REPORT ON BIOEQUIVALENCE STUDY

(Protocol No.: BEQ-814-OLME-2011, Version No.: 03, Date: 18th June 2012)

Study Title:

Bioequivalence study of single dose of Olmesartan Medoxomil Tablets 40 mg manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Benicar® (olmesartan medoxomil) Tablets 40 mg manufactured for Daiichi Sankyo, Inc., USA in healthy, adult, human subjects under fasting condition.

Study Design:

An open label, balanced, analyst blind, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 36 healthy, adult, human subjects under fasting condition.

Investigational Product Details			Dose
i) Test Formulation (T)	:	Olmesartan Medoxomil Tablets 40 mg Macleods Pharmaceuticals Ltd., India	1 x 40 mg
ii) Reference Formulation (R)	:	Benicar® (olmesartan medoxomil) Tablets 40 mg Manufactured for: Daiichi Sankyo, Inc., USA	1 x 40 mg

Duration of Clinical Phase	:	20th August 2012 – 10th September 2012
Duration of Bioanalytical Phase	:	01st September 2012 – 09th September 2012
Duration of Statistical Phase	:	14th September 2012 to 15th September 2012
Report Status	:	Final
Version	:	01
Dated	:	18th September 2012
Supersedes Version	:	None
Dated	:	Not Applicable

Sponsor	**Study Centre:**
Macleods Pharmaceuticals Ltd., G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai – 400 093, India Telephone No.: 91-22-28306435 / 28314611 Fax No.: 91-22-28304641	Macleods Pharmaceuticals Ltd., Bioequivalence Department G-2, Mahakali Caves Road, Shanti Nagar, Andheri (East), Mumbai – 400 093, India Telephone No.: 91-22-28306435 / 28314611 Fax No.: 91-22-28304641 Email: drashish@macleodspharma.com

Statement of Compliance: This study was conducted in compliance with ICH GCP including archiving of essential documents.

Principal Investigator : Dr. S. Vijay Kumar

Study Director : Dr. Ashish Mungantiwar

Sponsor's Representative : Mr. Amol Choulwar

2.0 SYNOPSIS OF THE REPORT

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Olmesartan Medoxomil Tablets 40 mg **Name of Active Ingredient:** Olmesartan medoxomil	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

Title of Study: Bioequivalence study of single dose of Olmesartan Medoxomil Tablets 40 mg manufactured by Macleods Pharmaceuticals Ltd., India in comparison with Benicar® (olmesartan medoxomil) Tablets 40 mg manufactured for Daiichi Sankyo, Inc., USA in healthy, adult, human subjects under fasting condition.

Investigator: Dr. S. Vijay Kumar, Principal Investigator

Study Centre: Macleods Pharmaceuticals Ltd., Bioequivalence Department

Publication (reference): Not Applicable

Study period:

Date of Screening	:	04th August 2012 – 18th August 2012
Duration of Clinical Phase	:	20th August 2012 – 10th September 2012
Period 1	:	20th August 2012 – 23rd August 2012
Period 2	:	27th August 2012 – 30th August 2012
Duration of Bioanalytical Phase	:	01st September 2012 – 09th September 2012
Duration of Statistical Phase	:	14th September 2012 to 15th September 2012

Objectives:

i) Pharmacokinetic: To evaluate the comparative oral bioavailability of single dose of Olmesartan Medoxomil Tablets 40 mg manufactured by Macleods Pharmaceuticals Ltd., India with Benicar® (olmesartan medoxomil) Tablets 40 mg manufactured for Daiichi Sankyo, Inc., USA in healthy, adult, human subjects under fasting condition.

ii) Safety: To monitor the safety and tolerability of a single oral dose of Olmesartan Medoxomil Tablets 40 mg when administered in healthy, adult, human subjects under fasting condition.

Methodology: Serial blood samplings (pre-dose and at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours post dose) were done before and up to 48.00 hours post-drug administration. Each blood sample (1 × 5 mL) were collected into 5 mL blood collection tube containing K_2EDTA as anticoagulant. Blood samples were collected bed side up to 4.00 hours post dose. Analysis of plasma samples for olmesartan was done using an in-house validated LC-MS/MS method. A non-compartmental method was used to calculate pharmacokinetic parameters using drug concentration time profile. Statistical comparison of the pharmacokinetic parameters of both the formulations was done to assess bioequivalence.

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Olmesartan Medoxomil Tablets 40 mg **Name of Active Ingredient:** Olmesartan medoxomil	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

Number of Subjects (planned and analysed): A total of 36 subjects were planned and enrolled. All these 36 subjects completed both the periods.

The plasma samples of all thirty-six subjects (subject number 01 to 36) completing the study was analyzed for olmesartan concentration level and the concentration data was utilised for pharmacokinetic and statistical evaluations.

Diagnosis and main criteria for inclusion: Healthy human subjects within the age range of 18 to 45 years with body-mass index (BMI) between 18.50 kg/m^2 and 29.99 kg/m^2 (both inclusive) with body weight not less than 50 kg (for males) and with body weight not less than 45 kg (for females) and having absence of significant disease, clinically significant laboratory values, absence of clinically significant medical history and normal physical examination during the screening and complying with inclusion and exclusion criteria were the criteria for inclusion.

i) Test Formulation (T): Olmesartan Medoxomil Tablets 40 mg
Batch No.: BOD7202A
Manufacturing Date: April 2012
Expiry Date: March 2014
Manufactured by: Macleods Pharmaceuticals Ltd., India
Dose: 1 Tablet
Mode of administration: Administered orally with 240 mL of drinking water.
Assay: 103%
Batch Size: 1,25,000 Tablets

ii) Reference Formulation (R): Benicar® (olmesartan medoxomil) Tablets 40 mg
Lot No.: 165733
Manufacturing Date: N/AV
Expiry Date: 09/2014
Manufactured for: Daiichi Sankyo, Inc., Parsippany, NJ 07054, USA NDC 65597-104-30.
Dose: 1 Tablet
Mode of administration: Administered orally with 240 mL of drinking water.
Assay: 104.5%
Batch Size: Not Applicable

Duration of treatment	Single dose in both periods

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Olmesartan Medoxomil Tablets 40 mg **Name of Active Ingredient:** Olmesartan medoxomil	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

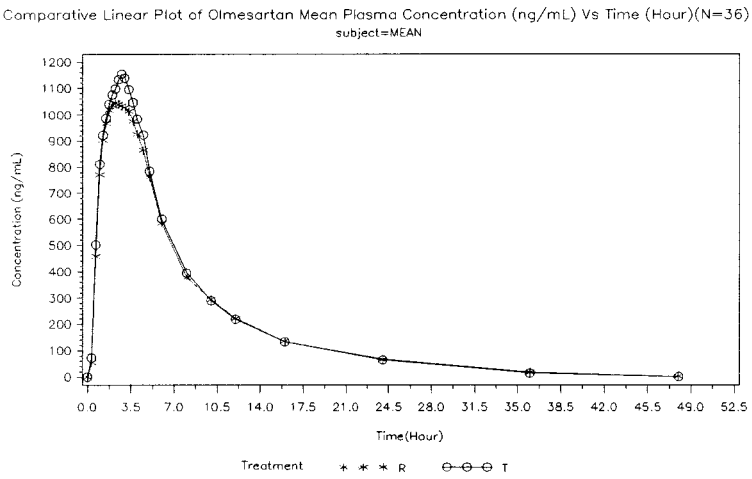
Criteria for Evaluation:

Efficacy: The 90 % confidence interval for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of olmesartan formed the basis for concluding the equivalence of Olmesartan Medoxomil in product R and T. If the confidence intervals are entirely included in the range of 80.00% – 125.00% for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ log-transformed then the products would be claimed to be bioequivalent.

Safety: To monitor the safety and tolerability of a single oral dose of Olmesartan Medoxomil Tablets 40 mg when administered in healthy, adult, human subjects under fasting condition.

Statistical Methods: The log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of olmesartan are analysed using an ANOVA model. Calculated 90% confidence interval for the ratio of both the products averages (geometric means) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$. Ratios of mean AUC_{0-t} to mean $AUC_{0-\infty}$ for test and reference are expressed in percentage and power test is performed using SAS® version 9.2.

SUMMARY - CONCLUSION
EFFICACY RESULTS:



The 90 % confidence intervals of ln-transformed parameters for olmesartan summarized below:

Geometric Mean, Ratio, Intra-Subject C.V., Power and 90 % Confidence Interval for Olmesartan

Pharmacokinetic Parameters	Geometric Mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90 % Confidence Interval (%)
	Test (T)	Reference (R)				
C_{max} (ng/mL)	1291.297	1217.856	106.03	19.38	99.67	98.22 - 114.46
AUC_{0-t} (ng*hrs/mL)	8686.445	8321.940	104.38	20.53	99.36	96.26 - 113.18
$AUC_{0-\infty}$ (ng*hrs/mL)	9099.327	8692.482	104.68	19.48	99.65	96.93 - 113.05

Name of the Sponsor: Macleods Pharmaceuticals Ltd., India **Name of the Finished Product:** Olmesartan Medoxomil Tablets 40 mg **Name of Active Ingredient:** Olmesartan medoxomil	Individual Study Table Referring to part of the Dossier **Volume:** N/AP **Page:** N/AP	(For National Authority Use only)

SAFETY RESULTS:

No adverse event occurred during entire course of the study. During post study safety assessment adverse events were reported for four subjects (subject number 04, 24, 26, and 31).

CONCLUSION:

The test product, Olmesartan Medoxomil Tablets 40 mg manufactured by Macleods Pharmaceuticals Ltd., India is bioequivalent to the reference product Benicar® (olmesartan medoxomil) Tablets 40 mg manufactured for Daiichi Sankyo, Inc., USA in healthy, adult, human subjects under fasting condition.

Both the formulations are well tolerated following a single dose administration of the investigational product.

Date of the report: 18th September 2012

3.0 TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

16.0 APPENDICES

16.1 Study Information

16.1.1 IEC Approved Protocol and Protocol Amendments

16.1.2 Sample Case Record Form

16.1.3 IEC Consulted and IEC Approved Informed Consent Form

16.1.4 List of Investigators and Important Participants in the Study

16.1.5 Statement of Investigators

16.1.6 Listing of Subjects Receiving Test Drug/ Investigational Product from Specific Batches Where More than One Batches were Used

16.1.7 Randomization Scheme and Codes

16.1.8 Audit Certificate

16.1.9 Documentation of Statistical Methods

16.1.9.1 Actual Time Points

16.1.9.2 Statistical And Pharmacokinetic Output

16.1.9.3 Statistical And Pharmacokinetic Sops

16.1.10 Documentation of Inter Laboratory Standardization Methods and Quality Assurance Procedures

16.1.11 Publications Based on the Study

16.1.12 Important Publications Referenced in the Report

16.2 Subject Data Listings

16.2.1 Discontinued Subjects

16.2.2 Protocol Deviations

16.2.3 Subjects Excluded from the Efficacy Analysis

16.2.4 Demographic Data

16.2.5 Individual Plasma Concentration Data

16.2.6 Individual Efficacy Response Data

16.2.7 Adverse Event Listing

16.2.8 Listing of Individual Laboratory Parameters by Subject

16.3 Case Record Forms

16.3.1 CRF's for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

16.3.2 Other CRF's Submitted

16.4 Individual Subject Data Listings

16.5 Bioanalytical Report

4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

µL	:	Microlitre
ADRs	:	Adverse Drug Reactions
ANOVA	:	Analysis of Variance
AST	:	Alanine Aminotransferase
AUC	:	Area Under Curve
AUC_{0-t}	:	Area under the concentration versus time curve calculated using the Trapezoidal rule upto the last measurable time point
$AUC_{0-\infty}$	:	Area under the concentration versus time curve from time zero to infinity
BLQ	:	Below Limit of Quantification
BMI	:	Body Mass Index
B.P	:	Blood Pressure
BPM	:	Beats Per Minute
CBC	:	Complete Blood Count
C_{max}	:	Concentration Maximum
CNS	:	Central Nervous System
COA	:	Certificate of Analysis
CPU	:	Clinical Pharmacology Unit
CSF	:	Cerebrospinal fluid
CV	:	Coefficient of Variance
^0C	:	Degree Centigrade
cGMP	:	Current Good Manufacturing Practices
D	:	Day
DLC	:	Differential Leucocyte count
ECG	:	Electro-Cardiogram
EDTA	:	Ethylene diamine tetra-acetic acid
ESR	:	Erythrocyte Sedimentation Rate
GCP	:	Good Clinical Practices
GGT	:	Gama Glutamyl Transpeptidase
GLP	:	Good Laboratory Practices
cGMP	:	current Good Manufacturing Practices
HBsAg	:	Hepatitis B Surface Antigen
HCV	:	Hepatitis C Virus
HIV	:	Human Immunodeficiency Virus
hrs	:	Hour(s)
I.D.	:	Identity
ICF	:	Informed Consent Form
ICH	:	International Conference on Harmonization
ICMR	:	Indian Council of Medical Research
IEC	:	Independent Ethics Committee

IP	:	Investigational Product
IU	:	International Unit
IUD	:	Intrauterine device
K_{el}	:	Elimination rate constant
K_e_first	:	First time point of the terminal log-linear phase used to estimate the terminal disposition rate constant (K_e) with bestfit regression method used.
K_e_last	:	Last time point of the terminal log-linear phase used to estimate the terminal disposition rate constant (K_e) with bestfit regression method used.
K_2EDTA	:	Di potassium Ethylene Diamine Tetra-Acetic Acid
LC-MS/MS	:	Liquid chromatography-tandem mass spectrometry
LDL	:	Low-density lipoprotein
L/kg	:	Liter / kilogram
L/h/kg	:	Liter / hour / kilogram
LLOQ	:	Lower Limit of Quantification
LSM	:	Least Square Means
ME	:	Medical Examination
mg	:	milligram
mcg/ml	:	microgram per millilitre
mL	:	milliliter
N/AV	:	Not Available
N/AP	:	Not Applicable
npoints	:	No. of time points of the terminal log-linear phase used to estimate the terminal disposition rate constant (K_e) with bestfit regression method used.
oz	:	Ounce
PA view	:	Posterior Anterior View
PCV	:	Packed Cell Volume
PK	:	Pharmacokinetic
QA	:	Quality Assurance
R	:	Reference Product
RBC	:	Red Blood Cell
RH	:	Relative Humidity
rpm	:	Revolution Per Minute
SAE(s)	:	Serious Adverse Event(S)
SADR	:	Serious Adverse Drug Reactions
SAS	:	Statistical Analysis System
SD	:	Standard Deviation
SGOT	:	Serum Glutamate Oxaloacetate Transaminase
SGPT	:	Serum Glutamate Pyruvate Transaminase
SOP(s)	:	Standard Operating Procedure(S)
SQ	:	Subject Questionnaire

T	:	Test Product
$t_{1/2}$	:	Terminal Half-life
t_{max}	:	Time of maximum measured plasma concentration. If maximum value occurs at more than one point, T_{max} is defined as the first point with this value in each period
TG	:	Triglycerides
USFDA	:	United States Food and Drug Administration
w/v	:	Weight by Volume

5.0 ETHICS

5.1 Independent Ethics Committee (IEC)

The protocol, BEQ-814-OLME-2011, version no. 02, dated: 08th December 2011 and English ICF, version no. 02, dated: 08th December 2011, Hindi and Marathi ICFs, version No. 01, dated 20th December 2011 were sent to IEC on 15th February 2012. The Independent Ethics Committee in its meeting held on 29th February 2012 gave provisional approval to the submitted protocol and ICFs.

The protocol, BEQ-814-OLME-2011, version no. 03, dated: 18th June 2012 and English ICF, version no. 03, dated: 18th June 2012, Hindi and Marathi ICFs, version no. 02, dated 18th June 2012 were sent to IEC on 27th June 2012. The Chairperson on behalf of Independent Ethics Committee on 27th June 2012 gave expedited approval to the submitted protocol and ICFs.

Approval was granted after the review of documents and the approved version which was followed for the study conducted bears the following version number and date:

Protocol : Version No. 03, dated: 18th June 2012
English ICF : Version No. 03, dated: 18th June 2012
Hindi ICF : Version No. 02, dated: 18th June 2012
Marathi ICF : Version No. 02, dated: 18th June 2012

Dr. Mrs. K.C.P. Walawalkar chaired the IEC meeting. The copy of the IEC approved protocol is appended as appendix 16.1.1. The details of IEC consulted along with approval letter and IEC approved ICFs are given in appendix 16.1.3. The IEC summary report regarding the conduct of the study was sent to IEC on 12th September 2012

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki; ICH GCP; Schedule-Y and other regulatory provisions under the Drug and Cosmetics Rules; GCP Guidelines issued by Central Drugs Standard Control Organization (CDSCO); "Ethical Guidelines for Biomedical Research on Human Subjects" published by Indian Council of Medical Research (ICMR) and in accordance with USFDA requirement.

5.3 Subject Information and Consent

Subjects from the pool of healthy volunteers who were screened within 21 days prior the dosing day were considered as potential participants in the study. Before admission of volunteers into the Clinical pharmacology unit (CPU) on the pre-study day, they were given a verbal presentation of the information on the study together with a written document (in the language that they can understand best) describing the purpose, procedures, and risks of the study together with a description of the obligations of the subjects. Volunteers gave their written consent for participating in the study by signing with date the informed consent form. The signed copy of the form is kept in the study ICF file at the investigator's/institution site and the subjects were also

given a copy for their own retention. A copy of the consent form used is appended in appendix 16.1.3. Before the volunteer undergo the pre-screening process for acceptance into healthy volunteer bank, they were also provided with written consent following both written and verbal information about the nature of the tests to be performed following which all willing volunteers gave their written consent.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

SPONSOR'S REPRESENTATIVE

Name : Mr. Amol Choulwar M.Pharm (Pharmacology)
Deputy Manager – Medical Services

Address : Macleods Pharmaceuticals Ltd.,
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri - (East), Mumbai 400 093, India.
Tel.: 91-22-28306435 / 28314611
Ext. No.: 160
Fax: 91-22-28304641

BIOEQUIVALENCE DEPARTMENT PERSONNEL

Study Director:

Name : Dr. Ashish Mungantiwar (Ph.D. Pharmacology)

Address : Macleods Pharmaceuticals Ltd.,
Bioequivalence Department,
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri - (East), Mumbai 400 093, India.
Tel.: 91-22-28306435 / 28314611
Ext. No.: 105
Mob. No.:+919867023914
Fax: 91-22-28304641
Email: drashish@macleodspharma.com

Principal Investigator:

Name : Dr. S. Vijay Kumar (M.B.B.S.)

Address : Macleods Pharmaceuticals Ltd.,
Bioequivalence Department,
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri - (East), Mumbai 400 093, India.
Tel.: 91-22-28306435 / 28314611
Ext. No.: 136
Fax: 91-22-28304641

FACILITIES:

A) Clinical Facility : Macleods Pharmaceuticals Ltd.,
Bioequivalence Department,
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri - (East), Mumbai 400 093, India.
Tel.: 91-22-28306435 / 28314611
Ext. No.: 127/136
Fax: 91-22-28304641

B) Pathology Laboratory* : Macleods Pharmaceuticals Ltd.,
Pathology Department,
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri (East), Mumbai - 400 093, India.
Tel.: 91-22-28306435 / 28314611
Ext. No.: 249
Fax: 91-22-28304641

C) X-Ray Facility : Macleods Pharmaceuticals Ltd.,
Bioequivalence Department,
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri (East), Mumbai - 400 093, India.
Tel.: 91-22-28306435 / 28314611
Fax: 91-22-28304641

D) Bioanalytical Facility : Macleods Pharmaceuticals Ltd.,
Bioequivalence Department,
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri (East), Mumbai – 400 093, India.
Tel.: 91-22-28306435 / 28314611
Ext. No.: 142/ 145
Fax: 91-22-28304641

E) Statistical Operations : Macleods Pharmaceuticals Ltd.,
Bioequivalence Department,
G-2, Mahakali Caves Road, Shanti Nagar,
Andheri (East), Mumbai – 400 093, India.
Tel.: 91-22-28306435 / 28314611
Ext. No.: 147
Fax: 91-22-28304641

The list of investigators with their affiliations, their role in the study and their curriculum vitae are appended as appendix 16.1.4. The list of other important participants in the study is appended in appendix 16.1.4. The declaration statement by the principal investigator is appended as appendix 16.1.5.

7.0 INTRODUCTION

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.[1]

Olmesartan medoxomil

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium. Olmesartan blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in vascular smooth muscle. Its action is, therefore, independent of the pathways for angiotensin II synthesis.

An AT_2 receptor is found also in many tissues, but this receptor is not known to be associated with cardiovascular homeostasis. Olmesartan has more than a 12,500-fold greater affinity for the AT_1 receptor than for the AT_2 receptor.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is a mechanism of many drugs used to treat hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because olmesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II levels do not overcome the effect of olmesartan on blood pressure. [1]

Clinical Pharmacokinetics

Absorption

Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract.

The absolute bioavailability of olmesartan is approximately 26%. After oral administration, the peak plasma concentration (Cmax) of olmesartan is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan.

Distribution

The volume of distribution of olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses.

Metabolism and Excretion

Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile. [1]

Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. Olmesartan shows linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady-state levels of olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing. [2]

Gender Effect

Minor differences were observed in the pharmacokinetics of olmesartan in women compared to men. AUC and C_{max} were 10-15% higher in women than in men. [1]

Indications and Uses

Benicar® is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents. [1]

Adverse Reactions

In placebo-controlled trials, the only adverse reaction that occurred in more than 1% of patients treated with Benicar and at a higher incidence versus placebo was dizziness

The following adverse reactions occurred in placebo-controlled clinical trials at an incidence of more than 1% of patients treated with Benicar, but also occurred at about the same or greater incidence in patients receiving placebo: back pain, bronchitis, creatine phosphokinase increased, diarrhea, headache, hematuria, hyperglycemia, hypertriglyceridemia, influenza-like symptoms, pharyngitis, rhinitis and sinusitis.

Other potentially important adverse reactions that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment, in the more than 3100 hypertensive patients treated with Benicar monotherapy in controlled or open-label trials are listed below.

Body as a Whole: chest pain, peripheral edema

Central and Peripheral Nervous System: vertigo

Gastrointestinal: abdominal pain, dyspepsia, gastroenteritis, nausea

Heart Rate and Rhythm Disorders: tachycardia

Metabolic and Nutritional Disorders: hypercholesterolemia, hyperlipemia, hyperuricemia

Musculoskeletal: arthralgia, arthritis, myalgia

Skin and Appendages: rash

Facial edema was reported in five patients receiving Benicar. Angioedema has been reported with angiotensin II antagonists.

Laboratory Test Findings:

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.3 g/dL and 0.3 volume percent, respectively) were observed.

Liver Function Tests: Elevations of liver enzymes and/or serum bilirubin were observed infrequently. [1]

Precautions and Contraindications

PRECAUTIONS

Hypotension in Volume- or Salt-Depleted Patients

In patients with an activated renin-angiotensin aldosterone system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), symptomatic hypotension may be anticipated after initiation of treatment with Benicar. Initiate treatment under close medical supervision. If hypotension does occur, place the patient in the supine position and, if necessary, give an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with Benicar. In patients whose renal function may depend upon the activity of the renin-angiotensin aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and rarely with acute renal failure and/or death. Similar results may be anticipated in patients treated with Benicar. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of Benicar in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected. [1]

Contraindications

Benicar is contraindicated in patients with previously demonstrated hypersensitivity to any of the components of the product. [1]

Study Rationale

The Macleods Pharmaceuticals Ltd. has developed generic alternative to the reference-listed drug of Olmesartan Medoxomil Tablets 40 mg. Therefore, its bioequivalence with the reference-listed drug must be evaluated in both fasting and fed conditions. In the present study, the single

dose of test product Olmesartan Medoxomil Tablets 40 mg manufactured by Macleods Pharmaceuticals Ltd., India was compared with Benicar® (olmesartan medoxomil) Tablets 40 mg manufactured for Daiichi Sankyo, Inc., USA under fasting condition.

Justification of Choice of Reference Product

Benicar® (olmesartan medoxomil) Tablets 40 mg is qualified as acceptable reference listed drug product by USFDA.

8.0 STUDY OBJECTIVES

The bioequivalence study presented here was carried out for evaluating the following objectives:

8.1 Pharmacokinetic:

To evaluate the comparative oral bioavailability of single dose of Olmesartan Medoxomil Tablets 40 mg manufactured by Macleods Pharmaceuticals Ltd., India with Benicar® (olmesartan medoxomil) Tablets 40 mg manufactured for Daiichi Sankyo, Inc., USA in healthy, adult, human subjects under fasting condition.

8.2 Safety

To monitor the safety and tolerability of a single oral dose of Olmesartan Medoxomil Tablets 40 mg when administered in healthy, adult, human subjects under fasting condition.

9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan – Description

This was an open label, balanced, analyst blind, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study on 36 healthy, adult, human subjects under fasting condition.

ADMISSION AND STAY

Period 1:

On 20th August 2012, informed consent was presented to all the volunteers. At the time of check-in, eligibility was assessed by carrying out urine test for drugs of abuse, medical examination, confirming compliance to protocol based upon inclusion and exclusion criteria and recording vitals. Breath of the volunteer was analyzed to check the consumption of alcohol using breath alcohol analyzer. Thirty-six volunteers who were found to be compliant with the requirements of the protocol were checked in Clinical Pharmacology Unit (CPU) between 17:45 hours to 20:18 hours.

During the in-house stay, monitoring of vital signs and subject questionnaire at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00, and 24.00 post-dose (Time points being relative to the investigational product dosing) was done. Medical examinations were carried out at the time of check-in and check-out of the study.

All the subjects enrolled into the study were housed in the Clinical Pharmacology Unit (CPU) until check-out on 22nd August 2012.

The subjects were asked to visit the clinical facility for ambulatory blood sample collection at 36.00 and 48.00 hours post-dose. Vital signs and subject questionnaire was done at 36.00 and 48.00 hours post-dose and medical examinations were carried out at 48.00 hours post-dose.

Period 2:

On 27th August 2012, thirty-six subjects reported to the facility. At the time of check-in, eligibility was assessed by carrying out test for drugs of abuse, medical examination, confirming compliance to protocol based upon exclusion criteria and recording vitals. Breath of the subject was analyzed to check the consumption of alcohol using breath alcohol analyzer. Thirty-six subjects who were found to be compliant with the requirements of the protocol were checked in Clinical Pharmacology Unit (CPU) between 17:30 hours to 20:24 hours.

During the in-house stay, monitoring of vital signs and subject questionnaire at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00, and 24.00, post-dose (Time points being relative to the investigational product dosing) was done. Medical examinations were carried out at the time of check-in and check-out of the study.

All the subjects checked-in the study were housed in the Clinical Pharmacology Unit (CPU) until check-out on 29th August 2012.

The subjects were asked to visit the clinical facility for ambulatory blood sample collection at 36.00 and 48.00 hours post-dose. Vital signs and subject questionnaire was done at 36.00 and 48.00 post-dose and medical examinations were carried out at 48.00 hours post-dose.

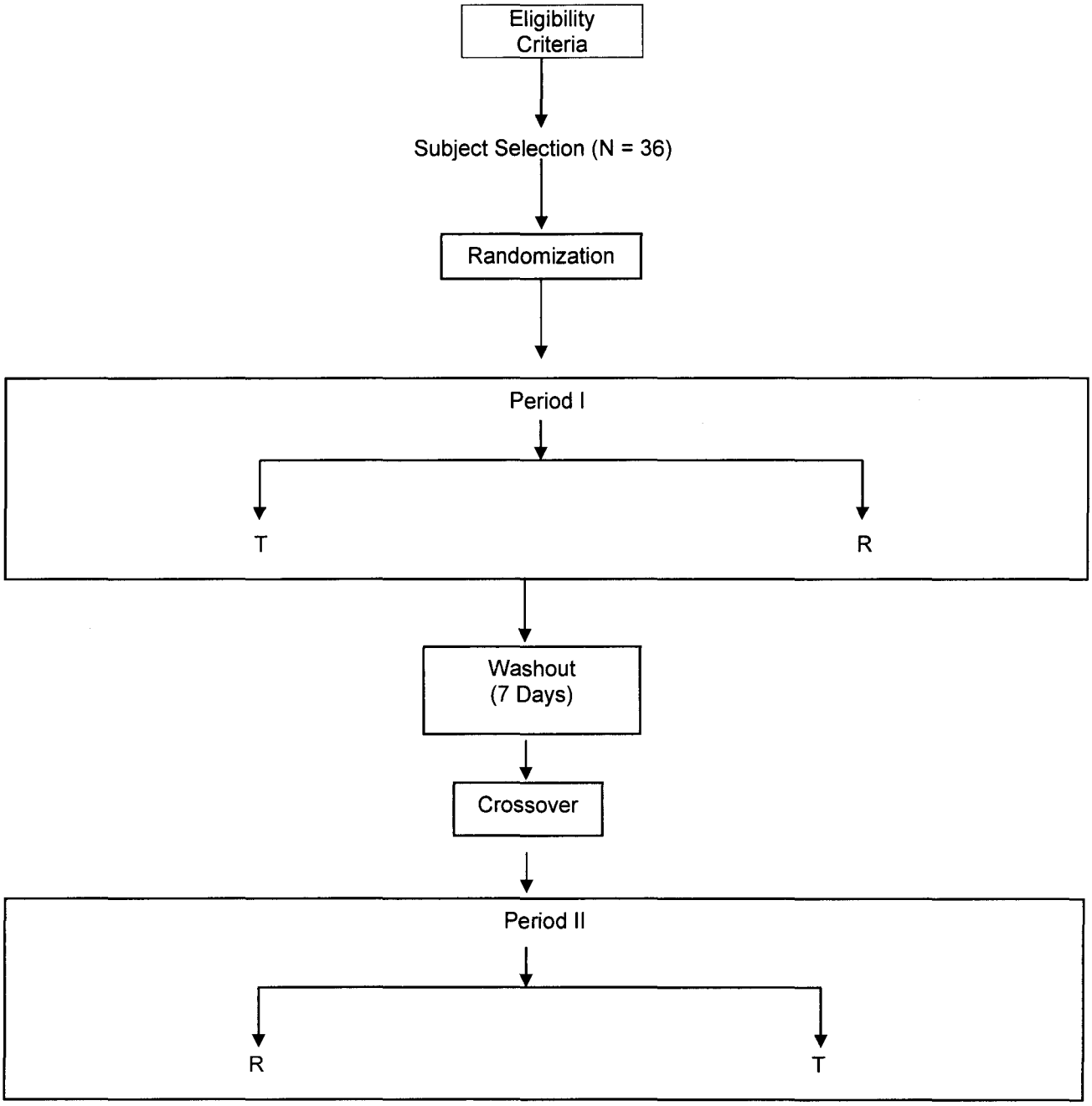
Washout Period:

There was a washout period of 7 days from the completion of dosing between two consecutive periods.

The study schematic is given in figure-1 on next page.

FIGURE – 1 STUDY PLAN

STUDY FLOW CHART



N: Number of Subjects

R: Reference Product

T: Test Product

9.2 Discussion of Study Design, Including the Choice of Control Group

It was an open labeled study. The analysts concerned, however, were blinded to the sequence of administration of test and reference product to the individual subjects.

The order of receiving treatment was randomized to avoid bias in allocation of sequence to the subjects.

There were two treatments: the sponsor's product was the test product while the innovator product was the reference product.

The subjects served as their own control, the study being crossover.

Since there were two treatments, the trial design was two period, two sequences. The effect of period and sequence on primary efficacy criteria was analyzed by ANOVA (Analysis of variance).

To reduce variability in the biomedical experimentation and to control factors, which may affect the evaluation and comparison of primary efficacy factors; healthy, adult, human subjects were selected.

The number of subjects to be included in the study was derived based on pharmacokinetic data available from the Published literature[3]"

With terminal elimination half-life of 13 hours for omesartan, the two dosing days i.e. for period 1, period 2, were separated by a washout period of 7 days.

9.3 Selection of Study Population

The general screening was carried out after obtaining the written consent on IEC approved 'Informed Consent for Screening' from the volunteers. The screening procedure included Demographic data including sex, completed age, height and weight, Body Mass Index (BMI), diet, history of tobacco use, intake of abusive/recreational drugs, alcohol intake, history of blood donation and history of participation in a drug research study. Medical history, including relevant past medical / surgical history, family history, history of allergies (food / drug / any other), past medication history in the last 90 days. Medical examination including recording of vital signs (Blood Pressure (BP), Pulse, Respiration and Temperature), general examination, physical and systemic examination. 12-lead ECG for heart rate, rhythm and specific finding (if any). Chest X-ray (PA view); Laboratory parameter investigation including Complete blood count – Leucocyte count, Erythrocyte count, Haemoglobin, Hematocrit, Platelet count, differential leucocyte count (DLC); and ESR, Blood grouping (if previously not performed by Bioequivalence department of Macleods Pharmaceuticals Ltd.), Biochemistry – blood sugar (fasting), cholesterol and triglycerides, Alkaline Phosphatase, Hepatic Profile – SGPT, SGOT, GGT and Serum Bilirubin (Total, Direct, Indirect), Renal profile – serum creatinine, BUN, Serum Calcium, Serum Electrolytes (sodium, potassium. chlorides) and Infectious Diseases – HbsAg, HIV and HCV and routine urine examination.

No clinically significant abnormalities in ECGs, Chest X-ray (PA view) were reported in subjects who were included in the study. Additionally, serological tests (HbsAg, HIV and HCV) were negative. The volunteers with laboratory values within normal limits or with clinically non-

significant values were called one day prior to the study for study informed consent form presentation.

All the baseline clinical and laboratory results are given in appendix 16.2.8 (Table A) and the individual clinical impression of ECG and chest X-ray (PA view) have been appended as appendix 16.2.8 (Table C). All the laboratory results, which were outside the Reference range but within the 'acceptable limit (For Acceptable limits refer Appendix V of protocol) were considered clinically non significant. There were few values as given below, which were outside the acceptable limits, however since the results were considered clinically non-significant based on clinical correlation, these subjects were included in the study.

Subject No.	Laboratory Parameter	Results	Reference Range
03	GGT	53.8 U/L	5.0-40.0 U/L
	Bilirubin Direct	0.37 mg/dL	< 0.30 mg/dL
04	Triglycerides	180.9 mg/dL	<150 mg/dL
06	Total Cholesterol	234.6 mg/dL	<200 mg/dL
07	GGT	45.8 U/L	5.0-40.0 U/L
12	ESR	19 mm/hr	<15 mm/hr
18	SGPT	41.1 U/L	4.0 – 36.0 U/L
19	Triglycerides	171.3 mg/dL	<150 mg/dL
22	Erythrocyte Count	3.82x million/µL	4.5-5.5 x million/µL
31	Total Cholesterol	230.5 mg/dL	<200 mg/dL
	Triglycerides	265.7 mg/dL	<150 mg/dL
33	Erythrocyte Count	3.70x million/µL	4.5-5.5 x million/µL

Only those volunteers who signed the study informed consent form were checked in for the study on the day of check-in (one day prior to dosing).

All the enrolled volunteers were found negative for breath alcohol test and urine test for drugs of abuse test [Cocaine (COC), Amphetamines (AMP), Marijuana (THC), Morphine (MOP), Barbiturates (BAR) and Benzodiazepine (BZO)].

Volunteers were given the rank orders based on their reporting time to the facility on pre-study day. Based on their rank orders and depending on the compliance to the requirements of the protocol, subject numbers were allotted serially. Thirty-six fit and consenting subjects fulfilling inclusion/ exclusion criteria and complying with the requirements of the protocol were enrolled in the study.

9.3.1 Inclusion Criteria

Subjects had to fulfill all of the following criteria to be considered for inclusion into this study:

1. Healthy volunteers within the age range of 18 to 45 years.
2. Presently non-tobacco users (smokers and chewers).
3. Willingness to provide written informed consent to participate in the study.
4. Body-mass index (BMI) between 18.50 kg/m^2 and 29.99 kg/m^2 (both inclusive) with body weight not less than 50 kg (for males) and with body weight not less than 45 kg (for females).

5. Absence of significant disease or clinically significant abnormal laboratory values or laboratory evaluation, medical history or physical examination during the screening.
6. Have a normal 12-lead ECG or one with abnormality considered to be clinically insignificant.
7. Have a normal chest X-ray PA view or one with abnormality considered to be clinically insignificant.
8. Comprehension of the nature and purpose of the study and compliance with the requirement of the distributed ICF.
9. Volunteer is regularly menstruating / Volunteer is in postmenopausal phase for at least 1 year / is surgically sterile (for females).
10. Volunteer of child bearing potential practicing an acceptable method of birth control for the duration of the study as judged by the investigator(s) such as condoms, foams, jellies, diaphragm, and intrauterine device (IUD) or abstinence etc. except hormonal contraceptives (for females).

9.3.2 Exclusion Criteria

The subjects were to be excluded based on the following criteria:

1. Personal history of allergy or hypersensitivity to Olmesartan or allied drugs.
2. Any major illness in the past 90 days or any clinically significant ongoing chronic medical illness e.g. Congestive Cardiac Failure (Heart failure), Hepatitis, Hypotensive episodes, Hyperglycemia etc.
3. Presence of any clinically significant abnormal laboratory values during screening e.g. significant abnormality of liver function test, renal (kidney) function test etc.
4. Severe cardiac, renal or liver impairment, gastro-intestinal disease or other conditions, any other organ or system impairment.
5. History of seizures, epilepsy or any kind of Neurological disorders.
6. Past history of Anaphylaxis or Angioedema.
7. Presence of disease markers of HIV or Hepatitis B or Hepatitis C virus.
8. History of chronic consumption of any kind of alcoholic beverages for more than 2 years or having consumed alcohol within 48 hours prior to dosing.
9. Consumption of products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) or tobacco products within 48 hours prior to dosing.
10. Consumption of grapefruit or grapefruit containing products or any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meat prior 7 days of investigational product administration.
11. Use of any recreational drug or a history of drug addiction.
12. Participation in any clinical trial within the past 90 days.
13. History of difficulty with donating blood or difficulty in accessibility of veins in left or right arm.
14. Donation of blood (one unit or 350 mL) within 90 days prior to receiving the first dose of study medication.

15. Consumption of any other prescription drug or over the counter (OTC) drugs (including vitamins and medicinal products from natural origin) within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks.
16. An unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to receiving any medication and throughout subject's participation in the study.
17. Recent history of dehydration from diarrhoea, vomiting or any other reason within a period of 48 hours prior to the study.
18. Known hypersensitivity to heparin.
19. Use of oral contraceptive in last 90 days (for females).
20. Pregnant / lactating volunteers (for females).

9.3.3 Removal of Subjects from Therapy or Assessment

The subjects were free to withdraw from the study at any time without having to give any reasons thereof. The Principal Investigator, at his discretion, could also withdraw the subject from the study for any of the valid reason, which he deems to be appropriate in view of the safety and well being of subject, GCP principles or objectives of the project, in particular for:

1. If the subject suffers from significant illness.
2. If the subject requires concomitant medications which may interfere with pharmacokinetic of the study drug.
3. If the subject has entered the study in violation of the inclusion and the exclusion criteria.
4. If the subject is found to be non co-operative.
5. If the subject decides to voluntarily dropout from the study.

In any of these cases the compensation to the subject would have been made as per the guidelines regarding these i.e. ICH-GCP and National guidelines (ICMR guidelines for Clinical Trials), and as per the compensation structure approved by IEC.

Whatever reason if a subject would not satisfactorily complete the study, would be asked to attend the post-study examination. Whenever possible, the post-withdrawal follow up would be done immediately after the subject is withdrawn. In case a subject is not willing to undergo such medical examination, it would be documented so.

9.4 Treatments

9.4.1 Treatments Administered

An oral dose of Reference product (R) or Test product (T) was administered with 240 mL (about 8 oz) of water at room temperature as per the randomization schedule under the supervision of the Medical Officer where end time of the dosing was recorded in Investigational product administration forms. Subjects received the 'treatments' in such a way that each subject completing the study received both the 'treatments' test and reference at the end of the study.

Subjects were dosed while in sitting posture and were instructed to avoid any strenuous activity following the investigational product administration. Subjects were in supine position up-to 4.00

hours post dose. During this interval, under supervision, subjects were permitted to use the washroom facilities. Thereafter the subjects were allowed to engage only in normal activities while avoiding severe physical exertion. However if any adverse event occurs at any time during housing the subjects would be placed in an appropriate posture.

9.4.2 Identity of Investigational Product(s)

i) Test Formulation (T):

Olmesartan Medoxomil Tablets 40 mg
Batch No.: BOD7202A
Manufacturing Date: April 2012
Expiry Date: March 2014
Manufactured by: Macleods Pharmaceuticals Ltd., India
Dose: 1 Tablet
Mode of administration: Administered orally with 240 mL of drinking water.
Assay: 103%
Batch Size: 1,25,000 Tablets

ii) Reference Formulation (R):

Benicar® (olmesartan medoxomil) Tablets 40 mg
Lot No.: 165733
Manufacturing Date: N/AV
Expiry Date: 09/2014
Manufactured for: Daiichi Sankyo, Inc., Parsippany, NJ 07054, USA NDC 65597-104-30.
Dose: 1 Tablet
Mode of administration: Administered orally with 240 mL of drinking water.
Assay: 104.5%
Batch Size: Not Applicable

9.4.3 Method of Assigning Subjects to Treatment Groups

The subjects were assigned to the sequence either test or reference product, according to the randomization schedule.

The order of receiving test or reference product for each subject during the study was determined according to randomization schedule (generated using SAS® version 9.2).

Subject number was allocated as per the rank order of the reporting time of the subject to the clinical facility.

9.4.4 Selection of Doses in the Study

The available strengths of Benicar® (olmesartan medoxomil) Tablets are 5 mg, 20 mg and 40 mg. The maximum recommended strength according to USFDA is 1 Tablet Benicar® (olmesartan medoxomil) 40 mg. Therefore, single oral dose of 1 Tablet of Benicar® (olmesartan medoxomil) 40 mg is chosen, since it is safe (well tolerable) for healthy volunteers and was expected to provide measurable plasma concentrations and single dose study is adequate for this product's bioequivalence.

9.4.5 Selection and Timing of Dose for Each Subject

Dosing was done between 08:00 hrs to 08:34 hrs (0.00 hrs) in the batch of two subjects during each period. The dosing interval between successive subjects was 2 minutes.

The test or reference products were orally administered to the subjects while in sitting posture, with 240 mL (about 8 oz) of drinking water at room temperature as per the randomization schedule under the supervision of the Medical Officer followed by examination of the oral cavity.

The subjects fasted for at least 10 hours prior to administration of the study drug. Fasting was continued for 4 hours post-dose, and then meals were provided at specified intervals. Drinking water was disallowed for 1 hour pre-dose and 1 hour post-dose administration, except 240 mL of drinking water during administration of the drug dose. Subsequently, drinking water was provided ad libitum.

9.4.6 Blinding, Packaging and Labeling

This study comprised of a randomized, open label design. Study monitors and subjects involved in the study were not blinded. However the analyst concerned, were blinded to the sequence of administration of test or reference products to the individual subject. The plasma sample storage vials were labeled; mentioning study number, period number, subject number, sample number, time point (hrs), and aliquot number, but the identity of product administered was not mentioned. The randomization schedule was in the custody of principal investigator and the investigational product dispensing raw data record was under lock and key until the completion of statistical analysis.

An adequate number of investigational products (IPs) in sealed condition along with certificate of analysis (COA) were received at Bioequivalence department of Macleods by the registered pharmacist.

Dispensing:

As per the randomization schedule, the registered pharmacist prepared the doses under the supervision of trained personnel and in the presence of quality assurance personnel in both the periods. Remaining investigational products were stored in their original container as retention samples in stability chamber at 22 ± 2°C and 60 ± 5% RH.

The dispensed investigational products were transferred to the drug-dispensing containers as unit doses. The IP dispensing containers used for dispensing were properly labelled for the study

number, period number, subject number, treatment code, batch/ lot number, initial and date of the person dispensing the product. The IP dispensing containers along with duplicate label (similar to that stuck on the dispensing container) were placed in zip lock bag.

Investigational product accountability included the records of the receipts, intake of investigational products during both the periods of the study and remaining quantities of investigational products.

The investigational products are stored in stability chamber at 22 ± 2°C and 60 ± 5% RH and inventory are maintained in the logbook of investigational product. Data for temperature and humidity was monitored and recorded regularly through data logger.

Only authorized personnel has access to the investigational product storage areas.

For certificate of analysis of test and reference products, refer appendix – 16.1.12.

9.4.7 Prior and Concomitant Therapy

Receipt of any other prescription drug or over the counter products (including vitamins and medicinal products from natural origin) within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks was an exclusion criterion. Further, the subjects were not supposed to consume any medication during the conduct of the study. All subjects, who checked-in the study, confirmed that they did not consume any medication within the 2 weeks of the start of first period or during the study.

9.4.8 Treatment Compliance

Subjects were provided with the identity card (I-card). While dosing, the staff on duty confirmed the subjects identity with I-card and the information mentioned on the investigational product administration form.

After administration of the dose of Investigational Product, examination of the oral cavity was performed under supervision of medical officer to assess the compliance to this procedure and the same was noted in the investigational product administration form of each subject. An additional label was affixed to the investigational product administration form in the appropriate place to confirm correct administration of Investigational Product. The time of actual dose administration was recorded in the investigational product administration form.

Investigational product accountability record and evaluation of the plasma drug concentration of the samples confirmed 100% compliance of all the subjects from whom the data was analyzed.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed

Efficacy Measurements Assessed

The following pharmacokinetic parameters (variables) of olmesartan were estimated after drug administration under fasting conditions:

Primary Efficacy Variables

C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

Secondary Efficacy Variables

$T_{1/2}$, K_e, T_{max}, npoints, K_e_first & K_e_last

These parameters were derived individually for each subject from their olmesartan concentration in plasma. Actual time of blood collection was considered for pharmacokinetic calculations.

For estimation of PK parameters, concentrations that were below level of quantification (BLQ) were assigned a value of zero if they preceded quantifiable samples in the initial portion of the profile. A BLQ that occurred at the end of the profile was set to zero. A BLQ or zero concentration that was embedded between two quantifiable points was assigned a value of missing. If consecutive BLQs in the terminal portion of the profile were followed by quantifiable determinations, these quantified values were excluded from PK analysis by assigning them a value of missing. In the calculations of PK parameters, missing values was ignored. Plasma concentrations used to determine PK parameters would be listed.

The pharmacokinetic parameters were calculated by non-compartmental methods using SAS® version 9.2.

The calculations of the individual pharmacokinetic parameters were carried out as follows:

C_{max} : Maximum measured plasma concentration following each treatment.

AUC_{0-t} : The area under the plasma concentration versus time curve from time zero to the last measurable concentration, as calculated by the linear trapezoidal method.

$AUC_{0-\infty}$: The area under the plasma concentration versus time curve, from zero to infinity.

$AUC_{0-\infty}$ is calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable concentration to the elimination rate constant.

T_{max} : Time of maximum measured plasma concentration. If maximum value occurs at more than one point, T_{max} is defined as the first point with this value in each period.

K_{el} : Apparent first order elimination or terminal rate constant calculated from semi log plot of the plasma concentration versus time curve. The parameters were calculated by linear least square regression analysis using at least the last three non-zero plasma concentration.

$T_{1/2}$: Time required for the plasma drug concentration to decrease to one half.

npoints : No. of time points of the terminal log-linear phase used to estimate the terminal disposition rate constant (K_e) with bestfit regression method used.

K_e_first : First time point of the terminal log-linear phase used to estimate the terminal disposition rate constant (K_e) with bestfit regression method used.

K_e_last: Last time point of the terminal log-linear phase used to estimate the terminal disposition rate constant (K_e) with bestfit regression method used.

Note:

- In case the pre-dose concentration obtained is greater than 5 percent of C_{max}, the subject was to be dropped from bioequivalence study evaluations.
- In case the subject experience emesis during the course of study, the data was to be deleted from statistical analysis if vomiting occurs within 2 times median T_{max} during the study.

Safety Measurements Assessed

Safety was evaluated by monitoring clinical adverse events during study periods. Vital signs (Blood Pressure, Temperature and Pulse Rate) and subject questionnaire was done at the time of check-in, pre dose and at 1.00, 3.00, 6.00, 9.00, 24.00, 36.00 and 48.00 hours post-dose (Time points being relative to the investigational product dosing). Medical examinations were carried out at the time of check-in, checkout and at 48.00 hours ambulatory visits of both the periods.

Subjects were monitored for adverse events, if any, throughout the course of the study by asking them if they were feeling fine or had any discomfort, at the time of clinical examination and recording of vital signs and recording the same in their respective CRF. The following evaluations were done at screening and in the follow-up phase:

- Medical examination (vital signs, 12 lead ECG and general and systemic examination).
- Clinical laboratory tests (hematology, clinical biochemistry) and urine analysis (only during pre study screening).

9.5.2 Appropriateness of Measurements

The plasma samples of subjects were analyzed by a validated LC-MS/MS method. The limit of quantification of 20.44 ng/mL for olmesartan was enough to quantify the analyte from the plasma samples collected up to 48.00 hours after drug administration. The linearity range of 20.44 ng/mL to 2499.89 ng/mL for olmesartan was enough to quantify the expected concentration range of Olmesartan from subject plasma with the proposed dose of single dose Olmesartan medoxomil 40 mg.

9.5.3 Primary Efficacy Variable(s)

The following pharmacokinetic parameters were assessed as primary efficacy variables,

C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

1.	Peak plasma concentrations	C_{max}
2.	Area under plasma concentration-Time curve from time of administration until the time of last quantifiable concentration	AUC_{0-t}
3.	Area under plasma concentration-Time curve up to infinity	$AUC_{0-\infty}$

9.5.4 Drug Concentration Measurements

Concentration of olmesartan was measured in plasma samples of the subjects Blood samples (1 × 5 mL) were collected in 5 mL blood collection tube containing K_2EDTA as anticoagulant. The venous blood samples were withdrawn pre-dose and at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours post-dose (time points being relative to the investigational product dosing). Blood samples were collected bed side up-to 4.00 hours post-dose.

Post-dose samples up to 24.00 hrs collected through an indwelling cannula placed in a forearm vein. The pre-dose samples were collected within one hour prior to investigational product dosing.

The post-dose samples up to 24.00 hours in house stay were collected within 2 minutes of the scheduled time where the end time of collection to the nearest minute was recorded. Similarly, the post-dose samples during each ambulatory visit were collected within one hour of the scheduled time where the end time of collection to the nearest minute was recorded. However there were few deviations in this regard. Refer section 10.2 'Protocol Deviation'.

During each ambulatory visit, the blood sample was collected up to two hours of specified schedule time of blood collection. No ambulatory blood sample collection was made after 2 hours of specified schedule time of blood collection for any subject.

Intravenous indwelling cannula was kept in place as long as required by injecting not more than 0.5 mL of 5 IU/mL of heparin in normal saline solution during the collection of multiple samples. In such a case, the blood sample was collected after discarding the first 0.5 mL of heparinised blood from the tubing. Blood would also be withdrawn from vein by using disposable syringe and needle if the cannula was blocked /removed or the cannula is removed for other reasons.

Each blood sample (1 x 5 mL) was collected into 5 mL blood collection tube containing K_2EDTA as anticoagulant. The blood samples collected at each time point were centrifuged at 4 to 8 °C and 4000 rpm for 10 minutes to separate plasma, after receiving the blood samples from all the subjects. The separated plasma was aliquoted in duplicate in prelabelled polypropylene tubes during each period. These tubes were labelled with study number, period number, subject number, sample number, time point (hrs) and aliquot number.

These tubes were transferred to a deep freezer maintained below –50°C or colder for storage and further analyzed by bioanalytical section.

The investigational products were administered in fasting conditions and no food was served till four hours post-dose. No fluid, except 240 mL drinking water administered with the investigational products was allowed from 1 hour pre-dose and 1 hour post-dose. At all other times, drinking water was given ad-libitum. The investigational products were administered to the subjects while in sitting posture and were instructed to avoid any strenuous activity following the investigational product administration. Subjects were in supine position up-to 4.00 hours post-dose. During this interval, under supervision, subjects were permitted to leave the bed for brief periods, e.g. to use the washroom facilities. Thereafter the subjects were allowed to engage only in normal activities while avoiding severe physical exertion.

Subjects were instructed to abstain from alcohol and products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) and tobacco products for at least 48 hours, prior to dosing and during their participation in the study including the ambulatory visit.

Subjects were instructed to abstain from grapefruit or grapefruit containing products or any cruciferous vegetables (eg. broccoli, brussels sprouts, etc.) or char-broiled meat prior 7 days of investigational product administration including the ambulatory visit.

Subjects were instructed to abstain from an unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to receiving the first investigational product and throughout their participation in the study including the ambulatory visit.

Validated LC-MS/MS method was employed for the estimation of olmesartan in plasma. During estimation of olmesartan in plasma quality control samples were distributed throughout each batch of study samples.

Whenever possible, samples from each subject were analyzed on the same standard curve. Samples with drug concentration greater than upper limit of the validated range of the analysis would be reanalyzed as per the standard test procedure based on method validation report.

The analysts concerned were blinded with respect to the randomization code, and as a result to the order of administration of the study medication.

9.6 Data Quality Assurance

The quality control personnel performed the quality control check of the case report forms and of all source documentation.

The Quality Assurance department of Macleods Pharmaceuticals Bioequivalence Department conducted both in process and retrospective audits of both Clinical, Bioanalytical and, Pharmacokinetic and Statistical phase of the study. The audits were conducted as per in-house standard operating procedure as appended in appendix 16.1.10. The findings in brief were reported to the management.

The Quality Assurance statement is appended as appendix 16.1.8.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Following were the plans for statistical analysis:

- Use descriptive statistics (number of subjects, mean, SD, CV, minimum and maximum) to summarize the plasma concentrations at each time of measurement.
- For purpose of descriptive Linear and semi-logarithmic plots of the mean and individual plasma concentration by scheduled sampling time provided.
- Report missing samples or unreportable concentration values as 'missing/ not reported' and document the reason for the same.
- Consider actual time of blood collection for pharmacokinetic calculations.
- Use SAS® system version 9.2 for estimation of pharmacokinetic parameters and its statistical analysis for olmesartan from their plasma concentration data.
- Report the summary statistics for all pharmacokinetic parameters for both the test and reference products. The reported parameters are the minimum, maximum, arithmetic means, median, standard deviation and the coefficient of variation for untransformed data and relevant pharmacokinetic parameters are the arithmetic means and the standard deviation for the log-transformed (natural) data.
- Analyze the log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of olmesartan using an ANOVA model with main effects of sequence, subject nested within sequence, period, and formulation.

- Use a separate ANOVA model to analyze each of the parameters. Use a 5% level of significance to test significance of all effects.
- Include calculation of mean square error, coefficient of variance and the associated degree of freedom for each analysis of variance.
- Use SAS procedure 'PROC GLM' to perform analysis of variance.
- Calculate and report ratio of geometric means using the LSM for log transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$.
- Calculate ratio of test to reference for each subject for all relevant pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$).
- Report the geometric means of the test and reference product. And express ratios of mean AUC_{0-t} to mean $AUC_{0-\infty}$ for test and reference in percentage.
- Calculate the power of the ANOVA model to detect the ratio of the two products averages (geometric means) being equal to 125% (or 80%) at the 5 % significance level for analyses using the log-transformed data.
- Calculate the coefficient of variation using $\sqrt{e^{MSE}-1}$ with help of SAS® version 9.2. Where MSE is mean squared error obtained from Analysis of Variance model.
- Calculate a 90% confidence interval for the ratio of both the products averages (geometric means) by first calculating the 90% confidence interval for the differences in the averages (least square means) of the log-transformed data and then taking the antilogarithms of the obtained confidence limits.
- Claim the treatment to be bioequivalent if the confidence intervals of olmesartan are entirely included in the range of 80.00% – 125.00% for log-transformed AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

9.7.2 Determination of Sample Size

Following data are obtained from "Published literature". Based on 2 x 2 Crossover study of Olmesartan performed on 36 healthy male volunteers. [3] Sample from the first 36 subjects to complete the study were used for the statistical analysis. Thus, Intra-subject C.V. was not available; it was calculated using the available data as shown below:

The pharmacokinetic parameters and statistical results for Olmesartan are as follows:

Pharmacokinetic Parameters	Ratio (T/R) (%)	90 % C.I. (%)	
		Lower	Upper
C_{max}	96.30	90.17	102.85
AUC_{last}	96.36	90.73	102.34
$AUC_{0-\infty}$	96.64	91.13	102.47

Calculation:

Assume that n1 (Number of TR sequence) = 18 and n2 (Number of RT sequence) =18

MSE for C_{max} =0.027246, MSE for AUC_{last}=0.022820, and MSE for $AUC_{0-\infty}$=0.021649

Intra-subject C.V. for C_{max} = $100*\sqrt{e^{MSE}-1}$ =16.62%

Intra-subject C.V. for AUC_{last} = $100*\sqrt{e^{MSE}-1}$ =15.19%

Intra-subject C.V. for $AUC_{0-\infty}$= $100*\sqrt{e^{MSE}-1}$ =14.79%

Sample size is calculated using SAS®. The highest Intra-subject C.V. was observed to be 16.62%. Hence using this Intra-subject C.V. the sample size calculation is as follows:

Two-Sample Equivalence
Multiplicative Model Lower Bound = 0.80 Upper Bound = 1.25
Coefficient of Variation = 0.1662 Alpha = 0.05

Null Ratio	Power	N per Group
0.95	0.800	13
	0.850	15
	0.900	17
	0.950	21
1.00	0.800	11
	0.850	12
	0.900	13
	0.950	15
1.05	0.800	13
	0.850	14
	0.900	17
	0.950	21

The highest intra subject C.V. for olmesartan was observed to be 16.62% for C_{max} in the Published literature[3]. So to achieve 80% power a sample size of 13 per formulation was concluded sufficient to conclude bioequivalence. Thus accounting for dropout or withdrawal of subjects during conduct of the study, 36 healthy human subjects were decided to be recruited in a crossover study design to achieve the desired sample size to conclude bioequivalence.

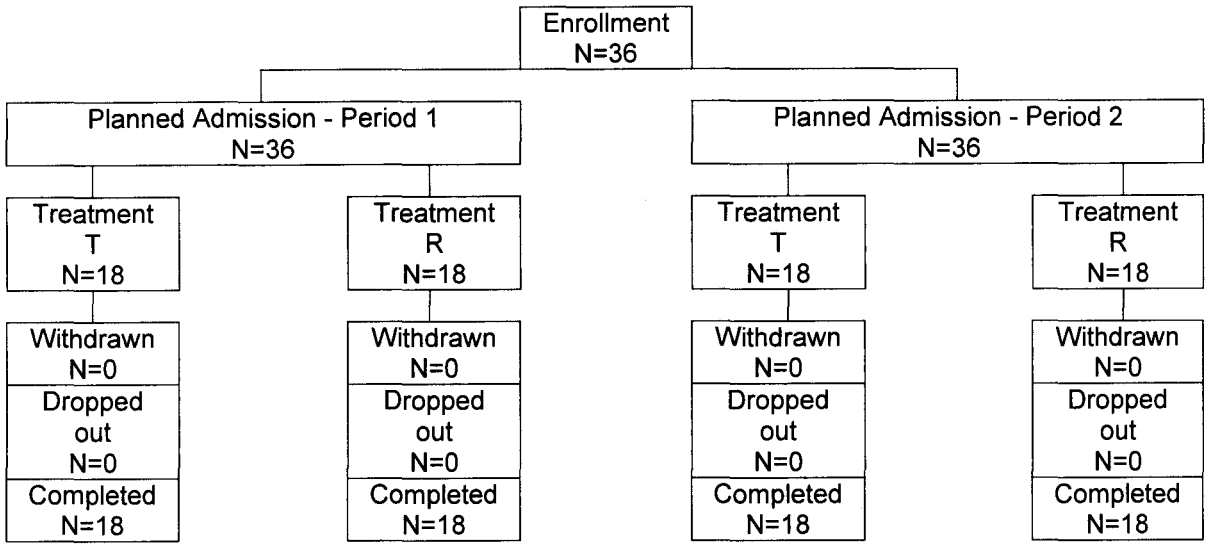
9.8 Changes in the Conduct of the Study or Planned Analyses

There were no changes in the conduct of the study or planned analyses.

10.0 STUDY SUBJECTS

10.1 Disposition of Subjects

A total of 36 subjects were planned and enrolled. All these 36 subjects completed both the periods.



10.2 Protocol Deviations

- As per protocol blood samples should be collected within one hour for all ambulatory visit samples. All actual times of the sample withdrawal were recorded in the bleed sheet. However, there were 03 deviations in period 1 and 01 deviation in period 2 from the schedule time of the collection above the permitted deviation time in the study.

Sr. No.	Subject No.	Sample Time Point (hrs)	Scheduled Time	Actual Time	Deviation in Hour	Reason for Deviation
Period 1						
1.	22	36.00	20:06 hrs	21:25hrs	1.32	Subject reported late
2.	34	36.00	20:30 hrs	21:48 hrs	1.30	Subject reported late
3.	35	36.00	20:32 hrs	21:46 hrs	1.23	Subject reported late
Period 2						
4.	29	48.00	08:20 hrs	09:54 hrs	1.57	Subject reported late

- As per protocol total 25 samples should be collected per subject in each period. However there were 05 deviations in period 1 and 04 deviations in period 2. Samples were not collected since the subjects did not report to facility.

Sr. No.	Time Point (Hrs)	Subject No.	
		Period 1	Period 2
1.	36.00	12, 29, and 36	08, 10 and 28
2.	48.00	29 and 36	08

The above deviations were duly incorporated during pharmacokinetic analysis.

The above deviations were recorded as protocol deviations and are recorded in appendix 16.2.2.

11.0 EFFICACY EVALUATION

11.1 Data Sets Analyzed

The plasma samples of all thirty-six subjects (subject number 01 to 36) completing the study was analyzed for olmesartan concentration level and the concentration data was utilised for pharmacokinetic and statistical evaluations.

11.2 Demographic and Other Baseline Characteristics

The demographic characteristics of the 36 subjects recruited and completed the study were as follows:

- Age between 20 and 42 years [30.9(mean) ± 6.16(SD) years].
- Height between 1.55and 1.76 meters [1.649 (mean) ± 0.0513 (SD) meters].
- Weight between 50.2 and 85.7 kg [63.51 (mean) ± 7.506 (SD) kg].
- BMI between 18.89 and 28.31 kg/m^2 [23.350 (mean) ± 2.3570 (SD) kg/m^2].

The demographic data is summarized in section 14.1. The demographic data for individual subjects are appended in appendix 16.2.4.

11.3 Measurements of Treatment Compliance

All the subjects took the medications as administered. Examination of the oral cavity immediately after drug administration was performed under supervision of medical officer to assess the compliance to this procedure. Further, the evaluation of the plasma drug concentration of the samples confirmed 100% compliance of the all the subjects from whom the data were analyzed.

Plasma levels of olmesartan in individual subjects at different time points following reference and test formulations are given in appendix 16.2.5.

11.4 Efficacy Results and Tabulations of Individual Subject Data

11.4.1 Analysis of Efficacy

The various un-transformed mean pharmacokinetic parameters estimated for both the reference and test formulations of olmesartan under fasting conditions are as follows:

Pharmacokinetic Parameters	Test product (N = 36)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	1331.028	334.5235	25.13	1304.42	758.50 - 2134.21
AUC_{0-t} (ng*hrs/mL)	9093.68692	2892.435511	31.81	8776.2609	3603.6013 - 19084.9916
$AUC_{0-\infty}$ (ng*hrs/mL)	9495.78922	2893.623199	30.47	9336.0358	3773.2673 - 19375.4325
T_{max} (hrs)	2.644	0.9855	37.28	2.50	1.00 - 5.00
$T_{1/2}$ (hrs)	6.87927	1.470224	21.37	6.7802	2.5362 - 9.7725
K_{el} (hr^{-1})	0.10687	0.033560	31.40	0.1022	0.0709 - 0.2733

Pharmacokinetic Parameters	Reference product (N = 36)				
	Arithmetic Mean	S.D.	C.V. (%)	Median	Range
C_{max} (ng/mL)	1259.430	333.7821	26.50	1231.34	631.71 - 2237.78
AUC_{0-t} (ng*hrs/mL)	8900.84430	3538.214990	39.75	8530.3849	3896.8732 - 20508.0540
$AUC_{0-\infty}$ (ng*hrs/mL)	9256.84868	3550.567756	38.36	8788.4691	4248.9587 - 20809.4492
T_{max} (hrs)	2.447	1.0097	41.26	2.25	1.00 - 5.00
$T_{1/2}$ (hrs)	7.24802	1.388780	19.16	7.1316	3.7136 - 10.3304
K_{el} (hr^{-1})	0.09952	0.022010	22.12	0.0972	0.0671 - 0.1867

The summary results are tabulated in section 14.2 and the individual subjects and mean pharmacokinetic parameters for both the test and reference formulations have been tabulated in appendix 16.2.6. The statistical output and pharmacokinetic from SAS® version 9.2 is appended in appendix 16.1.9.2.

The ln-transformed least square mean and 90% confidence interval based on least square mean obtained from ANOVA and ratio of geometric means for the pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for olmesartan under fasting conditions are summarized in the following table:

Geometric Mean, Ratio, Intra-Subject C.V., Power and 90 % Confidence Interval for Olmesartan						
Pharmacokinetic Parameters	Geometric Mean		Ratio (T/R) (%)	Intra Subject C.V. (%)	Power (%)	90 % Confidence Interval (%)
	Test (T)	Reference (R)				
C_{max} (ng/mL)	1291.297	1217.856	106.03	19.38	99.67	98.22 - 114.46
AUC_{0-t} (ng*hrs/mL)	8686.445	8321.940	104.38	20.53	99.36	96.26 - 113.18
$AUC_{0-\infty}$ (ng*hrs/mL)	9099.327	8692.482	104.68	19.48	99.65	96.93 - 113.05

ANOVA RESULTS:

Formulation Effect

Formulation effect found to be statistically insignificant for C_{max}, AUC_{0-t} & $AUC_{0-\infty}$.

Sequence Effect

Sequence effect found to be statistically insignificant for C_{max}, AUC_{0-t} & $AUC_{0-\infty}$.

Period Effect

Period effect found to be statistically insignificant for C_{max}, AUC_{0-t} & $AUC_{0-\infty}$.

RATIO AND 90% CONFIDENCE INTERVAL:

The ratio of geometric mean and 90% confidence interval for the ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} & $AUC_{0-\infty}$ were found to be respectively 106.03% & 98.22% - 114.46 %; 104.38% & 96.26% - 113.18% and 104.68% & 96.93% - 113.05%.

POWER AND INTRA SUBJECT VARIABILITY:

The power and intra subject variability for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} & $AUC_{0-\infty}$ were found to be respectively 99.67% &19.38 %; 99.36% & 20.53% and 99.65% & 19.48%.

11.4.2 Statistical / Analytical Issues

Statistical Issues

There were no statistical issues.

Analytical Issues

There were no analytical issues.

11.4.3 Tabulation of Individual Response Data

All individual subject concentration data that was used for pharmacokinetic analysis at each time point is appended as appendix 16.2.5. Individual plasma concentration time curves are presented in linear and log-linear scale in appendix 16.2.5.

11.4.4 Drug Dose, Dose Concentration and Relationships to Response

In the present bioequivalence study the pharmacokinetic end points were considered for the bioequivalence conclusion and hence the pharmacodynamic was not measured. Thus the drug dose, dose concentration and relationship to response were not evaluated.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not Applicable

11.4.6 By-Subject Displays

Not applicable

11.4.7 Efficacy Conclusions

The 90% confidence interval for the ratio (Test/Reference) of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of olmesartan were within the acceptable limits of bioequivalence 80.00% - 125.00%.

Thus it is concluded that the test product, Olmesartan Medoxomil Tablets 40 mg manufactured by Macleods Pharmaceuticals Ltd., India is bioequivalent to Benicar® (olmesartan medoxomil) Tablets 40 mg manufactured for Daiichi Sankyo, Inc., USA in healthy, adult, human subjects under fasting condition.

12.0 SAFETY EVALUATION

12.1 Extent of Exposure

All thirty-six subjects who completed the study were exposed to olmesartan medoxomil 40 mg, twice as per randomization schedule.

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Adverse Events

No adverse event occurred during entire course of the study.

There were few out of reference range laboratory values obtained at the post-study assessment but these were not clinically significant except for subject number 04, 24, 26 and 31. The details for the same are given in section 12.4.2. The clinically significant out of reference range values for the post study examination of the subject's laboratory investigations are tabulated in 14.3.4.

12.2.2 Displays of Adverse Events

No subject experienced adverse event during conduct of the study.

The clinically significant post-study out of reference range laboratory results are listed in section 14.3.4.

12.2.3 Analysis of Adverse Events

The out of reference range laboratory values obtained during post-study evaluation except for that listed in section 12.2.4 were considered to be clinically non significant. The relationship of the drug to the clinically significant out of reference range laboratory values obtained during post-study evaluation is given in section 12.2.4.

12.2.4 Listing of Adverse Events by Subjects

The relationship of the drug to the clinically significant out of reference range laboratory values obtained during post-study evaluation is as mentioned below:

Subject No.	Laboratory Parameter	Safety Assessment Results	Reference Range	Remark	Relationship with the Study Drug
04	Potassium	6.70 mmol/L	3.50 - 5.0 mmol/L	Increased	Unlikely
24	Haemoglobin	11.4 g/dL	13.0 - 17.0 g/dL	Decreased	Possible
	Hematocrit	35.2%	40.0 - 50.0%		
26	SGPT	60.2.U/L	4.0 - 36.0 U/L	Increased	Possible
	SGOT	39.8 U/L	8.0 - 33.0 U/L		
31	SGPT	71.1 U/L	4.0 – 36.0 U/L	Increased	Possible
	SGOT	42.3 U/L	8.0 – 33.0 U/L		
	GGT	46.5 U/L	5.0 – 40.0 U/L		

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

There was no serious adverse event reported in the study.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subjects and Each Abnormal Laboratory Value

Listed in appendix 16.2.8 are the various biochemical, hematological and urine sample assessment for the subjects, pre and post-clinical phase. The clinically significant out of reference

range values for the post-study examination of the subject's laboratory investigations are tabulated in 14.3.4.

12.4.2 Evaluation of Each Laboratory Parameters

There were few out of reference range laboratory values obtained at the post-study assessment, but these were not clinically significant except for subject number 04, 24, 26 and 31 who showed clinically significant post-study out of reference range laboratory value.

All the post-study safety assessment clinical and laboratory results are given in appendix 16.2.8, 'Listing of Individual Laboratory Parameters by Subject' [B- Laboratory Tests Report (Post-study safety Assessment)]. All the laboratory results, which were outside the reference range but within the 'acceptable limit', (for acceptable limit refer IEC approved Protocol, appendix V) were not considered clinically significant. There were few values as given below, which were outside the acceptable limits, however not considered clinically significant based on the clinical co-relation and have not been included as adverse events. For subject number 04, 24, 26 and 31 the laboratory result outside acceptable range are considered as clinically significant based on the clinical co-relation and are reported as adverse events.

Subject No.	Laboratory Parameter	Safety Assessment Results	Baseline Results	Reference Range	Remark
03	GGT	48.3 U/L	53.8 U/L	5.0 – 40.0 U/L	Clinically not Significant
04	Potassium	6.70 mmol/L	4.5 mmol/L	3.50 - 5.10 mmol/L	Clinically Significant
05	Hematocrit	35.7%	42.7%	40.0 – 50.0%	Clinically not Significant
06	Triglycerides	239.9 mg/dL	122.3 mg/dL	< 150.0 mg/dL	Clinically not Significant
	GGT	45.9 U/L	25.3 U/L	5.0 – 40.0 U/L	
12	Leucocyte count	11.70 x 1000 µ/L	10.30 x 1000 µ/L	4.00 - 10.0 x 1000 µ/L	Clinically not Significant
	ESR	21 mm/hr	19 mm/hr	< 15 mm/hr	
13	ESR	23 mm/hr	3 mm/hr	< 15 mm/hr	Clinically not Significant
18	Erythrocyte Count	3.89 million/µL	4.21 million/µL	4.00 – 5.5 million/µL	Clinically not Significant
22	Erythrocyte Count	3.95 million/µL	3.82 million/µL	4.00 – 5.5 million/µL	Clinically not Significant
	Triglycerides	200.9 mg/dL	151.2 mg/dL	< 150.0 mg/dL	
23	SGPT	51.4 U/L	36.5 U/L	4.00 - 36.00 U/L	Clinically not Significant
24	Haemoglobin	11.4 g/dL	12.3 g/dL	13.0 – 17.0 g/dL	Clinically Significant
	Hematocrit	35.2%	38.4%	40.0 – 50.0%	
26	Leucocyte count	11.10 x 1000 µ/L	6.98 x 1000 million/µL	4.00-10.0 x 1000 million/µL	Clinically not significant
	SGPT	60.2 U/L	34.7 U/L	4.00 - 36.00 U/L	Clinically Significant
	SGOT	39.8 U/L	24.1 U/L	8.0 - 33.0 U/L	

Subject No.	Laboratory Parameter	Safety Assessment Results	Baseline Results	Reference Range	Remark
28	Triglycerides	289.9 mg/dL	146.7 mg/dL	< 150.0 mg/dL	Clinically not significant
31	Total Cholesterol	221.1 mg/dL	230.5 mg/dL	< 200.0 mg/dL	Clinically not Significant
	Triglycerides	233.5 mg/dL	265.7 mg/dL	< 150.0 mg/dL	
	SGPT	71.1 U/L	28.0 U/L	4.00 - 36.00 U/L	Clinically Significant
	SGOT	42.3 U/L	19.9 U/L	8.0 - 33.0 U/L	
	GGT	46.5 U/L	35.5 U/L	5.0 – 40.0 U/L	
33	Erythrocyte Count	3.66 million/µL	3.70 million/µL	4.50 – 5.5 million/µL	Clinically not Significant

Note: The triglyceride levels of subjects are out side acceptable limit. Since the post-study safety assessment samples were collected post-prandially, the triglyceride levels are bound to be high and therefore raised triglyceride levels are clinically acceptable.

The clinically significant out of reference range values for the post-study examination of the subject's laboratory investigations are tabulated in 14.3.4.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Laboratory assessments, including urine test for drugs of abuse and alcohol breath test were carried out prior to the study.

In the pre-study assessments, all out of range clinical laboratory values were clinically acceptable, for the subjects enrolled in the study.

Vital signs and subject questionnaire was done at the time of check-in, pre-dose and at 1.00, 3.00, 6.00, 9.00, 24.00, 36.00 and 48.00 hours post-dose. Medical examinations were carried out at the time of check-in, check-out and at 48.00 hours post-dose of the study (time points being relative to the investigational product dosing). The individual recording of vital signs for both the periods has been appended as appendix 16.2.8 (Table D).

All the subjects enrolled and dosed had clinically acceptable vital signs values.

A medical officer was available within the clinical facility whenever the subjects were housed (from check-in to checkout and during ambulatory visit).

Safety assessments of all the enrolled subjects were carried out. Post-study safety assessments included: Medical examination including recording of vital signs [Blood Pressure (BP), Pulse and Respiration], general examination, physical and systemic examination. 12-lead ECG for heart rate, rhythm and specific finding (if any). Laboratory parameter investigation including complete blood count – erythrocyte count, platelet count, haemoglobin, hematocrit, leucocyte count, ESR and differential leucocyte count (DLC); Biochemistry –blood sugar (fasting), total cholesterol and triglycerides; Hepatic profile – SGOT, SGPT, GGT, alkaline phosphatase and serum bilirubin (total, direct, indirect), Renal profile – serum creatinine, BUN, calcium, electrolytes (sodium, potassium, chlorides).

No clinically significant abnormalities in ECGs were reported in subjects during post-study safety assessments. The individual clinical impression of ECG has been appended as appendix 16.2.8 (Table C).

Laboratory values outside the reference range were considered clinically not significant based on clinical co-relation and have not been included as adverse events except for few subjects as given in section 12.4.2. The clinically significant out of reference range values for the post-study examination of the subject's laboratory investigations are tabulated in 14.3.4 and the individual recordings of laboratory parameters are appended in appendix 16.2.8 (Table B).

12.6 Safety Conclusions

No serious adverse event occurred during the conduct of the study.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

A total of 36 subjects were planned and enrolled. All the subjects completed the study. Single dose administration of Olmesartan Medoxomil Tablets 40 mg was well tolerated and no new safety issues were identified during the study. There were few clinically relevant changes in laboratory safety variables for four subjects; of which AE experienced by three subjects were possibly related to the study drug and AE experienced by one subject was unlikely related to the study drug. No deaths, serious adverse events or adverse events classified as 'other significant AEs' occurred during the study.

The plasma samples of all the thirty-six subjects who completing the study were analyzed for olmesartan concentration level and the concentration data was utilised for pharmacokinetic and statistical evaluations.

The mean plasma concentration time profiles of olmesartan for the two treatments are shown in Figure 1 and 4 (Refer section 14.2 'Efficacy Data').

After oral administration of the reference product under fasting condition the olmesartan medoxomil was absorbed and metabolised to olmesartan with median t_{max} of 2.25 hrs. Where for other PK parameters mean C_{max} 1259.430 ng/mL (range 631.71 - 2237.78 ng/mL), AUC_{0-t} 8900.84430 ng*hrs/mL (range 3896.8732 - 20508.0540 ng*hrs/mL) and $AUC_{0-\infty}$ 9256.84868ng*hrs/mL (range 4248.9587 - 20809.4492ng*hrs/mL).

After oral administration of the test product under fasting fasting condition the olmesartan medoxomil was absorbed and metabolised to olmesartan with median t_{max} of 2.50 hrs. Where for other PK parameters mean C_{max} 1331.028 ng/mL (range 758.50 - 2134.21 ng/mL), AUC_{0-t} 9093.68692 ng*hrs/mL (range 3603.6013 - 19084.9916 ng*hrs/mL) and $AUC_{0-\infty}$ 9495.78922 ng*hrs/mL (range 3773.2673 - 19375.4325 ng*hrs/mL).

Bioequivalence was assessed using standard equations. The 90% confidence intervals for Cmax, AUC_{0-t} and $AUC_{0-\infty}$ for olmesartan were within the usual acceptable limit for 80.00-125.00%.

In summary, the test formulation is bioequivalent to the reference in terms of both the rate and extent of absorption.

Both the formulations are well tolerated following a single dose administration of the investigational product.

14.0 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Demographic Data of Subjects Recruited and Completed the Study:

	Age (Yrs)	Height (m)	Weight (kg)	BMI (kg/m^2)
Number	36	36	36	36
Median	30.00	1.65	64.65	23.18
Mean	30.9	1.649	63.51	23.350
Standard Deviation	6.16	0.0513	7.506	2.3570
Minimum	20	1.55	50.2	18.89
Maximum	42	1.76	85.7	28.31

14.2 Efficacy Data

Summary statistics of pharmacokinetic parameters for olmesartan after administration single dose of Olmesartan Medoxomil Tablets 40 mg in, 36 healthy, adult human male subjects under fasting conditions.

Product/Statistics	C_{max} (ng/mL)	AUC_{0-t} (ng*hrs/mL)	$AUC_{0-\infty}$ (ng*hrs/mL)
Untransformed Reference Product (R)			
Arithmetic Mean	1259.430	8900.84430	9256.84868
S.D.	333.7821	3538.214990	3550.567756
C.V. %	26.50	39.75	38.36
N	36	36	36
Test Product (T)			
Arithmetic Mean	1331.028	9093.68692	9495.78922
S.D.	334.5235	2892.435511	2893.623199
C.V. %	25.13	31.81	30.47
N	36	36	36
Ratio of Arithmetic Mean (% Bioavailability)			
T/R (%)	105.69	102.17	102.58
Ratio (%) for Mean AUC_{0-t} to Mean $AUC_{0-\infty}$			
Reference		96.15	
Test		95.77	
Log Transformed (Natural Log) Least Square Mean			
Reference	7.105	9.027	9.070
Test	7.163	9.070	9.116
Geometric Mean			
Reference	1217.856	8321.940	8692.482
Test	1291.297	8686.445	9099.327
Ratio of geometric Mean			
T/R (%)	106.03	104.38	104.68
90 % Confidence Interval (T/R)			
Lower limit (%)	98.22	96.26	96.93
Upper limit (%)	114.46	113.18	113.05
Power (%)	99.67	99.36	99.65
D.F.	34	34	34
Intra Subject C.V. (%)	19.38	20.53	19.48
Mean Square Error (MSE)	0.036880	0.041287	0.037251
P-value (ANOVA) for ln-transformed data			
Formulation	0.2045	0.3770	0.3218
Period	0.8007	0.5463	0.5340
Sequence	0.6323	0.7065	0.7149

Figure 1

Comparative Linear Plot of Olmesartan Mean Plasma Concentration (ng/mL) Vs Time (Hour)(N=36)

subject=MEAN

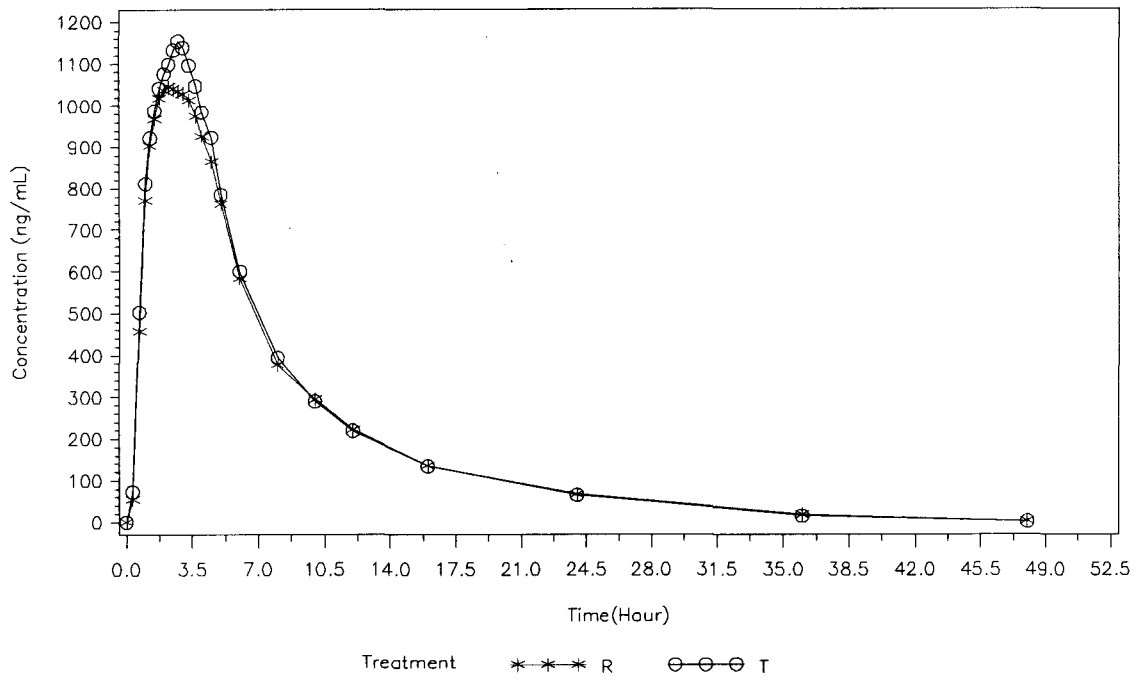
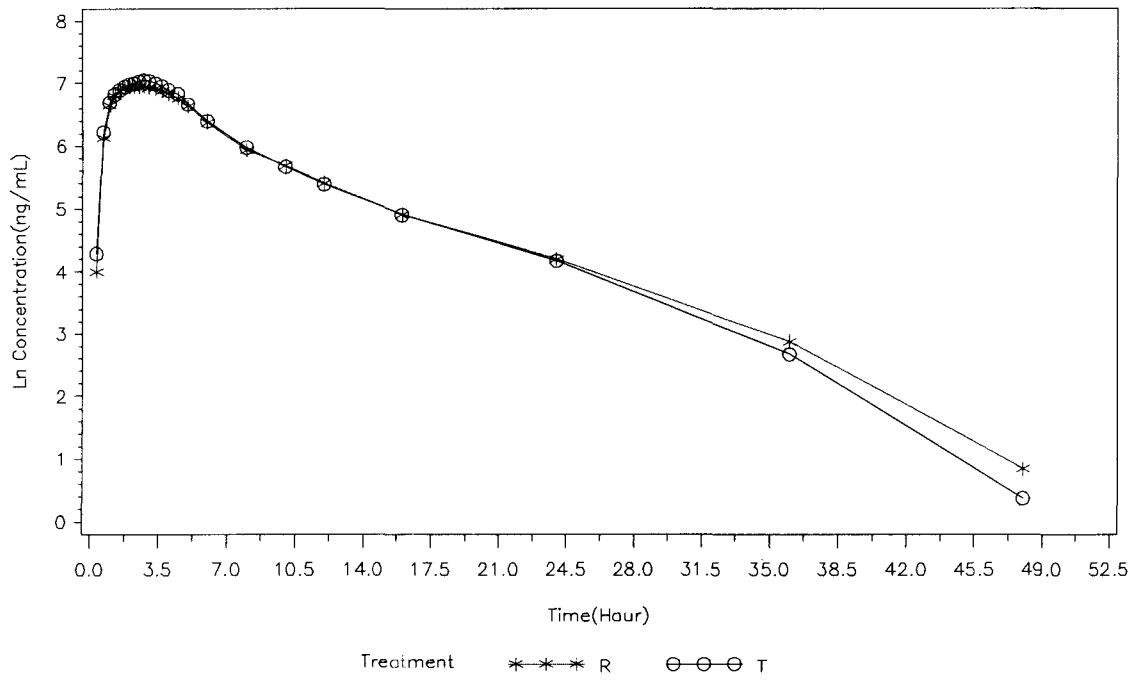


Figure 2

Comparative Semi Log Plot of Olmesartan Mean Plasma Concentration (ng/mL) Vs Time (Hour)(N=36)

subject=MEAN



14.3 Safety Data

14.3.1 Display of Adverse Events

No adverse event occurred during entire course of the study.

Four subjects (subject number 04, 24, 26 and 31) enrolled in the study were found to have clinically significant post-study laboratory values. The list of clinically significant post-study out of reference range laboratory values is listed in section 14.3.4.

The detailed description of the adverse events and their handling are given in appendix 16.2.7.

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

No deaths or other serious adverse events or any other significant adverse events were observed in the study.

14.3.3 Narrative of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable

14.3.4 Abnormal Laboratory Value Listing

Following table gives details of outside acceptable limit findings, which are clinically significant in laboratory test of subjects post study.

Subject No.	Laboratory Parameter	Reference Range	Safety Assessment Results	Follow-up Result	Comments
04	Potassium	3.50-5.10 mmol/L	6.70 mmol/L	4.00 mmol/L	Resolved
24	Haemoglobin	13.0 – 17.0 g/dL	11.4 g/dL	Not Done	Lost for follow-up
	Hematocrit	35.2 %	35.2 %		
26	SGPT	4.0 – 36.0 U/L	60.2 U/L	114.3 U/L	Lost for follow-up
	SGOT	8.0 – 33.0 U/L	39.8 U/L	68.6 U/L	
31	SGPT	4.0 – 36.0 U/L	71.1 U/L	Not Done	Lost for follow-up
	SGOT	8.0 – 33.0 U/L	42.3 U/L		
	GGT	5.0 – 40.0 U/L	46.5 U/L		

15.0 REFERENCE LIST

(Refer appendix 16.1.12; 'Important Publications Referenced in the Report')

1. U.S. Food and Drug Administration-Drug product label of Effexor XR®, NDA No. 020699, Approved on 02/05/2012.Cited on 28/05/2012
Available From:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020151s059,020699s100lbl.pdf
2. Public Assessment Report Decentralised Procedure, PAR Tardcaps 75mg and 150mg XL Capsules Cited on 20/06/2011, Available from:
http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con014356.pdf
3. Reference for ICF
Rx List cited on 28/05/2012 Available from:
http://www.rxlist.com/effexor-xr-drug/patient-images-side-effects.htm