CHAPTER 5

BIOEQUIVALENCE STUDY OF

VALSARTAN CAPSULE 80 mg
STUDY TITLE

A randomized two way, two period, two treatment cross over bioequivalence study of Capsule VALSARTAN 80 mg manufactured by ARISTO PHARMACEUTICALS LTD., in comparison with Capsule STARVAL manufactured by RANBAXY LABORATORIES LTD., in 12 healthy male, adult, human volunteers under fasting condition.

SUMMARY

On the basis of the pharmacokinetic parameters $C_{max}$, $T_{max}$, AUC $0-t$, $t_{1/2}$ and $k_{el}$ studied, it can be concluded that the Test preparation of VALSARTAN 80 mg, mfg. by ARISTO PHARMACEUTICALS LTD., is bioequivalent with the Reference preparation, Capsule STARVAL mfg. by RANBAXY LABORATORIES LTD.,. The relative bioavailability of the Test preparation of VALSARTAN 80 mg was 93.17% of that of the Reference preparation, Capsule STARVAL.

STUDY SITE

Drug Monitoring Research Institute
Sai Prasad, 125/A, Sion (W)
Mumbai – 400 022
Aims and Objectives

This study is required to assess the comparison of bioavailability and pharmacokinetic profile of single dose of VALSARTAN 80 mg Capsule.

The aim of this study is to compare SINGLE DOSE bioavailability of two preparations of VALSARTAN 80 mg. a TEST preparation of ARISTO PHARMACEUTICALS LTD., with the REFERENCE preparation in 12 healthy male, adult, human, volunteers in an open randomized, two way complete cross over trial.

Review and Consent Process

- **ETHICS REVIEW PROCEDURE**
  
The details of the study will be submitted to the properly constituted Ethical Review Board in advance of the study commencement. The study will not proceed until the approval of the Ethical Committee had been received.

- **INFORMED CONSENT**
  
  Before admission to the study each subject will be informed of the nature and the risks of the study and a written II formed consent will be obtained from the volunteers.

- **STUDY DESIGN**
  
  This bioequivalence study will be a single dose, randomized, complete cross over study in 12 healthy, male volunteers in a two way cross over fashion Blood samples will be taken at predetermined times and analyzed by HPCL.

  Subjects will be allocated to each treatment in accordance with the randomization. All the volunteers are required to participate in two dosing sessions. These sessions will be designated as Session 1 for the first dosing period and Session II for the second dosing period. Each dosing session involves drug administration on a single day. There will be washout period of 10 days in between two sessions.
Subject Selection Criteria

Subjects will be adult, healthy male volunteers selected from the panel of volunteers recruited by C.P.U. (Clinical Pharmacology Unit). Volunteers will be screened for inclusion in the study within 10 days before the commencement of the study.

- **SCREENING TESTS**

  The screening examination will be include complete physical and clinical examination various biochemical, haematological. They are:

  1. Complete physical and clinical examination & vital signs
  2. Complete Haemogram
  3. LFT (Liver Function Tests) (S. Bilirubin, SGOT/ FT, S. Alkaline Phosphate.
  4. RFT (Renal Function Tests) (Serum creatinine, BUN).
  5. S. Proteins
  6. Blood Sugar (Fasting)
  7. Urine routine examination
  8. Virologic I Tests (Hepatitis B Antigen, HIV antibody)

- **INCLUSION CRITERIA**

  A. Males (18 to 40 years) of age.
  B. Weight within 100% limit of weight according to the height.
  C. Healthy (eligible after physical, clinical, haematological and biochemical examination)
  D. Norma ECG
  E. Normal blood pressure & heart rate as measured after resting supine for three minutes. Normal B.P. is taken to be 100 to 1000mm Hg systolic and 50 to 90mm Hg diastolic supine. Normal heart rate is taken to be 70 to 90 beats per minute
  F. The volunteers should be able to communicate well with the investigator (as and when required by the investigator or the volunteer)
  G. The volunteer should be able to comply with the requirements of the entire study.
H. A written informed consent to participate in the study should be signed by the volunteer with a witness.

**EXCLUSION CRITERIA:**

A. Clinically relevant abnormal physical and/or clinical findings at the screening.
B. Clinically relevant abnormalities in the results of the laboratories screening evaluation immunocompromised status.
C. Administration of any investigation drug in the period 0 to 1 month before entry to the study.
D. Abnormal ECG.
E. A need for any medication during the period 0 to 14 days before entry to the study & during the study period.
F. Existence of any surgical & medical condition which in the judgement of the clinical investigator, might interfere with the kinetics of the drug.
G. Presence or history of allergy requiring treatment.
H. Loss of greater than 400 ml of blood in the period 0 to 12 weeks before entry to the study or during the study.
I. Serious adverse reaction or hypersensitivity to any drug.
J. Inability to communicate or cooperate with the investigator due to language problem, poor mental development or impaired cerebral function.
K. History of alcohol/ drug abuse/ smoking.

1. **SUBJECT WITHDRAWAL**

The study team will make every reasonable effort to complete the study. If a subject wishes to leave the study at any time, should be permitted to do so. Every reasonable effort will be made to complete a final assessment. The study team will advise the sponsor of the withdrawal of the subject from the study.

A subject may withdraw from the study in any of the following circumstances:-

1. Serious adverse events
2. Major violation of the protocol
3. Withdrawal of the consent
4. Termination of the study by the sponsor
5. Any systemic illness occurring during the study period requiring intake of other drugs.

Study Medication
Either of the preparations A/B x 1 Capsule (80mg) according to the randomization on the study day in each session.

2. PRODUCTS
REFERENCE PREPARATION (A):
Capsule DIOVAN
VALSARTAN 80mg Mfg. by NOVARTIS (U.S.A.)

3. TEST PREPARTION (B)
Capsule VALSARTAN
VALSARTAN 80mg Mfg. by ARISTO PHARMACEUTICALS LTD.,

4. DOSING PATTERN
The volunteers will be randomized on the previous day of study I. In study session I each volunteer will receive either the TEST preparation or the REFERENCE preparation of VALSARTAN 80 mg as single dose x 1 Capsule on the study day at a fixed time. In study session II, this order will be reversed as per the randomization.

5. CONCOMITANT MEDICATION/ FOOD
No concomitant medication (any other drug than VALSARTAN) will be taken two weeks prior to the trial date or during the period. This will be informed to the volunteer well in advance. Volunteers are also instructed to refrain from consuming alcohol and smoking and any other stimulant drinks/ food for a week.
prior to the study and during the study period. All the emergency drugs are always kept ready in CPU (Clinical Pharmacology Unit). Those volunteers who need to take any medication during the above mentioned period/ or those who suffer from any illness will inform the investigator and will be excluded from the trial.

6. SUPPLY OF DRUGS
The TEST drug will be supplied by the sponsor, together with the Certificate of Analysis and the statement of expiry date so as to be received by the clinical pharmacologist at least 7 working days before the start of the study. The test formulation will be provided by the sponsor in suitable containers and conditions. Prior to commencement of the study, sponsor will supply a complete Test material date sheet (TMDS) indicating the Test material identity, purity, stability, appearance, handling and safety instruction. The TMDS may cross refer to the sponsor a certificate of analysis. The clinical trial supplies will be stored under the control of the clinical pharmacologist, in a locked cupboard at ambient temperature unless otherwise advised by the sponsor. An accountability record of utilization will be maintained, unused materials will be disposed off in accordance with the instructions from the sponsor.

Blood Collection
Volunteers will assemble at 6.00 a.m. on the study day I of the session and session II after overnight fasting of 12 hours. Their TPR, BP will be recorded and an indwelling IV catheter will be introduced with strict aseptic precaution in the antecubital vein for blood collection. A total of 13 blood samples will be collected at 0 (before the drug administration) 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, and 48.0 hrs. After 0 hr blood collection volunteers will receive either of the formulations (Test or Reference) according to the flow chart and code number. Standard breakfast, lunch and dinner will be provided at 32 hrs, 6 and 13 hrs. after the drug administration. Volunteers will be permitted normal activities but excluding the strenuous exercise during the study. The above schedule will be strictly followed on the 24 hours bioequivalence study days,
of drug dosing session I and II. There will be 7 – 10 days gap between drug dosing sessions to allow complete elimination of the drug from the body. Volunteers will be monitored every hourly clinically on the study days in both the session.

7. ANALYSIS OF STUDY SAMPLES
Analysis for the VALSARTAN will be performed by HPCL. Blood samples will be collected in EDTA containing bulbs Plasma will be separated and frozen at -20°C until dispatch for drug analysis by HPCL.

8. ADVERSE EVENTS
Any adverse event occurring in the course of the study and one week after it will be reported by the volunteer to the investigators. The team also will monitor the volunteer clinically, every hourly on the study days and ask for any unusual event occurring during this period. They will notify the sponsor of any adverse events as soon as possible. The volunteer will be followed for a week after the last dose. Each and every ADR will be documented.

Emergency Procedures
Emergency equipment and drugs will be available in the CPU. In the unlikely event that they are required there use will be documented copies of randomized schedule will be held by the bio-statistician in sealed envelopes. The clinical pharmacologist may request that the envelop be opened in the event of emergency.

Critical Phases
All critical phases of the study will be supervised by medical and nursing personnel. Any deviations from the protocol will be recoded. The Clinical Pharmacology will personally monitor all the events.
Conditions for modifying or terminating the study protocol
All changes or revisions of this protocol will be documented, signed and dates by the Chief Investigator. The reason for the amendment will be stated.

9. CONDUCT OF STUDY
The study will be conducted in accordance with the guidelines set out in the declaration of Helsinki 1964.

10. DOCUMENTATION

- **DATA ENTRY**
  All data obtained during the course of the clinical phase of the study will be recorded directly and legibly into the Case Record Form in black ink. The case record forms will be prepared by the clinical pharmacologist. The following data will be entered on to a data base by the statistician, demographic, vital signs, adverse events. Clinical pathology data will be available in tabular form to be determined.

- **DATA PROTECTION**
  When personal data on subjects are stored or processed by computer the data must be protected to prevent their disclosure to unauthorized third parties.

- **STATISTICAL ANALYSIS**
  The aim of this study is to demonstrate equivalence within an acceptance range regarded as clinically relevant. In the case of parametric approach the inclusion of the classical 90% confidence interval for the chosen measure of relative bioavailability within the acceptance range (bioequivalence range) is the procedure to be used. The procedure is equivalent to the rejection of two one sided hypothesis concerning bioequivalence. The primary concern is to limit the risk of erroneously accepting bioequivalence.
Following logarithmic transformation AUC values will be subjected to analysis of variance (ANOVA) techniques including terms for sequence subject within sequence period and formulation. Using the error variance obtained from the ANOVA 90% conventional confidence interval (CI) for the ratio of the TEST preparation to the corresponding comparator formulation will be constructed concentration tabulated and graphically illustrated individual and mean kinetic results, adverse drug effect observed and conclusion. If the 90 % confidence interval for the measure of relative bioavailability (i.e. AUC ratio) should be within the acceptance range of 0.80 to 1.25 then the two formulations will be judged as bioequivalent. Similar methods will be used for the evaluation of $C_{\text{max}}$ values $T_{\text{max}}$ values will be analyzed in a similar manner without use of a log transformation. If the assumption of a lognormal (AUC, $C_{\text{max}}$) distribution or normal $T_{\text{max}}$ distribution in the parametric approach is doubtful a corresponding one parametric approach is recommended.

**REPORTING**

At the completion of the study a draft report will be dispatched to the sponsor. Upon receipt of approval or amendments or 6 weeks from the date of issue of the draft report the final report will be dispatched.

The trial report will include a summary, description of trial design, procedures finally employed, and validation results of analytical, description of pharmacokinetic procedures, complete statistical report, individual and mean drug plasma concentration tabulated and graphically illustrated and mean kinetic results adverse drug effects observed and conclusion.
# Protocol Deviation Form

<table>
<thead>
<tr>
<th>No.</th>
<th>Activity</th>
<th>Deviation Found</th>
<th>Remarks (If any)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Drug Storage Activity</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Subject Eligibility/Inclusion &amp; Exclusion Criteria</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Demographic Data</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Physical Examination</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Subject Check in</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Subject Housing</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Informed Consent Activity</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Catheter Insertion &amp; Removal</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Dose Administration</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Blood Sample Collection Data (Delay in blood sample collection in some of the blood sample collection points in some of the subjects)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Any sample Loss</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Vital sign measurement</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Plasma Sample Centrifugation</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Plasma Sample Storage</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Symptoms check list</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Adverse Event Recording Form</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Drop out: Refusal or withdrawal</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Sample Transfer to Analytical Department</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Sample Adverse Activity</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

- Deviation Found. Please refer attached sheet

- No Deviation Found
II. EVALUATION

○ PHARMACOKINETIC ANALYSIS

1. The measured drug concentration Vs time curves will be compared for each formulation for bioequivalence. The Profiles will be presented in tabular and graphical form for each subject.

2. The following values will be calculated for each subject on each formulation.

○ SINGLE DOSE PHARMACOKINETIC VARIABLES

1) Area under the plasma drug concentration Vs time curve upto 48 hrs (AUC 0-48)
2) Peak plasma drug concentration. \( (C_{\text{max}}) \)
3) Time of peak plasma concentration \( (T_{\text{max}}) \)
4) Plasma elimination half life \( (t_{1/2}) \)
5) Elimination constant \( (k_e) \)
6) Area under the plasma drug concentration Vs time curve upto infinity \( (AUC_{0-\text{inf}}) \)

Quality Assurance: Good Laboratory Practice and Good Clinical Research Practice Study will be conducted in accordance with guidance and good clinical research practice issued by CDSCO.