
NDA 18-225/s019 and 18-226/s025

Date of Submissions: July 18, 2000 and July 18, 2000
Dates of Review: May 8, 2001; November 15, 2001
Most recent FPL: September 1997

Applicant Name: Hoffmann-La Roche Inc.
Product Names:
NDA 18-225/S-019: Bumex® (bumetanide) 0.5, 1, and 2 mg Tablets

NDA 18-226/S-025: Bumex® (bumetanide) 0.25 mg/mL Injection

Evaluation:

These supplements provide for draft labeling revised by adding a *Geriatric Pharmacology* subsection to the **CLINICAL PHARMACOLOGY/** section and a **Geriatric Use** subsection to the **PRECAUTIONS/** section as follows:

> *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.
>
> **Geriatric Use:**

The Medical Officer Review completed by Juan Carlos Pelayo, M.D., dated May 2, 2001, indicates the data presented by the sponsor regarding the safety of bumetanide in the elderly population are deemed to be insufficient to allow for a categorical statement in the labeling.

Abiding by the *Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Addition of "Geriatric Use" Subsection in the Labeling* printed in the **Federal Register**/ Vol. 62, No. 166/ Wednesday, August 27, 1997, the following statement(s) should replace the sponsor's text in the **Geriatric Use** section:

> 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.

The *Geriatric Pharmacology* subsection of the **CLINICAL PHARMACOLOGY** section should be omitted.

A reference section was added as follows:
Reference:

This section should be deleted from the labeling.

In addition, the following minor text and editorial revisions were noted:

1. The labeling insert codes, revision date and copyright date were revised.
2. As described in the Annual Report (Y-021) dated, May 2, 2000, the **HOW SUPPLIED** section deleted:
   a. Tablets, 0.5 mg bottle 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, boxes of 10 (NDC 0004-1944-06).
3. The word "and" was deleted from the first sentence of the ninth paragraph of the **CLINICAL PHARMACOLOGY** section of the labeling as requested in the approval letter for Final Printed Labeling dated, February 10, 1998.

Recommendation:
Dr. Lipicky reviewed the supplemental new drug applications and the medical and bio-pharmaceutical reviews completed by the Division of Cardio-Renal Drug Products. He requested that the package insert contain the standard "Geriatric Use" labeling language printed in the **Federal Register** referenced above. An approvable letter should issue for these supplements as set forth under 21 CFR 314.70 (c) (i) [To add or strengthen a contraindication, warning, precaution, or adverse reaction]. The sponsor may submit Final Printed Labeling to

include the changes described in the approvable letters for the pending pediatric (SLR-018 & SLR-024) and geriatric (SLR-019 & SLR-025) labeling supplements for NDAs 18-225 and 18-226 [Bumex® (bumetanide)].

/S/

Daryl Allis, M.S., F.N.P.
Regulatory Health Project Manager

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