ABSOLUTE BIOAVAILABILITY OF BUMETANIDE
AFTER INTRAMUSCULAR INJECTION
A randomized, open, cross-over study comparing Bumetanide (2 mg / 4 ml)
administered by i.V. or i.M. route in normal healthy volunteers

Re. :
Laboratoires LEO Re. : BU 9301 F
Approval date of the Consultative Committee for Protection of Persons : January 28th, 1993

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Monitor :
[Redacted], Ph.D.
Laboratoires LEO S.A.

The study has been conducted at :
[Redacted], (F)

The clinical study report has been redacted using the following principles: Where necessary, information is anonymised to protect the privacy of study subjects and named persons associated with the trial as well as to retain commercial confidential information. Summary data are included but data on individual study subjects, including data listings, are removed. This may result in page numbers not being consecutively numbered. Access to anonymised data on individual study subject may be obtained upon approval of a research proposal by the Patient and Scientific Review Board. Appendices to the clinical study report are omitted. Further details and principles for anonymisation is available in the document LEOPHARMA PRINCIPLES FOR ANONYMISATION OF CLINICAL TRIAL DATA.
ABSOLUTE BIOAVAILABILITY OF BUMETANIDE
AFTER INTRAMUSCULAR INJECTION
A randomized, open, cross-over study comparing Bumetanide (2 mg / 4 ml)
administered by I.V. or I.M. route in normal healthy volunteers

STUDY PERSONNEL:

Investigator : [Redacted], M.D.
Co-Investigator : [Redacted], M.D.
Statistician : [Redacted]

Principal Clinical Project Coordinator : [Redacted], M.D.
Study Monitor : [Redacted], Ph.D.
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1. STATEMENT OF THE QUALITY ASSURANCE.

TITLE:

Absolute bioavailability of Bumetanide after intramuscular injection: A randomized, open, cross-over study comparing Bumetanide (2 mg / 4 ml) administered by I.V. or I.M. route in normal healthy volunteers.

Institut ASTER Re.

The Quality Assurance Unit (Q.A.U.) of [redacted] certifies that a quality control process was applied to each stage of data handling to ensure that all data is reliable and has been processed correctly.

This report is an authentic description of all procedures, observations and findings of the totality of the study.
2. SUMMARY.

TITLE:

Absolute bioavailability of Bumetanide after intramuscular injection: A randomized, open, cross-over study comparing Bumetanide (2 mg / 4 ml) administered by I.V. or I.M. route in normal healthy volunteers.

INVESTIGATOR: [Name], M.D.

CO-INVESTIGATOR: [Name], M.D.

PRINCIPAL CLINICAL PROJECT COORDINATOR: [Name], M.D.

STUDY MONITOR: [Name], Ph.D.

STUDY OBJECTIVES:

The objectives of the study were:

- to determine the absolute bioavailability of Bumetanide injection formulation at a dose of 2 mg in 4 ml administered by intramuscular route in normal healthy volunteers,
- to evaluate the other pharmacokinetic parameters of Bumetanide by measuring its serum levels and urinary elimination,
- to compare diuresis, natriuresis and kaliuresis between the two routes of administration,
- to assess the local tolerability of the formulation administered intramuscularly.

STUDY SUBJECTS:

- 18 healthy volunteers,
- Sex: male,
- Ethnic group: caucasian,
- Age: 20 to 30 years.

STUDY DESIGN:

This was an open study, randomized according to a cross-over design, comparing a single injection of Bumetanide 2 mg administered by intravenous or intramuscular route (table 1, page 22).
STUDY MEDICATION:

Solution (Burinex® injection, manufactured by Laboratoires LEO S.A. - France, and certified by Leo Pharmaceutical Products - Denmark) containing Bumetanide 0.5 mg per ml (in the following vehicle: Xylitol, disodium hydrogen phosphate, sodium dihydrogen phosphate and water for injection) distributed in amber glass ampoules of 4 ml, each ampoule containing 2 mg Bumetanide, batch n°.

ADMINISTRATION:

Each subject received a single dose of Bumetanide at each period: once a 2 mg / 4 ml intramuscular administration and once a 2 mg / 4 ml intravenous administration.

Each injection occurred in the morning by 8 a.m. and was administered by the investigator or his associate only or under his direct supervision.

2 mg dose was administered as one single intramuscular or intravenous injection.

For administration by intravenous route, a catheter was inserted into a forearm vein. Perfusion was initiated with a glucose 5% solution. Glucose infusion was stopped and Bumetanide was administered through the infusion set. The latter was washed with glucose 5% solution and removed.

EVALUATION CRITERIA:

- Clinical tolerance:

* Physical examination with the volunteer's subjective comments at inclusion (between Day -14 and Day -1) and on each administration day.

* Vital signs: blood pressure and pulse rate measurements,

  . Between Day -14 and Day -1: inclusion blood pressure and pulse rate
  . On each administration day: T0 (before administration), 5 min, 15 min, 30 min, 1.0 H, 2.0 H, 4.0 H, 8.0 H and 12.0 H hours after administration.

* Local tolerability of injection: end of injection, 0.5 H, 2.0 H, 4.0 H and 12.0 H.

* Clinical laboratory tests: before first dosing (between Day -14 and Day -1).

* Safety blood laboratory examinations (electrolytes): Before and 8 hours after drug administration.
Pharmacokinetics:

* Serum samples

Serum levels of Bumetanide were measured at:

T0 (prior to dosing) then at the following times: 5 min, 10 min, 20 min, 30 min, 35 min, 1.0 H, 1.5 H, 2.0 H, 2.5 H, 3.0 H, 4.0 H, 5.0, 6.0 H and 8.0 hours after each administration.

* Urinary samples

On each period, urinary samples for Bumetanide elimination, diuresis, natriuresis and kaliuresis measurements have been collected at the following intervals:

- 0 - 24 hours the day before administration,
- 0 - 1 hour,
- 1 - 2 hours,
- 2 - 4 hours,
- 4 - 6 hours,
- 6 - 12 hours after administration.

STATISTICAL ANALYSIS:

Descriptive statistics of subjects' characteristics were carried out by [name].

The statistical analysis of the data concerning sodium, potassium, chloride and bicarbonates levels was performed by [name]'s Statistics Department.

DESCRIPTIVE STATISTICS

Descriptive statistics: N, Mean, standard deviation (STD), minimum (MIN) and maximum (MAX) values are reported for sodium, potassium, chloride and bicarbonates levels for each treatment and each time.

The statistical analysis concerns the eighteen subjects.

COMPARISON OF VARIATIONS BETWEEN T=0H AND T=8H

The changes observed in the measures before administration and 8th hour measures were compared using a Student t test for paired data. The comparison was made for each treatment and each period.

ANALYSIS OF VARIANCE

The changes in biological parameters, measured before and 8 hours after injection were analysed.

An analysis of variance was performed using frequency as hypothesis effect and num(sequence) as an error term. If there was no sequence effect, treatments were compared.
STATISTICAL SOFTWARE AND OUTPUT OF RESULTS

Data entry and statistical analysis were performed using SAS/FSP and SAS/STAT from the SAS package (Version 6.04, SAS Institute, North Carolina, USA).

Individual data lists, descriptive statistics, SAS statistical analysis listings and values out of normal range are reported in Appendix VIII of this report.

STUDY COMPLETION : April 16th, 1993.
3. STUDY AMENDMENTS.

An amendment to the study protocol was written on the 23rd of March 1993.

According to this amendment, the following modifications were decided:

* the duration of subjects hospitalization was 48 hours (24 hours post-dosing) instead of 36 hours (12 hours post-dosing).

* the duration of rest after injection: subjects remained lying in their bed during at least 4 hours after drug injection instead of 2 hours.

This amendment is presented in Appendix VII of this report.
4. STUDY DEVIATIONS.

The study was carried out according to the protocol and to the protocol amendment, except for the following deviations:

- A number was assigned to the subject when he decided to participate in the study and not after inclusion screening. Hence, administrations were not performed in a chronological order corresponding to the subjects numbers.

- During interval [0 - 24] hours on Day 0 of both periods, the urine volume deep frozen was 5 ml instead of 2 X 7 ml.
5. RESULTS.

5.1. Clinical and biological parameters.

5.1.1. Volunteers.

Twenty-one healthy volunteers have signed the informed consent form and performed the inclusion tests. Two out of them have withdrawn their informed consent before the first administration period for personal reasons.

Nineteen volunteers entered the study. Eighteen volunteers completed the study.

One drop-out was observed:

- Subject number ■ was withdrawn from the study at the end of the first period because of a severe orthostatic hypotension with loss of consciousness occurring 1.5 hour after the first Bumetanide injection. This subject was replaced by subject number □.

Table 2 (page 23) summarizes the demographic data and baseline characteristics of the volunteers who completed the study.

The mean values (± S.E.M.) of these observed characteristics were:

- Age : 22.5 ± 0.5 years (range : 20 - 30 years).
- Body weight : 72.78 ± 1.88 kg (range : 62.0 - 92.4 kg).
- Height : 177.4 ± 1.8 cm (range : 165 - 196 cm).

5.1.2. Concomitant medication.

No associated medication was administered during the study.

5.1.3. Inclusion evaluation.

5.1.3.1. Clinical screening.

Each subject underwent a clinical examination at the time of inclusion into the panel. A clinical history was taken and a complete examination was performed at this time. On inclusion into the study, this examination was repeated and confirmed the previous examination.

The details of this examination are presented in each subject's case report form. No clinically relevant abnormality was observed during this examination.
5.1.3.2. Vital signs.

Individual values of blood pressure and pulse rate are presented in each case report form and in the statistical analysis presented in Appendix VIII of this report. No clinically relevant abnormality was reported for any subject.

5.1.3.3. Electrocardiograms.

The electrocardiograms are presented in individual case report forms. No clinically relevant abnormality was observed for any subject.

5.1.3.4. Laboratory survey.

All measured parameters are submitted to the official quality control programme of the French Ministry of Health (Decree of June 18th, 1979 setting the specifications mentioned on the article 6 of the decree n° 78-1148 of December 7th, 1978 relative to the quality control of the clinical chemistry data allowed by the article L. 716 - 14 of the Public Health Code, Official Bulletin n° 79/27, text n° 16887).

The laboratory parameters measured at the time of inclusion of the subjects into the study are presented in each case report form and in the statistical analysis presented in Appendix VIII of this report.

The inclusion laboratory surveys only revealed minor abnormalities (table 3, page 24). These abnormalities did not prevent the inclusion of these subjects in the study.

5.1.4. Evaluation during the study.

5.1.4.1. Clinical screening.

a) General tolerance:

The clinical tolerance was good for 18 subjects out of 19.
Two other subjects developed the following minor adverse events which did not prevent the study continuation:

- Local tolerance:
  
  * Pain at injection site after a 2 mg Bumetanide intramuscular injection:

  Two subjects out of eighteen complained of pain at injection site:

  Detailed observations are presented in each subject's case report form.
5.1.4.2. Vital signs.

All values of blood pressure and pulse rate are presented in each case report form and in the statistical analysis presented in Appendix VIII of this report.

Some values measured during the study period were not within the clinically normal or acceptable range and are presented in tables 4.1, 4.2 and 4.3, pages 25, 26 and 27.

The most frequent abnormalities observed were a decrease of systolic blood pressure and an increase of pulse rate when subjects stood up.

These abnormalities are directly related to hypovolemia induced by Bumetanide injections.

These abnormalities did not prevent the study continuation except for subject no.[-] who was withdrawn from the study for severe hypotension with fainting after a 2 mg Bumetanide intravenous injection.

5.1.4.3. Laboratory survey.

Individual data are presented in each case report form and in the statistical analysis presented in Appendix VIII of this report.

The biological tolerance was excellent.

Laboratory parameters measured during the study were within the normal or clinically acceptable range, except for three subjects who presented minor abnormalities (slight hypokaliemia, slight hyponatremia and slight hypochloremia) which are related to Bumetanide administration. (see table 5, page 28).

5.1.4.4. Samples for pharmacokinetic and pharmacodynamic evaluations.

All blood samples were withdrawn according to the protocol.

Urine was collected according to the protocol. Nevertheless the following subjects have not urinated during the following intervals:

- Subject no.[-] has not urinated during the interval [2 - 4] hours post intramuscular injection of period 1,
- Subject no.[-] has not urinated during the interval [4 - 6] hours post intravenous injection of period 1,
- Subject no.[-] has not urinated during the interval [4 - 6] hours post intravenous injection of period 2,
- Subject no.[-] has not urinated during the intervals [4 - 6] hours post intravenous and intramuscular injection of, period 1 and 2, respectively,
- Subject no.[-] has not urinated during the interval 4 - 6 hours post intramuscular injection of period 2.
2 mg Bumetanide injections by intravenous or intramuscular route increased significantly and quickly diuresis during the two first hours after injection and induced a hypovolemia in some volunteers.

According to the protocol water intake was restricted, hence some volunteers have not urinated during some urine collection intervals.

5.2. Statistical results.

5.2.1. Analysis of clinical examination.

5.2.1.1. Descriptive statistics.

Descriptive statistics are presented in Appendix VIII of this report (page 3 and page 4).

5.2.1.2. Comparison of values between T 0 and T 8.0 H.

The results of the comparison of the values observed at T 0 and T 8.0 H are presented in Appendix VIII of this report (page 5 to page 8).

This analysis showed the following significant results:

- Treatment A (I.V route):
  - Bicarbonates: increase of values between T 0 and T 8.0 H (p<0.02).
  - Chloride: decrease of values between T 0 and T 8.0 H (p<0.01).
  - Sodium: decrease of values between T 0 and T 8.0 H (p<0.03).

- Treatment B (I.M. route):
  - Bicarbonates: increase of values between T 0 and T 8.0 H (p<0.01).
  - Chloride: decrease of values between T 0 and T 8.0 H (p<0.01).
  - Sodium: decrease of values between T 0 and T 8.0 H (p<0.02).

- Period 1:
  - Bicarbonates: increase of values between T 0 and T 8.0 H (p<0.04).
  - Chloride: decrease of values between T 0 and T 8.0 H (p<0.01).
  - Potassium: decrease of values between T 0 and T 8.0 H (p<0.04).

- Period 2:
  - Bicarbonates: increase of values between T 0 and T 8.0 H (p<0.01).
  - Chloride: decrease of values between T 0 and T 8.0 H (p<0.01).
  - Sodium: decrease of values between T 0 and T 8.0 H (p<0.01).
5.2.1.3. Analysis of variance.

The results are presented in Appendix VIII of this report, p.9 to p.12.

The analysis did not show any significant difference between sequence AB and sequence BA, except for Potassium (p<0.01).
For Sodium, Chloride and Bicarbonates, no significant difference between the treatments was detected.

5.2.1.4. Values out of normal range.

Values out of normal range are presented in Appendix VIII of this report, p.13.
6. DISCUSSION.

Clinical tolerance:

Under the conditions of this study, 2 out of 19 subjects presented side effects (fainting, dizziness and muscular cramps) which might be related to 2 mg Bumetanide injection.

One of these subjects presented a severe hypotension with fainting 1.5 hour after intravenous injection and was withdrawn from the study because he fainted again 4.5 hours after injection with a severe decrease of systolic blood pressure at 49 mmHg when he sat up. As soon as subject tried to stand up or sit up, dizziness occurred and systolic blood pressure decreased till the 9th hour post-injection.

The second subject complained of dizziness without fainting when he stood up between the 2nd and 8th hour after 2 mg Bumetanide intravenous injection.

Another subject reported a minor adverse event (headache) which disappeared spontaneously and which is probably not related to Bumetanide. He complained also of muscular cramps of slight intensity probably related to Bumetanide administration.

All these side effects disappeared spontaneously without after effects.

The local tolerance after a 2 mg Bumetanide intramuscular injection was excellent. Only two subjects complained of pain appearing during injection and disappearing within two minutes after injection.

No local adverse reaction was observed at any injection site.

Concerning the vital signs, abnormal values were recorded when subjects stood up. A decrease of systolic blood pressure with an increase of pulse rate were often recorded one minute after subject stood up.

These modifications are directly related to Bumetanide injection and seem not dependent of the administration route.

Bumetanide is a strong loop diuretic.

Bumetanide intramuscular or intravenous injections induce quickly an important increase of diuresis in healthy volunteer. It is often followed by an increase of pulse rate to correct hypovolemia. If this reflex tachycardia is not sufficient to correct hypovolemia, orthostatic hypotension occurs.

Biological tolerance:

The biological abnormalities were rare and minor. Their incidence was similar after both treatments. These changes were not clinically relevant.

Such slight modifications of sodium, potassium and chloride levels can be observed after administration of all the others loop diuretics.
7. CONCLUSION.

Under the conditions of the study, the clinical and biological tolerance was good after 2 mg Bumetanide intravenous injection in all subjects participating in the study except for one subject who was dropped-out.

The general, local and biological tolerance of the new administration route (intramuscular route) was excellent.

Onset time of effect is quick for both routes of administration.

The vascular compliance being very different between young healthy volunteers and patients with severe left ventricular insufficiency or severe renal failure, the results of this study allow to use Bumetanide by intramuscular route in patients.
July 30th, 1993

8. SIGNATURES.

IN AGREEMENT WITH THE REPORT.

Principal Investigator

M.D.

30/07/93

date

Co-investigator

M.D.

30/07/93

date
Table 1: Randomization schedule

<table>
<thead>
<tr>
<th>SUBJECT'S NUMBER</th>
<th>SUBJECT'S CODE</th>
<th>PERIOD 1</th>
<th>PERIOD 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>Drop-out</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

- Treatment A: A single 2 mg intravenous injection of Bumetanide, batch n°  
- Treatment B: A single 2 mg intramuscular injection of Bumetanide, batch n°  
Table 2: Age, weight, height of the subjects and mean values.

<table>
<thead>
<tr>
<th>SUBJECT'S NUMBER</th>
<th>SUBJECT'S CODE</th>
<th>AGE (years)</th>
<th>WEIGHT (kg)</th>
<th>HEIGHT (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEANS</td>
<td>22.47</td>
<td>72.78</td>
<td>177.42</td>
<td></td>
</tr>
<tr>
<td>S.E.M.</td>
<td>0.54</td>
<td>1.88</td>
<td>1.83</td>
<td></td>
</tr>
<tr>
<td>RANGE</td>
<td>20 - 30</td>
<td>62.0 - 92.4</td>
<td>165 - 196</td>
<td></td>
</tr>
</tbody>
</table>
Table 3: Deviations from normal range in the inclusion tests.

<table>
<thead>
<tr>
<th>No</th>
<th>CODE</th>
<th>PARAMETERS</th>
<th>OBSERVED VALUES</th>
<th>ACCEPTABLE RANGE</th>
<th>INTENSITY</th>
<th>SYMPTOMATIC</th>
<th>INTERPRETATION</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>White cells</td>
<td>11.0 G/l</td>
<td>4.0 - 10.0 G/l</td>
<td>Slight</td>
<td>No</td>
<td>Not clinically relevant</td>
<td>6 days later: 9.8 G/l</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A.S.A.T.</td>
<td>54 IU/l</td>
<td>&lt; 50 IU/l</td>
<td>Slight</td>
<td>No</td>
<td>Not clinically relevant</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A.L.A.T.</td>
<td>56 IU/l</td>
<td>&lt; 50 IU/l</td>
<td>Slight</td>
<td>No</td>
<td>Not clinically relevant</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 4.1: Deviations from acceptable range in the vital signs during the study.

<table>
<thead>
<tr>
<th>No</th>
<th>Code</th>
<th>Period</th>
<th>Formulation</th>
<th>Hour</th>
<th>Abnormality</th>
<th>Parameters</th>
<th>Observed Values</th>
<th>Acceptable Range</th>
<th>Intensity</th>
<th>Symptomatic</th>
<th>Related with Study Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>A</td>
<td>15 min</td>
<td>Decrease</td>
<td>SSBP</td>
<td>97</td>
<td>100 - 150</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1.0 hour</td>
<td>Increase</td>
<td>SPR</td>
<td>110</td>
<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1.5 hour</td>
<td>Decrease</td>
<td>SSBP</td>
<td>93</td>
<td>100 - 150</td>
<td>Moderate</td>
<td>Fainting</td>
<td>Probable</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2.0 hour</td>
<td>Decrease</td>
<td>SSBP</td>
<td>84</td>
<td>100 - 150</td>
<td>Moderate</td>
<td>Dizziness</td>
<td>Probable</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>4.0 hour</td>
<td>Decrease</td>
<td>SSBP</td>
<td>62</td>
<td>100 - 150</td>
<td>Severe</td>
<td>Fainting</td>
<td>Probable</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>4.75 hour</td>
<td>Decrease</td>
<td>SSBP</td>
<td>49</td>
<td>100 - 150</td>
<td>Severe</td>
<td>Fainting</td>
<td>Probable</td>
</tr>
<tr>
<td>1</td>
<td></td>
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<td></td>
<td>8.0 hour</td>
<td>Increase</td>
<td>SPR</td>
<td>129</td>
<td>40 - 100</td>
<td>Moderate</td>
<td>Dizziness</td>
<td>Probable</td>
</tr>
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<td>12.0 hour</td>
<td>Increase</td>
<td>SPR</td>
<td>110</td>
<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>B</td>
<td>2.0 hour</td>
<td>Increase</td>
<td>SPR</td>
<td>110</td>
<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
</tr>
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<td>Increase</td>
<td>SPR</td>
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<td>Slight</td>
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<td>Probable</td>
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<td>SPR</td>
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<td>40 - 100</td>
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<td>LSBP</td>
<td>95</td>
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<td>Decrease</td>
<td>LSBP</td>
<td>95</td>
<td>100 - 150</td>
<td>Moderate</td>
<td>No</td>
<td>Probable</td>
</tr>
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<td>SPR</td>
<td>113</td>
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<td>B</td>
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<td>Decrease</td>
<td>LSBP</td>
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<td>Slight</td>
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<td>Possible</td>
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<tr>
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<td></td>
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<td>Decrease</td>
<td>LSBP</td>
<td>94</td>
<td>100 - 150</td>
<td>Slight</td>
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<td>Possible</td>
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</table>

Formulation A: 2 mg Bumetanide intravenous injection.
Formulation B: 2 mg Bumetanide intramuscular injection.

LSBP: Lying Systolic Blood Pressure,
SSBP: Standing Systolic Blood Pressure,
LPR: Lying Pulse Rate,
SPR: Standing Pulse Rate.
Table 4.2: Deviations from acceptable range in the vital signs during the study.

<table>
<thead>
<tr>
<th>No</th>
<th>CODE</th>
<th>PERIOD</th>
<th>FORMULATION</th>
<th>HOUR</th>
<th>ABNORMALITY</th>
<th>PARAMETERS</th>
<th>OBSERVED VALUES</th>
<th>ACCEPTABLE RANGE</th>
<th>INTENSITY</th>
<th>SYMPTOMATIC</th>
<th>RELATED WITH STUDY TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>2.0 hour</td>
<td>Decrease LSBP</td>
<td>96</td>
<td>100 - 150</td>
<td>Slight</td>
<td>No</td>
<td>Possible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>5 min</td>
<td>Increase SPR</td>
<td>104</td>
<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 min</td>
<td>Increase SPR</td>
<td>101</td>
<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td>0.5 hour</td>
<td>Increase SPR</td>
<td>110</td>
<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>1.0 hour</td>
<td>Increase SPR</td>
<td>130</td>
<td>40 - 100</td>
<td>Moderate</td>
<td>No</td>
<td>Probable</td>
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<td>Increase SPR</td>
<td>115</td>
<td>40 - 100</td>
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<td>No</td>
<td>Probable</td>
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<td>4.0 hour</td>
<td>Increase SPR</td>
<td>125</td>
<td>40 - 100</td>
<td>Moderate</td>
<td>No</td>
<td>Probable</td>
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<td></td>
<td>8.0 hour</td>
<td>Increase SPR</td>
<td>105</td>
<td>40 - 100</td>
<td>Slight</td>
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<td>Probable</td>
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<td></td>
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<td>5 min</td>
<td>Increase SPR</td>
<td>105</td>
<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
<td></td>
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<td>15 min</td>
<td>Increase SPR</td>
<td>110</td>
<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
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<tr>
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<td>0.5 hour</td>
<td>Increase SPR</td>
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<td>Moderate</td>
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<td>Probable</td>
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<td>Moderate</td>
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<td>Probable</td>
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<td>Probable</td>
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<tr>
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<td>4.0 hour</td>
<td>Increase LPR</td>
<td>111</td>
<td>40 - 100</td>
<td>Moderate</td>
<td>No</td>
<td>Probable</td>
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<td></td>
<td></td>
<td>8.0 hour</td>
<td>Increase LPR</td>
<td>111</td>
<td>40 - 150</td>
<td>Moderate</td>
<td>No</td>
<td>Probable</td>
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<td></td>
<td></td>
<td>12.0 hour</td>
<td>Increase LPR</td>
<td>111</td>
<td>40 - 150</td>
<td>Moderate</td>
<td>No</td>
<td>Probable</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Formulation A: 2 mg Bumetanide intravenous injection.
Formulation B: 2 mg Bumetanide intramuscular injection.

LSBP: Lying Systolic Blood Pressure,
SSBP: Standing Systolic Blood Pressure,
LPR: Lying Pulse Rate,
SPR: Standing Pulse Rate.
Table 4.3: Deviations from acceptable range in the vital signs during the study.

<table>
<thead>
<tr>
<th>N°</th>
<th>CODE</th>
<th>PERIOD</th>
<th>FORMULATION</th>
<th>ABNORMALITY</th>
<th>PARAMETERS</th>
<th>OBSERVED VALUES</th>
<th>ACCEPTABLE RANGE</th>
<th>INTENSITY</th>
<th>SYMPTOMATIC</th>
<th>RELATED WITH STUDY TREATMENT</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>B</td>
<td>2.0 hour</td>
<td>Decrease</td>
<td>SSBP</td>
<td>92</td>
<td>100 - 150</td>
<td>Slight</td>
<td>No</td>
<td>Possible</td>
<td></td>
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<tr>
<td>1</td>
<td>A</td>
<td>15 min</td>
<td>Increase</td>
<td>LSBP</td>
<td>152</td>
<td>100 - 150</td>
<td>Slight</td>
<td>No</td>
<td>None</td>
<td></td>
</tr>
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<td>A</td>
<td>6.0 hour</td>
<td>Decrease</td>
<td>SSBP</td>
<td>88</td>
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<td>Moderate</td>
<td>Dizziness</td>
<td>Probable</td>
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</tr>
<tr>
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<td>B</td>
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<td>Decrease</td>
<td>LSBP</td>
<td>98</td>
<td>100 - 150</td>
<td>Slight</td>
<td>No</td>
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</tr>
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<td>Decrease</td>
<td>SSBP</td>
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<td>100 - 150</td>
<td>Slight</td>
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<td>1</td>
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<td>SPR</td>
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<td>Slight</td>
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<td>Increase</td>
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<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
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<td>Slight</td>
<td>No</td>
<td>Probable</td>
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<td>Increase</td>
<td>SPR</td>
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<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
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<td>Increase</td>
<td>SPR</td>
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<td>Slight</td>
<td>No</td>
<td>None</td>
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<tr>
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<td>B</td>
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<td>Increase</td>
<td>SPR</td>
<td>109</td>
<td>40 - 100</td>
<td>Slight</td>
<td>No</td>
<td>Probable</td>
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<td>Increase</td>
<td>SPR</td>
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<td>Slight</td>
<td>No</td>
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<td>112</td>
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<td>Slight</td>
<td>No</td>
<td>Probable</td>
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</table>

Formulation A: 2 mg Bumetanide intravenous injection.
Formulation B: 2 mg Bumetanide intramuscular injection.

LSBP: Lying Systolic Blood Pressure,
SSBP: Standing Systolic Blood Pressure,
LPR: Lying Pulse Rate,
SPR: Standing Pulse Rate.
Table 5: Biological abnormalities during the study.
(8 hours after 2 mg Bumetanide injection by intravenous or intramuscular route)

<table>
<thead>
<tr>
<th>N°</th>
<th>CODE</th>
<th>TREATMENT</th>
<th>PARAMETERS</th>
<th>OBSERVED VALUES</th>
<th>ACCEPTABLE RANGE</th>
<th>INTENSITY</th>
<th>SYMPTOMATIC</th>
<th>INTERPRETATION</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>2 mg Bumetanide by intravenous route</td>
<td>Potassium</td>
<td>2.9 mmol/l</td>
<td>3.0 - 5.5 mmol/l</td>
<td>Slight</td>
<td>No</td>
<td>Not clinically relevant</td>
<td>7 days later : 3.4 mmol/l</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>2 mg Bumetanide by intramuscular route</td>
<td>Potassium</td>
<td>2.9 mmol/l</td>
<td>3.0 - 5.5 mmol/l</td>
<td>Slight</td>
<td>No</td>
<td>Not clinically relevant</td>
<td>7 days later : 3.5 mmol/l</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2 mg Bumetanide by intramuscular route</td>
<td>Sodium</td>
<td>132 mmol/l</td>
<td>134 - 154 mmol/l</td>
<td>Slight</td>
<td>No</td>
<td>Not clinically relevant</td>
<td>No</td>
</tr>
<tr>
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<td>Chloride</td>
<td>94 mmol/l</td>
<td>96 - 115 mmol/l</td>
<td>Slight</td>
<td>No</td>
<td>Not clinically relevant</td>
<td>No</td>
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