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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Medical Review(s)

MEDICAL OFFICER REVIEW

NDA: 18-225 (SLR-019) and 18-226 (SLR-025)
DRUG NAME: Bumex® (bumetanide) Tablets/Injection
SPONSOR: Hoffmann-La Roche Inc.
TYPE OF DOCUMENT: Geriatric Labeling Supplement
DATE RECEIVED: July 19, 2000
DATE REVIEW COMPLETED: April 30, 2001
MEDICAL OFFICER: Juan Carlos Pelayo, M.D.

INTRODUCTION

In order to comply with the requirement of Section 21 CFR 201.57(f)(10), a "Geriatric Use" subsection of prescription drug labeling that provides information on the safe and effective use of drugs in elderly patients aged 65 and over, the sponsor submitted clinical and pharmacokinetic data and a revised labeling.

To this end the sponsor provided the following information:

1. A literature search (dated March 7, 2000; based on the ROSCOPES database) covering the life of the product through March 7, 2000 identified few studies that targeted the use of bumetanide in elderly patients. One pharmacokinetic/pharmacodynamic study and one general clinical study were identified:
   a) Oberbauer R, Krivanek P, Tumheim K. Pharmacokinetics and pharmacodynamics of the diuretic bumetanide in the elderly. *Clin Pharmacol Ther.* 1995; 57(1): 42-51.
   b) Ghosh MK, Mondal BK, Pippen CAR. Treatment of elderly patients with congestive cardiac failure: a comparison of bumetanide with frusemide/amiloride. *Curr Therapeut Res.* 1991; 50(Suppl. A): 15-26.

2. The sponsor also reviewed Hoffmann-La Roche Inc. safety information which provided a breakdown of the frequency of Bumex® adverse events reported worldwide in patients 65 years and over compared with the frequency of events in patients aged less than 65 years (cumulative over the life of the product through February 29, 2000). The sponsor concluded that the numbers of individual event reports were too small upon which to base any safety assumptions.

3. The original New Drug Applications for NDA 18-225 - Bumex® (bumetanide) Tablets and NDA 18-226 - Bumex® (bumetanide) Injection were also reviewed by the sponsor in order to determine the number/percentage of geriatric patients that participated in Bumex® clinical trials. In NDA 18-225, 175 of 489 patients were 60 years of age or older; 58 of 489 patients were 70 years of age or older. In NDA 18-226, 22 of 107 patients were 60 years of age or older; 10 of 107 patients were 70 years of age or older. When these data are combined, 197 of 596 patients (33%) in Bumex® clinical trials were 60 years of age or older; 68 of 596 patients (11%) were 70 years of age or older. The sponsor indicated that no mention could be found in the subject NDAs that either of these age groups demonstrated any difference in safety or efficacy relative to younger patients.

Based on the aforementioned information, the sponsor "have added a new "Geriatric Use" subsection under the PRECAUTIONS section of the package inserts using appropriate wording as recommended by FDA in paragraph (ii)(B) in 21 CFR § 201.57 (f)(10), and a new "Geriatric Pharmacology" subsection under the CLINICAL PHARMACOLOGY section to incorporate the pharmacokinetic and pharmacodynamic data found in the published study (Oberbauer, *et al.*). These data are also described briefly under the Geriatric Use subsection."

RESULTS

In this section of the medical review the results from the study of Oberbauer, *et al.*, are reviewed. This study compares the pharmacokinetics and pharmacodynamics of the diuretic bumetanide when administered orally and intravenously to elderly vs. young subjects. The authors argued that "with increasing age, renal function declines hence it is possible that in the elderly persons renal excretion and consequently the clinical effects of diuretics [such as bumetanide] are decreased, although plasma levels may be increased."

The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in elderly vs. young subjects were analyzed after oral and intravenous administration.

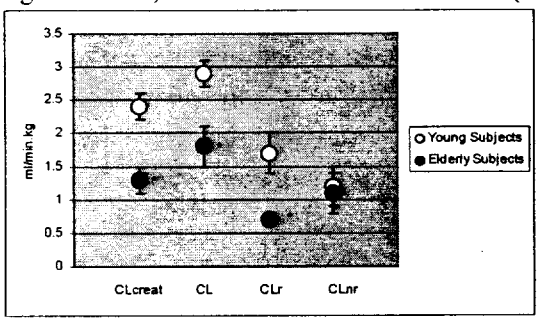
Ten patients, age range 65 to 73 years, constituted the elderly group, and the young group consisted of 10 normal subjects, age range 23 to 35 years. Subjects received 0.5 mg of bumetanide orally. At least one week later in 8 elderly patients and in 6 young subjects bumetanide 0.5 mg was given intravenously.

ORAL ADMINISTRATION

In the elderly, as a result of a decreased creatinine clearance and thus lower renal clearance, the total clearance of bumetanide was lower than in the young. The cumulative urinary excretion of bumetanide was significantly lower in elderly subjects than in young subjects (133±14 vs. 200±25 µg/7hr, $p<0.05$, respectively). The volume of distribution and the elimination rate constant were decreased in the elderly as compared with the young but the differences did not reach statistical significance (0.24±0.03 vs. 0.38±0.08 L/kg and 0.43±0.003 vs. 0.54±0.07 hr^{-1}, respectively). The absolute bioavailability was not different between the two groups

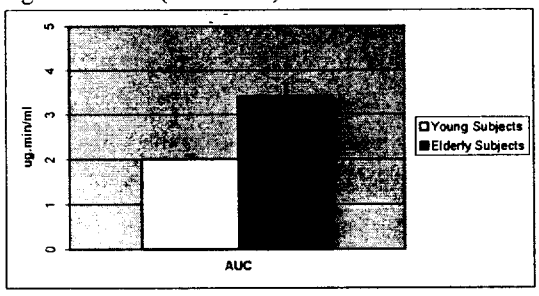
In comparison to the young subjects AUC and Cmax in the elderly were increased (Figures 2 and 3, respectively).

Figure 1. Total, Renal and Non-Renal Clearances (Mean±SD) of Bumetanide after Oral Administration.



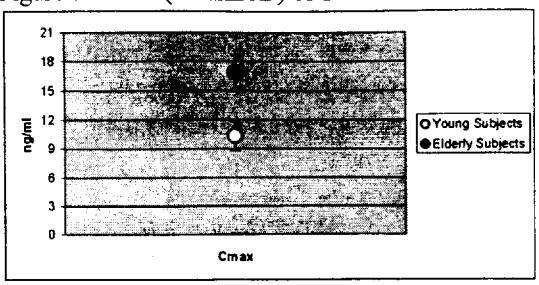
[CLcreat: creatinine clearance; CL: total clearance; CLr: renal clearance; CLnr: non-renal clearance. *$p<0.05$ vs. young subjects.]

Figure 2. AUC (Mean±SD) of Bumetanide after Oral Administration.



[*$p<0.05$ vs. young subjects]

Figure 3. Cmax (Mean±SD) of Bumetanide after Oral Administration.



[*p<0.05 vs. young subjects]

Table 1 summarizes cumulative urine volume, sodium and potassium excretion and fractional sodium excretion in elderly and young subjects. In spite of increased Cmax, elderly subjects had lower cumulative urine volume ($p<0.005$) and sodium excretion ($p<0.1$) as compared with young subjects. Of note, when the urinary excretion of sodium is corrected by the glomerular filtration rate, i.e., creatinine clearance, the FE_{Na} is not different between the groups.

Table 1. Pharmacodynamic Parameters (Mean±SD) of Oral Administration of Bumetanide.

Variable	**Elderly Subjects N=10**	**Young Subjects N=10**
Cumulative Urine Volume (ml/kg · 7 hr)	18.8±2.7	39.5±5.2*
Cumulative Urine Na^+ Excretion (mmol/kg · 7 hr)	1.49±0.18	2.08±0.27
FE_{Na} (%)	3.57±0.52	3.56±0.6
Cumulative Urine K^+ Excretion (mmol/kg · 7 hr)	0.59±0.08	0.70±0.11

[*p<0.005 vs. young subjects]

INTRAVENOUS ADMINISTRATION

The pharmacokinetics and pharmacodynamics of the diuretic bumetanide in elderly vs. young subjects after intravenous administration are shown in Table 2. AUC was increased in elderly subjects as compared with young subjects. Total clearance was lower in elderly subjects than in young subjects because of a decreased renal clearance. Elderly subjects had lower cumulative urine volume and sodium excretion than young subjects did. Of note, when the urinary excretion of sodium is corrected by the glomerular filtration rate, i.e., creatinine clearance, the FE_{Na} is not different between the groups.

Table 2. Pharmacodynamic Parameters (Mean±SD) of Intravenous Administration of Bumetanide.

Variable	**Elderly Subjects N=8**	**Young Subjects N=6**
AUC (μg · min/ml)	5.2±1.0	3.3±0.9
Cumulative Urinary bumetanide excretion (μg · 7hr)	178±15	263±31*
CL (ml/min · kg)	1.6±0.3	2.9±0.6*
CLr (ml/min · kg)	0.5±0.1	1.2±0.3*
CLnr (ml/min · kg)	1.1±0.2	1.7±0.4
V (L/kg)	0.32±0.06	0.37±0.07
Cumulative Urine Volume (ml/kg · 7 hr)	21.9±3.7	44.0±6.3**
Cumulative Urine Na^+ Excretion (mmol/kg · 7 hr)	0.76±0.19	2.35±0.44**
FE_{Na} (%)	5.3±0.9	4.9±0.9
Cumulative Urine K^+ Excretion (mmol/kg · 7 hr)	0.34±0.03	0.46±0.05

[*p<0.005 vs. young subjects]

COMMENTS

The data presented by the sponsor regarding the safety of bumetanide in the elderly population is deemed to be insufficient to allow for a categorical statement in the labeling. Thus, the wording in the package insert should clearly reflect the lack of data on the matter.

The results from the study by Oberbauer, *et al.*, point out differences in pharmacokinetics and pharmacodynamics of the diuretic bumetanide, regardless route of administration, between the distinct populations studied. These documented differences are unequivocally the result of reduced renal function, i.e., decreased creatinine clearance, in the older group. Thus, one should conclude that a reduction in the glomerular filtration rate, in any subject regardless of age, 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 notwithstanding an increased Cmax.

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/s/

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