CLINICAL STUDY REPORT

BIOAVAILABILITY OF 2 mg FORMULATIONS FOR NASAL AND RECTAL ADMINISTRATION OF BUMETANIDE

EVALUATION OF THE BIOAVAILABILITY OF 2 mg OF BUMETANIDE IN THE FOLLOWING FORMULATIONS: NASAL SPRAY; SUPPOSITORY; IN COMPARISON WITH 1 mg BUMETANIDE ADMINISTERED AS EITHER TABLET (immediate release) OR AS INTRAVENOUS INJECTION (reference) IN HEALTHY VOLUNTEERS

A Single-Centre, Randomised, Open Cross-over Study

BUN 9403 DE STUDY
Medical Department
Leo Pharmaceutical Products
Denmark

FINAL
16 September 1998
COMPLIANCE WITH
GOOD CLINICAL PRACTICE

This Study was designed to comply with the European Community Commission Guideline 3/3976/88 (as of July, 1991) on Good Clinical Practice.
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## APPENDICES

- **Appendix I** - Statistical Report not completed as per 16 September 1998
- **Appendix II** - Individual Subject Data not completed as per 16 September 1998
- **Appendix III** - Analysis Certificates; Audit Certificate
- **Appendix IV** - Study Protocol - included in Clinical Report Appendix VI
- **Appendix V** - Case Record Form Book included in Clinical report, Appendix VI
- **Appendix VI** - Clinical Report (July 1995)
- **Appendix VII** - Analytical Report; bumetanide not completed as per 16 September 1998
- **Appendix VIII** - Serum concentration Report; bumetanide
- **Appendix IX** - Urine concentration Report; bumetanide
ABSTRACT

Study Objective: To evaluate and compare the maximum serum concentration ($C_{\text{max}}$) of bumetanide, time to $C_{\text{max}}$ ($T_{\text{max}}$), of two 2 mg formulations of bumetanide (single dose) nasal spray and suppository respectively, and to compare the absolute and relative bioavailability and pharmacodynamic effect of the former two formulations with intravenous injection of 1 mg bumetanide and single dose of a 1 mg bumetanide tablet (immediate release) as reference, respectively, in healthy volunteers.

Study Design: This was a single-centre, randomised, open cross-over, bioavailability study with additional comparison of pharmacodynamic effect of nasal and rectal administration versus oral and intravenous dosing. The study comprised three phases; i) an initial eligibility assessment with physical examination and laboratory tests, ii) a drug administration phase with four, single doses of bumetanide nasal, rectal, oral and i.v. administration at 7 days intervals, and iii) a follow-up assessment including repeat laboratory analyses. Blood and urine samples were to be collected from subjects during the first 12 and 24 hours, respectively, after each dose of bumetanide. Subjects were to be randomised for the order in which they received the doses of bumetanide.

Eligibility Criteria: Healthy male volunteers, aged 18 to 55 years were included in the study. Excluded were those subjects known or suspected to be hypersensitive to bumetanide, those with a history of significant gastrointestinal disorders, those with pre-treatment haematology or clinical biochemistry results showing clinically significant deviation, those taking medications considered to be enzyme inducers or inhibitors. Subjects should also maintain an alcohol- and methylxanthine-free diet for 48 hours prior to each study day and for the duration of the sampling period following each dose.

Study Medication: Bumetanide 2 mg nasal spray containing 5 ml 20 mg/ml solution (1 puff = 100 μl), 2 mg suppository, 1 mg tablets, and solution for injection 0.5 mg/ml produced and certified by Leo Pharmaceutical Products, Ballerup, Denmark.
Sample Size: A total of 24 subjects completed the study.

Assessments: At a pre-study screening physical examination including vital signs and ECG and routine haematology and clinical biochemistry tests and screening for drug abuse, hepatitis B–virus surface–antigen (HBsAg) and HIV–antibodies were performed within a 14 day–period prior to the first drug administration. Routine haematology and clinical biochemistry tests were performed in all subjects at pre-study screening and within 7 days of last drug administration. Following each of the four bumetanide doses for pharmacokinetic assessment, 16 blood samples were taken over 12 hours, and urine samples were collected in 8 fractions over 24 hours for pharmacodynamic assessments. Adverse event reports were to be elicited during all drug administration phases and at end of study.

Primary Evaluation Parameter: Concentration of bumetanide measured in serum and urine by HPLC assay. Pharmacokinetic parameters: $C_{\text{max}}$, $T_{\text{max}}$ and AUC, calculated from the serum concentration–versus–time curve and urinary recovery from urine concentration data of bumetanide. The measurements of urine volume and excretion of sodium, potassium and creatinine post–dosing were to be used for pharmacodynamic assessment.
### Schedule of Study Procedures

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<thead>
<tr>
<th>Study Procedure</th>
<th>Phase I (Pre-study Period)</th>
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### Results:

The serum and urine concentrations and pharmacokinetic parameters (including bioavailability assessments) after single dose administration of 2 mg bumetanide in the two new pharmaceutical formulations (nasal spray, suppository) compared to references, 1 mg bumetanide as tablet and i.v. solution are illustrated in Figure I and Table II and in Appendix II. The pharmacodynamic assessments and comparisons are shown in Figures IV and V and in Tables III and IV.

### Conclusions:

Bumetanide single dose (2 mg) pharmacokinetic and pharmacodynamic assessments of two new pharmaceutical formulations, nasal spray and suppository for rectal application compared to administration of tablet and i.v. solution (1 mg bumetanide) did not show any pharmacokinetic improvement in terms of increased bioavailability versus tablet. On the contrary, the suppository formulation had a very poor bioavailability. The pharmacodynamic evaluation did neither indicate improved effect (measured as urine volume or sodium excretion) nor did the two new formulations, nasal spray and suppository display a quicker onset of effect compared to tablet.

For figures and tables, see Section 7.
CLINICAL STUDY REPORT APPROVAL

Medical Director

[Name, M.D.]
Medical Department
Leo Pharmaceutical Products
DK-2750 Ballerup
DENMARK

Signature: 
Date: 26 Sept 1998

Statistician

[Name, M.Sc.Stat.]
Leo Pharmaceutical Products
DK-2750 Ballerup
DENMARK

Signature: 
Date: 

REPORT AUTHORS

, M.Sc.Pharm.
Medical Department
Leo Pharmaceutical Products
DK–2750 Ballerup
DENMARK

Leo Pharmaceutical Products
DK–2750 Ballerup
DENMARK
INVESTIGATORS AND STUDY CENTRE

PRINCIPAL INVESTIGATOR

Mr. [redacted], Physician
GERMANY

STUDY CO-ORDINATOR AT

Dr. [redacted]
GERMANY

LABORATORY FOR HAEMATOLOGY AND CLINICAL BIOCHEMISTRY ASSAYS

[redacted]
GERMANY

LABORATORY FOR BUMETANIDE ASSAY

Analytical Chemical Research Dept.
Leo Pharmaceutical Products
DK-2750 Ballerup
DENMARK
COMPANY PERSONNEL

PRINCIPAL CLINICAL PROJECT CO-ORDINATOR

, M.Sc.Pharm.
Medical Department
Leo Pharmaceutical Products
DK-2750 Ballerup
DENMARK

STATISTICIAN

Leo Pharmaceutical Products
DK-2750 Ballerup
DENMARK

COMPUTERISATION OF DATA

Leo Pharmaceutical Products
DK-2750 Ballerup
DENMARK

SECRETARY OF CLINICAL STUDY REPORT

Leo Pharmaceutical Products
DK-2750 Ballerup
DENMARK
INTRODUCTION AND RATIONALE

1.1 BUMETANIDE

Bumetanide (Burinex®) is a potent loop diuretic which is reported to be 40 to 70 times more potent than furosemide on a milligram-for-milligram basis (1,2,3). The dose response curve is linear at doses between 0.25 and 2.5 mg (1). Its general therapeutic characteristics are similar to both furosemide and ethacrynic acid.

Intravenous and oral bumetanide have a comparable diuretic response. This observation implies that the drug is completely absorbed following oral administration (4). The absolute bioavailability of oral bumetanide reported in the literature ranges from 59 – 95%, with a median of about 80% (3,5,6). Following oral administration, diuresis occurs within 30 minutes and peaks at 60 to 180 minutes, with a duration of action of approximately 6 hours (1). The usual oral dose of bumetanide is 0.5 to 2.0 mg daily. Higher doses are used in patients with renal failure.

1.1.1 Metabolism and Excretion

Published elimination half-lives for bumetanide range from 1 to 1.5 hours (6,7,8). It undergoes hepatic and renal metabolism and elimination, with 80% of the drug excreted within 48 hours (7,8). Most of bumetanide is renally excreted in the first 6 hours after dosing (9). From 50 to 60% of the drug is excreted unchanged in the urine (7). Metabolism of bumetanide occurs via the butyl side chain with the 3' alcohol being the major metabolite in the urine. In the bile and faeces, the major metabolite is the 2' alcohol. All metabolites excreted either in the urine or bile are inactive conjugates, primarily glucuronides (8).
1.1.2 Protein Binding

Bumetanide is 90 – 97% bound to albumin in plasma when evaluated using Sephadex batch and ultrafiltration methods (7,10), with no apparent binding to erythrocytes (7).

1.2 PRESENT STUDY: RATIONALE

Bumetanide (Burinex) is the most potent loop diuretic currently available. Bumetanide is currently available in tablets for oral administration and solution for i.v./i.m. injection. The high potency of bumetanide and its favourable physicochemical properties may make it more suitable than other loop diuretics for administration via alternative routes.

A rapidly-absorbed formulation of a loop diuretic which may be administered less invasively than an injection could provide a useful alternative in many instances where a rapid diuresis is required. In addition, such a formulation may be useful in patients unable to swallow tablets.

Bumetanide solution for intranasal administration and bumetanide rectal suppositories have been formulated to address these needs.

Administration of bumetanide via the nasal route has been evaluated in rabbits. The serum concentrations peaked at approximately 10 minutes, and compared to i.v. injection higher serum concentrations were maintained for the first 1–2 hours following administration. The absolute bioavailability was about 50% (data on file at Leo Pharmaceutical Products).

Rectal administration of bumetanide in a suppository formulation has been evaluated in rabbits as well. $T_{\text{max}}$ ranged from 10 to 30 minutes, and absolute bioavailability was approximately 50% (data on file at Leo Pharmaceutical Products).

Thus, nasal and rectal administration of bumetanide have been found feasible based on bioavailability data from rabbits.
Based on the assumption of the approximate 50% absolute bioavailability, the present study will use doses of 2 mg (i.e., 100 µL of 20 mg/mL solution) for nasal administration and 2 mg suppositories. If bioavailability, unexpectedly, in humans is significantly greater than in rabbits, effective doses well within the usual therapeutic range will still have been administered.
2 INVESTIGATIONAL PLAN

The entire study protocol and amendments (3) are included in Appendix VI. Below in the section follows the summary including table with study procedures, compliance with ethical responsibilities and insurance and liability issues.

Information on study drug formulations produced and certified by Leo Pharmaceutical Products and treatment (drug administration) is given in Appendix VI.

Study Objective: To evaluate and compare the maximum serum concentration ($C_{max}$) of bumetanide, time to $C_{max}$ ($T_{max}$), of two 2 mg formulations of bumetanide (single dose) nasal spray and suppository respectively, and to compare the absolute and relative bioavailability and pharmacodynamic effect of the former two formulations with intravenous injection of 1 mg bumetanide and single dose of a 1 mg bumetanide tablet (immediate release) as reference, respectively, in healthy volunteers.

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**Primary Evaluation Parameter:** Concentration of bumetanide measured in serum and urine by HPLC assay. Pharmacokinetic parameters: $C_{\text{max}}$, $T_{\text{max}}$, $AUC_{0-T}$ and $AUC_{0-\infty}$, calculated from the serum concentration–versus–time curve and urinary recovery from urine concentration data of bumetanide. The measurement of urine volume and excretion of sodium, potassium and creatinine post–dosing were to be used for pharmacodynamic assessment.
## 2.1 STUDY PROCEDURES SCHEDULE, CHART

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<td></td>
<td>Day -14 to -1 Day 1</td>
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<td>Day 14</td>
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<td>Informed Consent</td>
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<td>Blood and urine sampling for haematology and clinical biochemistry</td>
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<td>Blood(^1) and Urine(^2) Sampling</td>
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<td>Drug Administration(^3)</td>
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<td>Recording of Adverse Events</td>
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1) for determination of bumetanide
2) for determination of bumetanide and assessment of urine volume and sodium, potassium and creatinine excretion
3) bumetanide single dose, one formulation per period in randomised order:
   a) 2 mg nasal spray; b) 2 mg suppository; c) 1 mg tablet; d) 1 mg i.v. injection
2.2 COMPLIANCE WITH ETHICAL RESPONSIBILITIES

This study was notified to the German Health Authorities (The government of Swabia). Prior to the commencement of subject recruitment the protocol was submitted to an independent ethics committee and the ethics committee of the Bavarian Physicians' Chambers.

The investigators signed a statement to confirm:

a) that the study was to be conducted to conform with the Declaration of Helsinki II as adopted by the 18th World Medical Assembly, 1964, and subsequent amendments, Tokyo, 1975, Venice, 1983, and Hong Kong, 1989.

b) that the protocol was to be approved by the above mentioned two ethics commissions (A written record of such approval has been provided to Leo Pharmaceutical Products.)

c) that the subjects' written, informed consent to participate in the study was obtained prior to enrollment in the study.

All subjects received written information. This information emphasized that participation in the study was voluntary and that the subject may withdraw from the study at any time.

2.3 INSURANCE AND LIABILITY

Subjects enrolled in the study were covered by 1) the insurance of [insert company name], Germany), and 2) the liability insurance of Leo Pharmaceutical Products/Løvens kemiske Fabrik in the event of medication-related injury or death.
3 RESULTS

Individual subject data are listed in Appendix II and summarized in the clinical report (Appendix VI including Tables 1–5). Data are listed in order of randomisation code number. The reference to Case Record Form Book (CRF) number for individual subjects is presented in Appendix II, Table II.1a.

3.1 STUDY PERIOD

The first subject attended visit 1 (pre-study assessment) on January 20, 1995.

The first and last bumetanide dosages were administered on January 21, 1995 and February 11, 1995, respectively.

The last subject attended the last study visit (follow-up assessment) on February 27, 1995.

The duration of the study was, therefore, 5 weeks.

Individual data on visit dates and intervals between visits/dosing periods are included in Appendix II, Tables II.1.a,b and Appendix VI, Table 2 and the clinical report, Appendix VI.

3.2 STUDY POPULATION

3.2.1 Disposition of study subjects

3.2.1.1 Recruitment of subjects
A total of 24 subjects were recruited for the study.
3.2.1.2 Randomised subjects

All recruited subjects complied with the eligibility criteria were randomised and completed the entire study period including four periods with administration of different formulations of bumetanide.

3.2.1.3 Subjects for pharmacokinetic, -dynamic and safety evaluation

All 24 subjects randomised completed the study according to the protocol and are considered in the analyses for pharmacokinetics, pharmacodynamics and safety.

3.3 BASELINE CHARACTERISTICS OF SUBJECTS

The baseline characteristics for the 24 subjects entered in the study are presented in this section.

3.3.1 Sex distribution and age

A total of 24 male subjects were included in the study. The mean age was 31.6 years (range 22–50). The individual subject demographic data are presented in Appendix II, Table II.2 and Appendix VI, Table 1.

3.3.2 Medical history

A medical history taken at visit 1 confirmed the eligibility of all subjects to participate in the study. No subject had a history of significant gastrointestinal disease, nor were there any significant concurrent illnesses. Individual data on medical histories including concurrent medication are recorded in Appendix II, Table II.3.

Individual data on tobacco and alcohol consumption are given in Appendix II, Table II.4.
3.3.3 Physical examination

All subjects were considered to be healthy according to the physical examination.

The mean values for the subjects' height, weight, and vital signs at enrollment, i.e. respiratory rate, heart rate, blood pressure, and temperature are given in Table I. In addition, all subjects had an ECG performed. No subject had ECG abnormalities (details are presented in Appendix VI (Clinical Report, Sections 2.3 and 5.2)). Also, the physical examination included checking of organ systems for abnormalities (e.g. head, eyes, ears, nose, throat and skin).

Table I: Height, weight and vital signs following physical examination of subjects (n=24) at time of enrollment (visit 1)

<table>
<thead>
<tr>
<th>Subject's height (cm)</th>
<th>Mean</th>
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<td>Height (cm)</td>
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<td>Respiratory rate/min.</td>
<td>15.38</td>
<td>2.45</td>
<td>10.00</td>
<td>21.00</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>67.04</td>
<td>12.04</td>
<td>42.00</td>
<td>93.00</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>124.63</td>
<td>10.42</td>
<td>110.00</td>
<td>141.00</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77.33</td>
<td>6.89</td>
<td>58.00</td>
<td>90.00</td>
</tr>
<tr>
<td>Temperature, oral (°C)</td>
<td>36.35</td>
<td>0.31</td>
<td>35.50</td>
<td>36.00</td>
</tr>
</tbody>
</table>

Individual subject data concerning height, weight and vital signs are presented in Appendix II, Tables II.2 and 5 a–d.

3.3.4 Baseline haematology and clinical biochemistry

At enrollment no subject had laboratory values outside the reference range. All subjects had negative tests for Hepatitis–B–surface–antigen (HBsAg), human immunodeficiency virus 1 and 2 antibody (HIV) and for drug abuse (screening tests for: opiates, alcohol, amphetamine, cocaine, cannabinoids, barbiturates, and benzodiazepines).
Individual data are presented in Appendix II, Tables II.6 a–d.

3.4 PROTOCOL DEVIATIONS

Violation of protocol eligibility criteria did not occur in any subject. However, deviations from protocol are summarised below.

1) Nasal spray:
   Subject no. 1 missed part of dose (a drop)
   Weights before and after dose seemed ok
   Too strong, and too much volume of spray dose (100 µl)

2) I.v. injection:
   From urine collection data it is assumed that subject nos. 3 and 4 could have been injected partly subcutaneously
   Not reported by investigator

3) Sampling:
   Subject no. 6 no sample, neither 5 nor 10 min. after i.v.
   Time deviations before blood sampling max. 4 min. (n=2); 3 min. (1); 2 min. (3); 1 min. (15)
   10 subjects were not able to supply all (15 min.) samples within the first 2 hours.
   3 of these 10 subjects also lacked either a 4–6 h or a 8–12 h sample.

   For details see Appendix VI.

3.5 PHARMACOKINETIC RESULTS

Prior to each study drug dosing day each volunteer was checked for compliance with protocol specifications (e.g. on medication, fluid intake). Individual data are presented in Appendix II, Table II.7. Recordings of the individual data for sampling of blood and urine following each dosing with bumetanide are presented in Appendix II, Tables II.8 a,b. The
serum and urine concentrations and the pharmacokinetic parameters for bumetanide presented below are calculated from the individual data obtained from the 24 subjects who received all four single dosages of 2 mg bumetanide (nasal and rectal formulation) and 1 mg bumetanide as immediate release tablet and i.v. injection according to a 4-period cross-over study design. (For individual data see Appendix II, Tables II.9-11).

3.5.1 Serum concentrations of bumetanide after administration of 2 mg doses of bumetanide as rectal and nasal formulations (test) and 1 mg bumetanide as immediate release tablet and i.v. formulations (reference)

Actual sampling times were recorded during the drug administration and sampling phases of this study. In a few instances, these sampling times varied slightly from the proposed time according to the study protocol. Proposed sampling times were used for the calculation of all pharmacokinetic parameters. The largest deviation from proposed sampling time was 4 min. which occurred at two occasions. Other deviations were 1, 2, or 3 min. For details see Appendix VI, Clinical Report, Table 4).

Serum concentrations of bumetanide were determined by HPLC assay. The Figures I and II below show the arithmetic plots of the mean serum concentration versus time curves in full and reduced scale, and Table II lists the mean AUC, \( C_{\text{max}} \), and \( T_{\text{max}} \) values of bumetanide after the administration of the four dosages of bumetanide to fasting subjects. Bumetanide was detected in all first post-dosing samples (at 5 min.) following i.v. formulation and at 10 min. in some samples (in all at 20 min.) following tablet administration.

Following nasal and rectal administration bumetanide could be detected in some samples at 5 min. post dosing (in all samples at 20 min.), and it was still detectable in some samples at 8 hours.

Figure III shows the distribution of \( T_{\text{max}} \) values for nasal and rectal formulations versus tablet. No major difference between mean AUC-values after administration of three of the four different pharmaceutical formulations (i.v., tablet or nasal spray) of bumetanide was observed. However, rectal administration (suppository) revealed an unexpected and substantially lower value for AUC compared to the above three formulations. Also, \( C_{\text{max}} \)
following dosing with suppository was lower than after tablet and nasal spray. \( T_{\text{max}} \) values tended not to be that different comparing nasal spray and tablet administration. Thus, the bioavailability of bumetanide in nasal spray formulation did not exceed that of tablet, and the suppository displayed a substantially lower bioavailability than tablet.

3.5.2 Urine concentrations of bumetanide after administration of 2 mg doses of bumetanide as rectal and nasal formulations (test) and 1 mg bumetanide as immediate release tablet and i.v. formulations (reference)

The urine concentrations of bumetanide were determined by HPLC assay in the samples collected in eight intervals up to 24 hours post dosing (See Appendix II).

Figures I, II and III, as well as Table II are listed in Section 7.

3.6 PHARMACODYNAMIC ASSESSMENTS

The pharmacodynamic assessments were done by measurement of urine volume excreted following administrations of each of the four drug formulations and by measurement of sodium concentration in urine vs. time.

Fig. IV and V and Tables III and IV illustrate the cumulative effect of the four bumetanide formulations on urine excretion.

Apparently no major difference was observed between nasal and tablet p.o. administration. It should be noted as seen from the individual curves (Appendix I) that huge interindividual variations in dynamic data was observed. The rectal formulation (suppository) seems to give a slower onset in pharmacodynamic effect compared to the other three formulations (nasal, tablet, i.v.).

Figure VI illustrates the comparison between bumetanide formulations and urine volume excreted during the first 45 min. after drug administration via nasal, i.v. and p.o. route.
The urine concentrations of potassium, sodium and creatinine measured in the individual urine samples collected in eight protocol specified intervals up to 24 hours post dosing are presented in Appendix II.

Figures IV, V and VI as well as Tables III and IV are listed in Section 7.

3.7 CONCOMITANT TREATMENT

During the study period no subject was given or reported taking any concomitant medication.

3.8 SAFETY OF STUDY DRUGS

3.8.1 Adverse Events

Neither serious nor severe adverse events were observed. All of the reported/observed adverse events were of a mild intensity lasting less than 18 hours. Eight subjects reported 20 adverse events. Five subjects reported adverse events after one dose, 1 subject after 2 dosings, and 3 subjects after all four administrations. The most frequent reported adverse events were headache and tiredness. Details on severity and duration of the individual adverse events and the possible relationship to drug administration are given in Appendix VI, (Clinical Report, Section 5.1 and Table 5).

All adverse events were resolved at end of study.

No subject withdrew from the study due to adverse events. No serious or unexpected adverse events were experienced and no persistent adverse event was reported.

No irritation in nose or throat was reported after the nasal application by spray.

No general complaints related to nasal or rectal dose administration.
Individual data are presented in Appendix II, Table II.3.

3.8.2 Laboratory abnormalities

At the screening examination (visit 1) all volunteers had haematology and clinical chemistry parameters within the limits for inclusion as specified in the study protocol, and screenings for drug abuse, HIV-antibodies and hepatitis B-antigen were negative.

No clinically significant deviations from baseline values were seen for individual subjects at the follow-up assessment for haematology and clinical biochemistry parameters, except for three cases. The comparison between the pre-treatment and the end of study assessments is presented in Tables V, VI, and VII. Individual laboratory results for the pre-treatment and end-of-study haematology and clinical biochemistry tests are presented in Appendix II. Tables 14–16.

In seven cases the end of study value (4 days after last drug administration) for a laboratory parameter deviated from baseline and was outside the reference range. At follow-up all parameters had returned to normal range or to the volunteer's baseline, except for 1 subject (no. 15) where final outcome data is not available (leucocytes in urine; glucose in serum).

For details see Appendix VI, Clinical Report, Section 5.2.

Tables V, VI and VII are listed in Section 7.
4 DISCUSSION

This study was conducted to evaluate and compare the bioavailability and pharmacodynamic effect of 2 mg bumetanide administered as i.v., nasal spray and suppository formulations and one immediate release tablet (reference) in healthy subjects. The assessment was based on the pharmacokinetic parameter, area under serum concentration versus time curve (AUC). In addition, the pharmacodynamic effects of the different formulations of 2 mg bumetanide were compared by means of urine volume and sodium excretion.

This was a single-centre, randomised, cross-over, pharmacokinetic study performed in Germany. According to the protocol, 24 male subjects should complete the study including: i) pre-study eligibility assessments, ii) four single dose drug administrations periods, iii) follow-up assessment. A total of 24 subjects passed the eligibility assessments and completed the entire study period. All 24 contributed with the scheduled number of 16 blood samples during the first 12 hours after each dosing as well as with urine samples, 8 collections during 24 hours post dosing, with accurate collection and recording of the urine voided. The interval between the four dosing periods of bumetanide was as scheduled one week. Overall, the subjects' compliance with the study protocol was good with very few (and minor) deviations in sampling and collection schedule.

Subjects were randomised for the order of treatment (dose–formulation). Only the investigator actually responsible for dispensing of doses had access to the randomisation schedule. It was not possible to blind subjects and staff at the time of dosing due to the different routes of administration. Persons conducting the analysis of bumetanide samples were blinded. At the end of the study all study medication was accounted for.

The assays for bumetanide in serum and urine were performed at Analytical–Chemical Research Department, Leo Pharmaceutical Products, Ballerup, Denmark, where a validated HPLC method was available. Samples were stored at -20° C.

From the results for bumetanide concentration in serum and the calculations of mean pharmacokinetic parameters it can be concluded that nasal spray administration did not show
marked difference compared to tablet and i.v. dosing. However, the rectal (suppository) administration revealed substantially lower values for the AUC and $C_{max}$, $T_{max}$ values tended not to be that different comparing nasal and tablet administration. The pharmacokinetic parameters agreed well with previously reported data for bumetanide following i.v. and tablet administration.

The pharmacodynamic effects of bumetanide i.e. prompt onset of diuresis and urinary sodium excretion following administration of the i.v. and tablet formulation were comparable to results from previous studies (2,3). However, no major difference was observed between nasal and tablet administration and a huge interindividual variation was observed.

The rectal formulation (suppository) seemed to give a slower onset of the pharmacodynamic effect compared to i.v., tablet and nasal spray.

A total of 8 subjects reported 20 adverse events. Headache and tiredness were the most frequently reported. All adverse events resolved within day of onset. No patient withdrew from the study due to adverse events. No serious or unexpected adverse events were experienced by subjects in this study.

No reporting of irritation in nose or throat after nasal application or other more general complaints related to nasal and rectal drug administration.
CONCLUSION

Bumetanide single dose (2 mg) pharmacokinetic and pharmacodynamic assessments of two new pharmaceutical formulations, nasal spray and suppository for rectal application compared to administration of tablet and i.v. solution (1 mg bumetanide) did not show any pharmacokinetic improvement in terms of increased bioavailability versus tablet. On the contrary, the suppository formulation had a very poor bioavailability. The pharmacodynamic evaluation did neither indicate improved effect (measured as urine volume or sodium excretion) nor did the two new formulations, nasal spray and suppository display a quicker onset of effect compared to tablet.
6 REFERENCES

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7 FIGURES AND TABLES

Figures I – VI

Tables II – IV
BUN 9403 DE study, subject 1 – 24
SERUM CONCENTRATION

ng/ml

Time (hours)
Fig. II

**BUN 9403 DE study, subject 1–24**

**SERUM CONCENTRATION**

ng/ml

- IV
- PO
- nasal
- rectal

Time (hours)
Distribution of Tmax following administration of 1 mg bumetanide: tablet compared with 2 mg nasal spray and suppository in healthy subjects (mean, n=24)
BUN 9403 DE study
CUMULATED VOLUME 0 - 2 hours

ml

0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00
Time (hours)
BUN 9403 DE study
CUMULATED VOLUME 0 - 8 hours

ml

Time (hours)
BUN 9403 study: Volume versus AUC
Table II

Bumetanide pharmacokinetic parameters (mean values)

<table>
<thead>
<tr>
<th>Dose</th>
<th>( \text{AUC}_{0-\infty} ) (h x ( \mu \text{g/l} ))</th>
<th>( C_{\text{max}} ) (( \mu \text{g/l} ))</th>
<th>( T_{\text{max}} ) hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>I.v. 1 mg (n=24)</td>
<td>80.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tablet 1 mg (n=24)</td>
<td>70.8 (87.8 %)</td>
<td>35.78</td>
<td>1.14</td>
</tr>
<tr>
<td>Nasal 2 mg (n=24)</td>
<td>81.5 (101.4 / 50.7 %)</td>
<td>36.36(^1)</td>
<td>0.74</td>
</tr>
<tr>
<td>Supp. 2 mg (n=24)</td>
<td>29.3 (36.4 / 18.2 %)</td>
<td>15.18</td>
<td>1.21</td>
</tr>
</tbody>
</table>

\(^1\) First max

For 7 subjects (nos: [redacted]), two \( C_{\text{max}} \) were observed

<table>
<thead>
<tr>
<th>Dose</th>
<th>( C_{\text{max}_1} )</th>
<th>( T_{\text{max}_1} )</th>
<th>( C_{\text{max}_2} )</th>
<th>( T_{\text{max}_2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal (n=7)</td>
<td>30.29</td>
<td>0.58</td>
<td>32.87</td>
<td>1.93</td>
</tr>
<tr>
<td>Nasal (n=17)</td>
<td>38.86</td>
<td>0.81</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### BUN 9403 DE

**Effekt - kumulativ urinudskillelse (ml)**

Mean SD range samt procent versus i.v. (1 mg)

<table>
<thead>
<tr>
<th>Tid (min.)</th>
<th>Dosis: Nasal (2 mg)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Dosis: Tablet (1 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urin (ml)</td>
<td>Mean</td>
<td>± SD</td>
<td>Range</td>
<td>%</td>
<td>Mean</td>
</tr>
<tr>
<td>0 - 15</td>
<td>129</td>
<td>96</td>
<td>(20 - 318)</td>
<td>56</td>
<td>60</td>
<td>139</td>
</tr>
<tr>
<td>0 - 30</td>
<td>204</td>
<td>141</td>
<td>(59 - 630)</td>
<td>45</td>
<td>38</td>
<td>173</td>
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<tr>
<td>0 - 45</td>
<td>435</td>
<td>205</td>
<td>(71 - 887)</td>
<td>60</td>
<td>42</td>
<td>307</td>
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<tr>
<td>0 - 60</td>
<td>698</td>
<td>228</td>
<td>(351 - 1138)</td>
<td>74</td>
<td>59</td>
<td>558</td>
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<tr>
<td>0 - 75</td>
<td>975</td>
<td>303</td>
<td>(521 - 1510)</td>
<td>83</td>
<td>77</td>
<td>889</td>
</tr>
<tr>
<td>0 - 90</td>
<td>1112</td>
<td>340</td>
<td>(587 - 1803)</td>
<td>88</td>
<td>85</td>
<td>1072</td>
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<tr>
<td>0 - 105</td>
<td>1360</td>
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<td>97</td>
<td>97</td>
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<td>0 - 120</td>
<td>1481</td>
<td>462</td>
<td>(699 - 2456)</td>
<td>101</td>
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</tbody>
</table>

<table>
<thead>
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<th>Tid (min.)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urin (ml)</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td>0 - 30</td>
<td>450</td>
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<td>0 - 60</td>
<td>949</td>
</tr>
<tr>
<td>0 - 120</td>
<td>1471</td>
</tr>
<tr>
<td>TREAT</td>
<td>MEAN</td>
</tr>
<tr>
<td>----------</td>
<td>------</td>
</tr>
<tr>
<td>iv</td>
<td></td>
</tr>
<tr>
<td>0-15 min</td>
<td>229.95</td>
</tr>
<tr>
<td>0-30 min</td>
<td>449.93</td>
</tr>
<tr>
<td>0-45 min</td>
<td>723.66</td>
</tr>
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<td>0-1 h</td>
<td>948.70</td>
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<td>0-1h 15 min</td>
<td>1160.78</td>
</tr>
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<td>0-1 h 30 min</td>
<td>1258.07</td>
</tr>
<tr>
<td>0-1 h 45 min</td>
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