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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

NDA 18-225
BUMEX^R (bumetanide) Tablets

SUBMISSION DATES:
Supplement SLR-019: July 18, 2000

NDA 18-226
BUMEX^R (bumetanide) Injection
Hoffmann-La Roche, Inc.
Nutley, New Jersey

SUBMISSION DATES:
Supplement SLR-019: July 18, 2000

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Supplemental SLR NDA/Revised Geriatric Labeling

SUBMISSIONS:

Reference is made to the approved NDAs 18-225 and 18-226 for Bumex^R (bumetanide) Tablets and Injection, respectively. Bumex^R is an agent indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.

Reference is also made to the Final Rule published in the Federal Register on August 27, 1997, which amends CFR 201.57, "Specific Requirements on Content and Format of Labeling for Human Prescription Drugs", adding a "Geriatric Use" subsection to the Precautions section of the labeling. In compliance with that Final Rule, supplements SLR-019 to NDA 18-225 and SLR-025 to NDA 18-226 dated July 18, 2000, provide revised labeling that includes information on the use of Bumex in elderly patients aged 65 and over. Specifically, the revised labeling proposes a new "Geriatric Use" subsection under the PRECAUTIONS section and a new "Geriatric Pharmacology" subsection under the CLINICAL PHARMACOLOGY section, using the language recommended by FDA. The proposed geriatric labeling changes are based on clinical data from the original NDA and published pharmacokinetic/pharmacodynamic and clinical literature for bumetanide in elderly patients and patients with congestive heart failure. The proposed clinical pharmacology geriatric information is based on the following reference:

- Pharmacokinetics and Pharmacodynamics of the Diuretic Bumetanide in the Elderly, Oberbauer R., et.al., *Clin Pharmacol Ther*. 1995; 57(1): 42-51. This article describes a study conducted in 10 male or female patients (aged 65-73 years) and 10 young subjects (aged 23-35 years). Because of the primary interest in the effects of the physiological consequences of aging and not in the effects of age-related diseases, only elderly subjects without manifested heart, lung, liver, and kidney disease were included in the study. After a standard breakfast, a dose of 0.5 mg of bumetanide was given orally. In addition, in 8 of the elderly and 6 of the young subjects, 0.5 mg of bumetanide was injected intravenously. A period of 1 week elapsed between the 2

dosing regimens. In this study the PK and PD of bumetanide in a group of elderly without major health problems with the corresponding values in another group of young subjects was compared. The PK parameters were obtained from measurements of the concentrations of bumetanide in plasma and urine by the use of HPLC. The PK and PD parameters after oral and IV administrations are presented in Table 1.

TABLE 1

Pharmacokinetic and pharmacodynamic parameters of oral administration of 0.5 mg bumetanide to elderly and young subjects

	Elderly subjects (n = 10)	Young subjects (n = 10)	2p
AUC (μg · min/ml)	3.4 ± 0.3	2.0 ± 0.1	<0.005
Cumulative urinary bumetanide excretion (μg/7 hr)	133 ± 14	200 ± 25	<0.05
CL (ml/min · kg)	1.8 ± 0.3	2.9 ± 0.2	<0.02
CL_R (ml/min · kg)	0.7 ± 0.1	1.7 ± 0.3	<0.005
CL_{NR} (ml/min · kg)	1.1 ± 0.3	1.2 ± 0.3	NS
V (L/kg)	0.24 ± 0.03	0.38 ± 0.08	NS
k_e (hr^{-1})	0.43 ± 0.03	0.54 ± 0.07	NS
$t_{1/2}$ (hr)	1.7 ± 0.2	1.5 ± 0.3	NS
F*	0.79 ± 0.12	0.75 ± 0.11	NS
C_{max} (ng/ml)	16.9 ± 1.8	10.3 ± 1.5	<0.05
Cumulative urine volume (ml/kg · 7 hr)	18.8 ± 2.7	39.5 ± 5.2	<0.005
Cumulative urine Na^+ excretion (mmol/kg · 7 hr)	1.49 ± 0.18	2.08 ± 0.27	<0.10
FE_{Na} (%)†	3.57 ± 0.52	3.56 ± 0.36	NS
Cumulative urine K^+ excretion (mmol/kg · 7 hr)	0.59 ± 0.08	0.70 ± 0.11	NS

2p. Two-tailed significance probability; NS, 2p > 0.10.

Pharmacokinetic and pharmacodynamic parameters of intravenous administration of 0.5 mg bumetanide to eight elderly and six young subjects
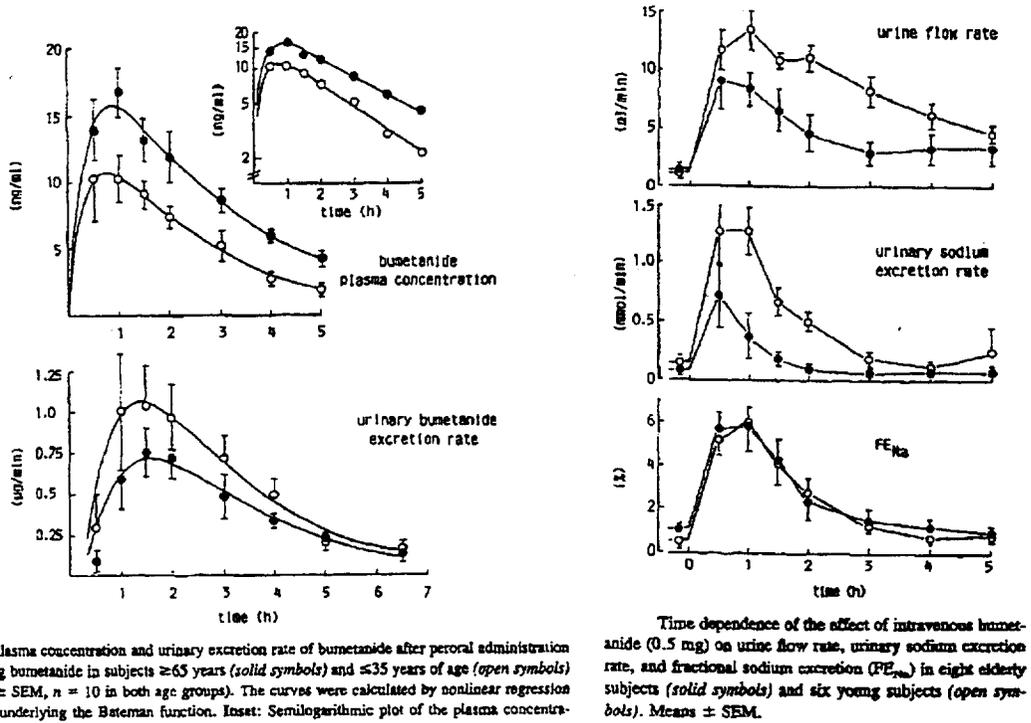
	Elderly subjects	Young subjects	2p
AUC (μg · min/ml)	5.2 ± 1.0	3.3 ± 0.9	NS
Cumulative urinary bumetanide excretion (μg/7 hr)	178 ± 15	263 ± 31	<0.05
CL (ml/min · kg)	1.6 ± 0.3	2.9 ± 0.6	<0.05
CL_R (ml/min · kg)	0.5 ± 0.1	1.2 ± 0.3	<0.05
CL_{NR} (ml/min · kg)	1.1 ± 0.2	1.7 ± 0.4	NS
V (L/kg)	0.32 ± 0.06	0.37 ± 0.07	NS
k_e (hr^{-1})	0.34 ± 0.05	0.43 ± 0.07	NS
Cumulative urine volume (ml/kg · 7 hr)	21.9 ± 3.7	44.0 ± 6.3	<0.01
Cumulative urine Na^+ excretion (mmol/kg · 7 hr)	0.76 ± 0.19	2.35 ± 0.44	<0.01
FE_{Na} (%)*	5.3 ± 0.9	4.9 ± 0.9	NS
Cumulative urine K^+ excretion (mmol/kg · 7 hr)	0.34 ± 0.03	0.46 ± 0.05	NS

*Average of the values from ½ to 1½ hours after bumetanide administration.

The results showed that the volume of distribution, half-life, and absolute bioavailability were not different between the two age groups. In the elderly, the total clearance of bumetanide was significantly reduced compared to the young control subjects. However, it should be noted that this reduction in total clearance was due to a decrease of renal clearance, whereas the nonrenal clearance of bumetanide was not altered. Practically identical differences in the pharmacokinetics and pharmacodynamics of bumetanide between elderly and young persons were found when the diuretic was injected intravenously as compared to the oral administration.

The plasma concentration and urinary excretion rate of bumetanide after oral administration and the time dependence of the diuretic effect of bumetanide in the 2 groups are illustrated in Figure 1. As shown in this Figure, after oral administration of 0.5 mg of bumetanide, plasma concentrations of bumetanide were higher in the elderly that in the younger group. Both urine flow and sodium excretion rate were increased less in the elderly than in young persons, but the effect of fractional sodium excretion did not differ in the 2 groups. Clearly, the diuretic effect was reduced in the elderly, but potassium excretion was not markedly different.

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FIGURE 1

Plasma concentration and urinary excretion rate of bumetanide after peroral administration of 0.5 mg bumetanide in subjects ≥65 years *(solid symbols)* and ≤35 years of age *(open symbols)* (means ± SEM, n = 10 in both age groups). The curves were calculated by nonlinear regression analysis underlying the Bateman function. Inset: Semilogarithmic plot of the plasma concentration-time curves.

Time dependence of the effect of intravenous bumetanide (0.5 mg) on urine flow rate, urinary sodium excretion rate, and fractional sodium excretion (FE$_{Na}$) in eight elderly subjects *(solid symbols)* and six young subjects *(open symbols)*. Means ± SEM.

Overall, the decrease in urinary bumetanide excretion is most likely a consequence of the physiologic age-dependent decline in renal function because there is a linear relation between renal bumetanide clearance and creatinine clearance (Figure 2) and together with this reduction, the diuretic and natriuretic effects of bumetanide are also reduced in the elderly.

FIGURE 2

$$CL_{ren} = 0.01 + 0.69 \; CL^{Cr}$$
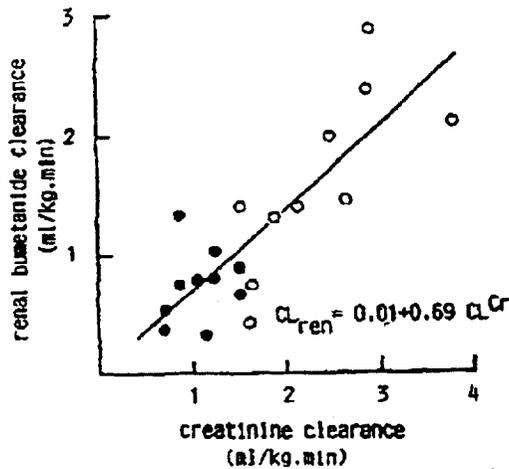
Relation between the individual values of the renal clearance of bumetanide (CL$_{ren}$) obtained in the present study and the corresponding values of the creatinine clearance (CL^{Cr}). The *solid symbols* represent the values in elderly subjects; the *open symbols* represent the values in young subjects.

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It is important to notice that his relationship holds not only for the decrease in kidney function in elderly subjects but also for other conditions of decreased function, such as renal failure in young subjects and decreased renal function in the neonate state.

The overall clinical implications when usual doses of bumetanide are given to elderly subjects are that higher plasma levels will result because renal clearance is reduced. Hence the risk of extrarenal adverse events (i.e., myalgia, hearing impairment, vertigo, hypotension, nausea, and hyperglycemia) is increased, although the diuretic effect is decreased. A further reduction in diuretic efficacy is to be expected in cases of hyperuricemia or when other endogenous acids are increased because there will be competitive inhibition of tubular excretion by these acids. Therefore, simultaneous treatment with acidic drugs (i.e., nonsteroidal antiinflammatory drugs or uricousuric agents) should be avoided. In addition, the use of higher doses of bumetanide to the elderly is not recommended because it will further increase plasma levels and the potential for toxic effects, whereas the increase in diuretic response is limited because of decreased filtration of Na^+ by the aged kidney.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the proposed geriatric labeling changes for Bumex^R Tablets and Injection, included in Supplement SLR-019 to NDA 18-225 submitted on July 18, 2000 and Supplement SLR-025 to NDA 18-226 submitted on July 18, 2000. The sponsor's proposed changes are as follow:

Sponsor's Proposed Text:

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 ± 0.3mL/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:

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OCPB Labeling Recommendation:

1. Based on the review of the provided information, OCPB/DPEI is of the opinion that the proposed geriatric text for the "Geriatric Pharmacology" subsection of Bumex's labeling is appropriate and acceptable. However, with respect to the information included in the "Geriatric Use" subsection, it should be noted that the medical reviewer of DCRDP, Dr. Juan Carlos Pelayo considered that the information provided to support the safety of bumetanide in the elderly population was insufficient to allow for a categorical statement in the labeling. Thus, Dr. Pelayo recommended that the proposed wording of the labeling should be changed to clearly reflect the lack of safety data for bumetanide on this population.

   Also, Dr. Pelayo pointed out that the reduction of renal function observed in the elderly population (i.e., decreased creatinine clearance) could happen in any subject that has a reduction in the glomerular filtration rate regardless of age and this would lead to a reduced filtered load and thus lessen the diuresis and natriuresis caused by the inhibitory action of bumetanide on the renal tubules increasing the levels of the plasma concentration of bumetanide.

2. In addition, it should be noted that the labelings for both Bumex^R Tablets and Injection do not include under the "CLINICAL PHARMACOLOGY" section, a "Pharmacokinetic" subsection. Therefore, it is recommended that the labeling for this product be revised as appropriate, in order to incorporate pharmacokinetic information for bumetanide. If the sponsor decides to follow OCPB's advice and update the labelings for Bumex Tablets and Injection, the pharmacokinetic labeling information can be based on in-house data and/or published literature. It is recommended that the following format be followed:

   The "Pharmacokinetics" portion should present information for bumetanide under the subheadings of *Absorption, Distribution, Metabolism, and Excretion*. Following this, there should be a section with the heading of *Special Populations*, where pharmacokinetic information under the subheadings of *Geriatric, Pediatric, Gender, Race, Renal Insufficiency, and Hepatic Insufficiency* should be included. After that, should be a section with the heading of *Drug-Drug Interactions*, in which available drug interaction information should be included. Finally, a *Pharmacokinetic/Pharmacodynamic* section should be presented, if such information is available. Where relevant information is lacking it should be so stated.

3. The sponsor should be informed that some of the FDA's guidances include specific recommendations for certain sections of the labeling. Examples of those guidances are: "In Vivo Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and

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Recommendations for Dosing and Labeling", "Pharmacokinetics in Patients with Impaired renal Function: Study design, Data Analysis, and Impact on Dosing and Labeling", Pharmacokinetics in patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (Draft Guidance), etc. These guidances are available in the FDA's web-site.

Please convey the Recommendation as appropriate to the sponsor.

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Patrick Marroum, Ph.D. _____ /S/ _____

cc: NDA 18-225 and NDA 18-226, HFD-110, HFD-860 (Dorantes, Mehta), and CDR (Biopharm)

/s/

Angelica Dorantes
7/24/01 12:03:25 PM
BIOPHARMACEUTICS

Patrick Marroum
7/24/01 03:11:12 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

NDA 18-225
BUMEX^R (bumetanide) Tablets

SUBMISSION DATE:
Supplement SLR-018: April 8, 1999

NDA 18-226
BUMEX^R (bumetanide) Injection
Hoffmann-La Roche, Inc.
Nutley, New Jersey

SUBMISSION DATE:
Supplement SLR-024: April 8, 1999

**REVIEWER:** Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: Supplemental SLR NDA/Revised Pediatric Labeling

SUBMISSIONS:

Reference is made to the approved NDAs 18-225 and 18-226 for Bumex^R (bumetanide) Tablets and Injection, respectively. Bumex^R is an agent indicated for the treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome.

Supplements SLR-018 to NDA 18-225 and SLR-024 to NDA 18-226 dated April 8, 1999 provide revised labelings for Bumex^R Tablets and Injection, respectively. Specifically, the revised labelings propose a new "Pediatric Pharmacology" subsection under the CLINICAL PHARMACOLOGY section of the package insert. The proposed pediatric information is based on the following 3 references:

1. Pharmacokinetics of Bumetanide in Critically Ill Patients, J. E. Sullivan, et.al. *Clin Pharmacol Ther.* 1996;60: 405-413. This article describes a single dose-ranging study conducted in 58 infants aged 0-6 months who required diuretic therapy. The doses ranged from 0.005 to 0.10 mg/kg. Serum and urine samples were collected at specific times during the study. Data were evaluated by standard noncompartmental pharmacokinetic techniques. The results showed Cmax bumetanide concentrations at 5 minutes after administration. AUC and Cmax bumetanide concentrations showed linear increases over the twenty-fold dose range; whereas Vdβ, Vdss, Cl, Clr, T1/2, and MRT values were independent of dose. Peak urinary excretion rates of bumetanide increased linearly with increasing doses.
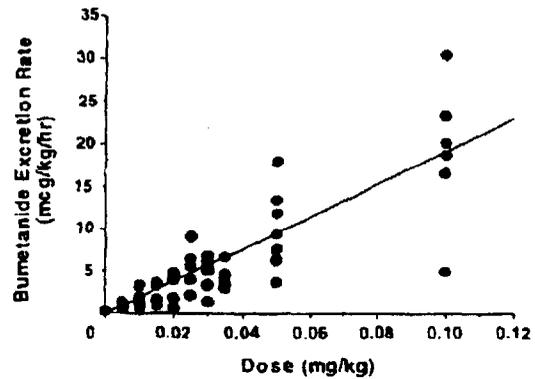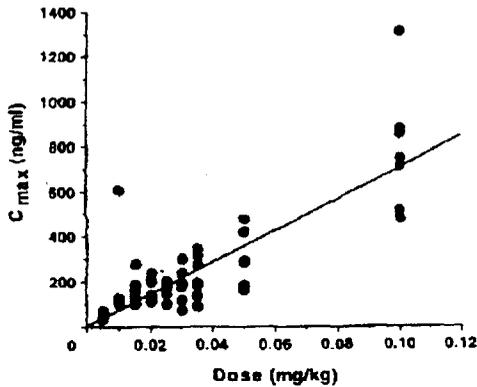
The mean percentage of bumetanide recovered in the urine from 0-12 hours was $40\pm15\%$ of the administered dose.

The given doses of bumetanide were well tolerated in acutely ill volume-overloaded infants aged 0-6 months.
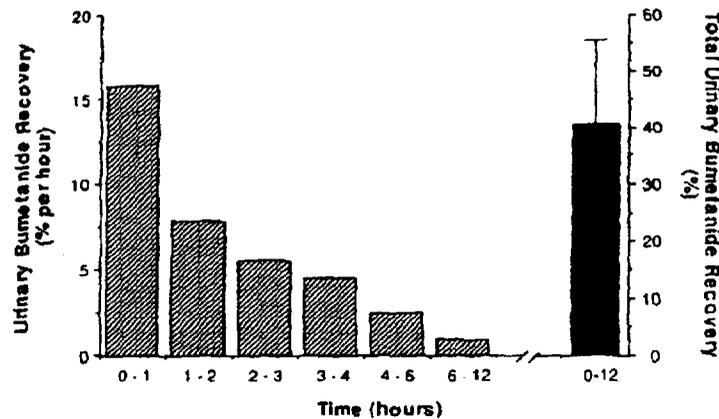
Urinary recovery of bumetanide. *Light bars on the left* represent percentages of total dose of administered bumetanide recovered per hour for each collection interval. *The dark bar on the right* depicts the mean $\pm$ SD of the total percentage of bumetanide dose recovered from 0 to 12 hours $(40\% \pm 15\%)$ after administration of bumetanide $(n = 58)$.

2. **Dose-Ranging Evaluation of Bumetanide Pharmacodynamics in Critically Ill Infants, J. E. Sullivan, et al. *Clin Pharmacol Ther*. 1996;60: 424-434.** This publication describes the pharmacodynamic part of the above dose-ranging study. Individual changes in urine flow rate and electrolytes excretion were plotted against corresponding bumetanide excretion rates, taken as the effective dose of the drug. The results showed that peak bumetanide excretion rates increased linearly with increasing doses. Maximal diuretic responses occurred 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 proportionally higher bumetanide excretion rate but no increased diuretic effect. Lower dose of bumetanide had the greatest diuretic efficiency, suggesting that continuous infusion of low doses of bumetanide or intermittent low-dose boluses may produce optimal diuretic responses in critically ill infants.

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3. **Analysis of the Variability in the Pharmacokinetics and Pharmacodynamics of Bumetanide in Critically Ill Infants, J. E. Sullivan, et al.** *Clin Pharmacol Ther.* 1996;60: 414-423. This paper describes the effect of age and disease on the pharmacokinetics and pharmacodynamics of bumetanide Fifty-three of the patients participating in the above dose-ranging study were divided into 2 groups: those heart disease (31 infants) and those with pulmonary disorders (22 infants).   The results showed that age and disease influenced the pharmacokinetics of bumetanide significantly.   Half-life decreased markedly in the first month of life.   Total clearance, renal clearance, and nonrenal clearance of bumetanide all increased with age, but the ratio of renal clearance to nonrenal clearance remained constant about 0.4.
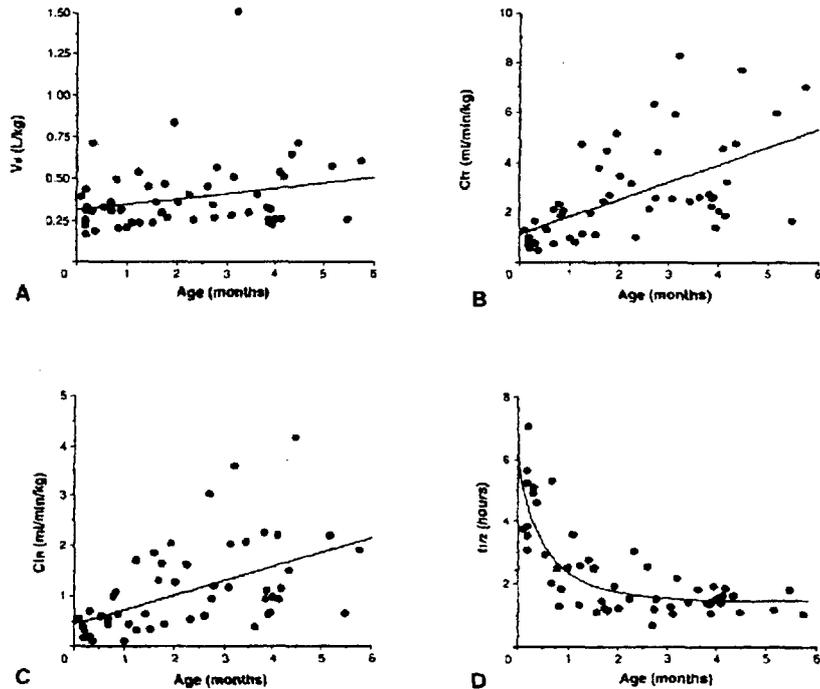
Age dependence of pharmacokinetic parameter estimates. Simple linear regression analysis was used to determine the relationship between age and volume of distribution (V_d), total clearance (CL_T), renal clearance (CL_R), and percentage of bumetanide recovered. The relationship between half-life ($t_{1/2}$) and age was exponential. Age did not have a significant effect on V_d (A). Other pharmacokinetic parameter estimates for bumetanide were significantly different with increasing age: CL_T ($R^2 = 0.35; p < 0.001$; B); CL_R ($R^2 = 0.27; p < 0.001$; C); and $t_{1/2}$ ($R^2 = 0.52; p < 0.001$; D).

Patients with lung disease exhibited a significantly greater clearance and shorter half-life, than those with heart disease, whereas volume of distribution was similar in both groups.

Estimates of pharmacokinetic parameters for bumetanide by disease group

Disease group	V_d (L/kg)	CL_T (ml/min/kg)*	CL_{NR} (ml/min/kg)*	CL_R (ml/min/kg)*	$t_{1/2}$ (hr)*	MRT (hr)*
Heart disease	0.38 ± 0.17	2.12 ± 1.71	1.26 ± 0.99	0.87 ± 0.85	2.71 ± 1.59	3.36 ± 2.36
Lung disease	0.43 ± 0.27	3.43 ± 2.02	2.07 ± 1.35	1.36 ± 0.86	1.74 ± 1.00	1.97 ± 1.35

V_d, Volume of distribution; CL_T, total clearance; CL_{NR}, nonrenal clearance; CL_R, renal clearance; $t_{1/2}$, half-life; MRT, mean residence time.
*$p < 0.05$.

Dose-response curves for urine flow rate and electrolyte excretion were similar between disease groups. The time course of the effect of bumetanide excretion rate on pharmacodynamic responses was similar between disease groups, as was the duration of the diuretic effect.
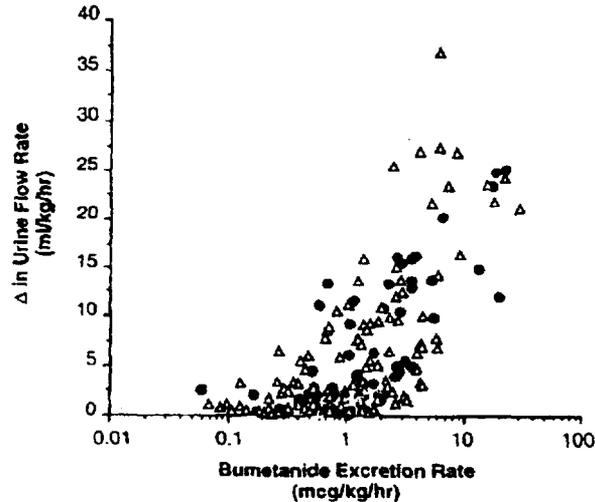
Urine flow rate log dose-response curves. Polynomial regression analysis was used to determine the relationship between urine flow rate and bumetanide excretion rate for patients in the group of patients with lung disease *(solid circles)* and in the patient group with heart disease *(open triangles; R^2 = 0.61 and R^2 = 0.51, respectively)*. Similar patterns were shown for patients in both groups for electrolyte excretion (data not shown).

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the proposed pediatric labeling changes for Bumex[R] Tablets and Injection, included in Supplements SLR-018 and SLR-024 to NDA 18-225 submitted on April 8, 1999, respectively. Based on the review of the above information, OCPB/DPEI recommends some modifications to the sponsor's proposed "Pediatric Pharmacology" subsection of Bumex's labeling. The recommended labeling changes are based on the same 3 articles used by the sponsor plus the following reference:

The Pharmacokinetics of Bumetanide in the Newborn Infant, Lopez-Samblas, et al. *Biol Neonate* 1997; 72:265-272. This paper describes the pharmacokinetics of bumetanide in neonates receiving intravenous doses of 0.05 or 0.10 mg/kg of bumetanide during the first week of life. Half-life of bumetanide was 6-7 hrs. Nonrenal clearance accounted for 58-97% of the serum clearance with the presence of certain oxidative metabolites of bumetanide in the urine. Therefore, elimination of Bumex appeared to be considerably slower in neonatal patients compared with adults, possibly because of immature renal and/or hepatobiliary function in this population. Therefore, dosing intervals <12 h were not recommended in pre-term infants because of bumetanide's long half-life and the risk for drug accumulation.

Sponsor's Proposed Text:

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 pharmacokinetic 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 neonates, mean serum concentrations following a single 0.05 mg/kg dose ranged from 126 μg/L at 1 hour to 57 μg/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 ▬▬▬ 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 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]

OCPB Recommended Text:

1. The proposed text of the "Pediatric Pharmacology" subsection of the labeling should be revised to include the following changes:

Pediatric Pharmacology: Small pharmacokinetic 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. Overall, there is a large interpatient variability in serum bumetanide concentration in the infant population. 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. Area under the curve and peak serum bumetanide concentrations showed linear increases over the twenty-fold dose range; whereas volume of distribution, total clearance, renal clearance, and half-life were independent of dose.

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. Plasma half-life of bumetanide in pre-term infants is approximately 6 times longer than in adults. Full term infants have half-lives that are double the normal adult values.

Mean volume of distribution in neonates has been reported to range from 0.26 L/kg to 0.38 L/kg. Nonrenal clearance (i.e., metabolism and biliary excretion) accounted for 58-97% of the serum clearance. In neonates, metabolism of bumetanide with subsequent excretion of metabolites in the urine or bile and biliary excretion of bumetanide appear to be the principal routes of elimination of bumetanide. 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 Therefore, dosing intervals <12 h are not recommended in pre-term infants because of bumetanide's long half-life and the risk for drug accumulation[1].

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 infants aged 4 days to 6 months given Bumex doses ranging from 0.005 mg/kg to 0.1 mg/kg 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]. The mean percent of bumetanide recovered in the urine from 0-12 hours was 40±15% of the administered dose[2]. The pharmacodynamic results showed that the time course patterns for urine flow rate and electrolyte excretion were similar for all dosage groups. Lower doses of bumetanide had the greatest diuretic efficiency, suggesting that continuous infusion of low doses or intermittent low-dose boluses may produce optimal diuretic responses in critically ill infants[3].

The contributions of age and disease were also investigated in 53 of the 58 critically ill over-loaded infants. Patients were divided into 2 groups: those heart disease (31 infants) and those with pulmonary disorders (22 infants). The results showed that age and disease influenced the pharmacokinetics of bumetanide significantly. Half-life decreased markedly in the first month of life. Total clearance, renal clearance, and nonrenal clearance of bumetanide all increased with age, but the ratio of renal clearance to nonrenal clearance remained constant about 0.4. Patients with lung disease exhibited a significantly grater clearance and shorter half-life, than those with heart disease, whereas volume of distribution was similar in both groups. Dose-response curves for urine flow rate and electrolyte excretion were similar between disease groups. The time course of the effect of bumetanide excretion rate on pharmacodynamic responses was similar between disease groups, as was the duration of the diuretic effect[4].

2. The list of pediatric references needs to be modified as follows:
    (1) A.M. Lopez-Samblas, et al. *Biol Neonate* 1997; 72:265-272.
    (2) J. E. Sullivan, et al. *Clin Pharmacol Ther.* 1996;60: 405-413
    (3) J. E. Sullivan, et al. Clin Pharmacol Ther. 1996;60: 424-434

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(4) J. E. Sullivan, et al. Clin Pharmacol Ther. 1996;60: 414-423

3. In addition, it should be noted that the labelings for both Bumex[R] Tablets and Injection do not include under the "CLINICAL PHARMACOLOGY" section, a "Pharmacokinetic" subsection. Therefore, it is recommended that the labeling for this product being revised as appropriate, in order to incorporate pharmacokinetic information for bumetanide. The pharmacokinetic labeling information can be based on the sponsor's data and/or published literature. If the sponsor decides to follow OCPB's advice and update the labelings for Bumex Tablets and Injection, it is recommended that the following labeling format be followed:

> The "Pharmacokinetics" portion should present information for bumetanide under the subheadings of *Absorption, Distribution, Metabolism, and Excretion*. Following this, there should be a section with the heading of *Special Populations*, where pharmacokinetic information under the subheadings of *Geriatric, Pediatric, Gender, Race, Renal Insufficiency, and Hepatic Insufficiency* should be included. After that, should be a section with the heading of *Drug-Drug Interactions*, in which available drug interaction information should be included. Finally, a *Pharmacokinetic/Pharmacodynamic* section should be presented, if such information is available. Where relevant information is lacking it should be so stated.

4. The sponsor should be notified that some of the FDA's guidances include specific recommendations for certain sections of the labeling. Examples of those guidances are: "In Vivo Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosing and Labeling", "Pharmacokinetics in Patients with Impaired renal Function: Study design, Data Analysis, and Impact on Dosing and Labeling", Pharmacokinetics in patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (Draft Guidance), etc. These guidances are available in the FDA's web-site.

Please convey the Recommendation as appropriate to the sponsor.

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Patrick Marroum, Ph.D. _____

cc: NDA 18-225 and NDA 18-226, HFD-110, HFD-860 (Dorantes, Mehta), and CDR (Biopharm).

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/s/

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