Title Page

STUDY PROTOCOL

A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Levanix (Levofloxacin) 500mg Coated Tablets of Neopharma LLC., with Levaquin (Levofloxacin) 500mg Coated Tablets of Anchieta Comercio de Medicamentos Delivery Ltda., in Normal, Healthy, Adult, Male and Female Human Subjects Under Fasting Condition.

Study Code	ARL/16/560
Draft Version No.	01
Date	04 January 2016
Superseded Version No.	None
Date	Not Applicable

STUDY CENTER
Principal Investigator: Dr. Alpesh Patel, M.D. (Pharmacology)
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SPONSOR
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PROTOCOL SYNOPSIS

Title	A Randomized, Open Label, Balanced, Two-Treatment, Two-Period, Two-Sequence, Single Dose, Crossover, Bioequivalence Study of Levanix (Levofloxacin) 500mg Coated Tablets of Neopharma LLC., with Levaquin (Levofloxacin) 500mg Coated Tablets of Anchieta Comercio de Medicamentos Delivery Ltda., in Normal, Healthy, Adult, Male and Female Human Subjects Under Fasting Condition.
Background	Levofloxacin is a synthetic broad spectrum antibacterial agent. Levofloxacin is indicated for the treatment of mild, moderate and severe infections caused by susceptible strains of the designated microorganism. The present study will be conducted to assess the suitability of the test product as a bioequivalent generic version of the reference product.
Study Design	A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover design.
Objectives	**Primary Objective:** To demonstrate the bioequivalence between **Test Product (T):** Levanix (Levofloxacin) 500mg Coated Tablets and **Reference Product (R):** Levaquin (Levofloxacin) 500mg Coated Tablets, in normal, healthy, adult, male and female human subjects, under fasting conditions. **Secondary Objective:** To monitor the safety and tolerability of a single oral dose of investigational medicinal products (IMPs).
No. of Subjects	A total 24 (12 male and 12 female) normal, healthy, adult, human subjects will be enrolled.
Assessment of Subjects	A. <u>On Screening day:</u> Breath alcohol test, demographic data, medical / clinical history, physical examination including vital signs, 12-lead Electrocardiogram (ECG), chest X-ray (P/A view) (if required based on any significant past medical history and/or positive finding in respiratory system examination), haemogram, biochemistry, serology (HIV, Hepatitis B and Hepatitis C and Anti HBc IgM) and urinalysis will be performed. B. <u>On Check-in day:</u> Breath alcohol test, relevant medical / clinical history, physical examination including vital signs, Urine screen for drug abuse for commonly abused substances, serum pregnancy test for female subjects will be done. C. <u>During Confinement Period:</u>

	Well being assessment, physical examination including vital signs measurement. D. <u>Post Study Evaluation:</u> Well being assessment, physical examination (including vital signs), 12-lead ECG, serum pregnancy test for female subjects, haemogram, biochemistry and urinalysis will be performed. **Note:** 1. Well being assessment and breath alcohol analysis will be done during subject's visit for follow-up and ambulatory PK samples if applicable. 2. Any other assessment including laboratory test(s) will be done if judged necessary by the PI/Sub-investigator/Co-investigator person at any time during the course of study.
Restrictions	**Food restriction:** Subjects will fast overnight from at least 10.00 hours (hrs) before dose administration and for at least 04.00 hrs post-dose in each study period. **Fluid Restriction:** Water will not be allowed to the subjects from at least 01.00 hr pre-dose until at least 01.00 hr post-dose except 200 mL ± 2 mL of water at ambient temperature given during dose administration in each study period. **Postural Restriction:** Subjects will remain upright (sitting) for the first 02.00 hrs post-dose except for any procedural reason. In case of an AE, subject will be given appropriate (supine/semi-supine) position in each study period.
Meals	Standardized meals will be served as per the details provided in *Appendix G* in each study period.
Dose Administration	Single oral dose (1 x 500 mg Tablet) of the test product or reference product will be administered as per the randomization schedule with 200 mL ± 2 mL of water at ambient temperature under fasting condition.
Washout	The successive study periods will be separated by at least 7 calendar days.
Housing	Subjects will be housed for at least 10.50 hrs prior to dosing and up to 24.00 hrs post-dose.
Study Duration	The duration of the clinical phase will be approximately 11 days.
Blood Sample Collection (5 mL per sample)	Total number of blood samples: 21 per period. Sampling hrs: Pre dose (collected within 30 min. prior to dosing), Pre-dose, 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.00, 02.25, 02.50, 03.00, 03.50, 04.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00 and 48.00 hrs post dose.

	Blood samples will be collected in Na- Heparin Vacutainers. Blood samples after 24.00 hrs will be collected on ambulatory basis.
Total blood loss	The approximate volume of blood loss during the study will be 238 mL for male and 242 mL for female.
Sample processing	All the blood samples will be centrifuged under refrigeration at 3500 RPM, 10 minutes and 5°C ± 3°C. Plasma samples will be placed in deep freezer maintained at -20°C ± 5°C.
Analytical Method	Levofloxacin in plasma will be quantified using a validated analytical method.
Pharmacokinetic Parameters Evaluated	The following PK parameters will be analyzed: **Primary:** C_{max} and AUC_{0-t} **Secondary:** AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf}, AUC_{0-inf}/AUC_{0-t}, T_{max}, K_{el} and $t_{1/2}$
Statistical Evaluation	Pharmacokinetic and Statistical analysis will be done using SAS® 9.2 or higher version. The drug concentration of Levofloxacin in plasma for each subject, each sampling time and each product will be reported. Descriptive statistics (mean, median, standard deviation, coefficient of variation, minimum and maximum) will be computed for each pharmacokinetic parameter for the test and reference product. ANOVA will be performed on log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} and on un-transformed pharmacokinetic parameters T_{max} for Levofloxacin. The 90% confidence interval will be constructed for the ratio of geometric least square mean of the test and reference product, obtained from the log-transformed pharmacokinetic parameters. Difference of T_{max} between the products will be analyzed by nonparametric Wilcoxon test. Bioequivalence will be concluded if: The 90% confidence interval of geometric mean ratio of log transformed pharmacokinetic parameters C_{max} and AUC_{0-t} between test and reference products falls within the range of 80.00% to 125.00% for Levofloxacin.

INVESTIGATOR'S STATEMENT

I recognize that all information concerning this study and the medication provided by the sponsor may not be previously published and is confidential information.

I accept that the sponsor and the Ethics Committee must approve the protocol and subsequent changes to the protocol in writing before its implementation (except where it is necessary to eliminate immediate hazards to participating subjects or when such changes may involve only administrative aspects of the study).

I hereby give my consent to conduct the study in accordance with this protocol. I agree to comply with all requirements of the current version of the Declaration of Helsinki, the current ICH GCP Guidelines, Schedule Y, ANVISA regulatory guidelines as well as relevant National Laws and Regulations. I agree to comply with all relevant SOPs required for the conduct of this study and further agree to ensure that all associates assisting in the conduct of study are informed regarding their obligations.

_____ Date: _____
Principal Investigator (DD/MM/YY)

Dr. Alpesh Patel, M.D. (Pharmacology)
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Sarkhej-Gandhinagar Highway,
Bodakdev, Ahmedabad -380059, INDIA.
Tel.: +91 79-4023 1600
Fax: +91 79-40029317

SPONSOR'S STATEMENT

I, on behalf of **Neopharma LLC.,** have read, understood & approve this protocol. I hereby give my consent to conduct the study in accordance with this protocol. I agree to comply with all requirements regarding the obligations of sponsor and all other pertinent requirements of the current version of the Declaration of Helsinki, the current ICH GCP, ANVISA regulatory guidelines as well as relevant National Laws and Regulations.

_____ Date: _____

Sponsor's Authorized Signatory

Sponsor's Representative:
Name: Mr. Rajendra H Bhandari
Designation: Advisor to the Board
Address:
Neopharma LLC
Plot A-1 89-95, Industrial City of Abu Dhabi (ICAD),
Mussafah, P O Box 72900,
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LIST OF ABBREVIATIONS

ADRs	Adverse drug reactions
AE(s)	Adverse Event(s)
ANOVA	Analysis of Variance
ANVISA	Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency)
AUC	Area Under the Curve
AUC_{0-t}	Area Under The Concentration Versus Time Curve Calculated Using The Trapezoidal Rule Up To The Last Measurable Time Point
AUC_{0-inf}	Area Under The Concentration Versus Time Curve From Time 0 To Infinity
BA	Bioavailability
BE	Bioequivalence
β-hCG	Serum Beta Human Chorionic Gonadotropin level
BLQ	Below the Limit of Quantification
BP	Blood Pressure
BUN	Blood Urea Nitrogen
cc	Cubic Centimeter
CHO	Carbohydrate
CI	Confidence Interval
cm	Centimeter (s)
cmm	Cubic Millimeter
C_{max}	Maximum Observed Drug Concentration In Plasma
CNS	Clinically Non-Significant
COA	Certificate of Analysis
CPU	Clinical Pharmacological Unit
CRF	Case report Form
CS	Clinically Significant
C_t	Last measurable drug concentration
CV	Coefficient of Variation
°C	Degree Celsius
dL	Deciliter
EC	Ethics Committee
ECG	Electrocardiogram
g	Gram
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin In Blood
HBc IgM	Hepatitis B core Immunoglobulin M
HBsAg	Hepatitis B Surface Antigen
HCl	Hydrochloride
HCV	Hepatitis C Virus
HIV	Human Immuno Deficiency Virus
Hpf	High Power Field
hr(s)	Hour(s)

ICH	International Conference on Harmonization
ICU	Intensive Care Unit
ICCU	Intensive Cardiac-Care Unit
IMP	Investigational Medicinal Product
IU	International Unit
K_{el}	Elimination Rate Constant
kg	Kilogram(s)
L	Liter
LC-MS/MS	Liquid Chromatography-Mass Spectrometer / Mass Spectrometer
Log	Logarithm to the base 'e'
LOQ	Limit of Quantification
LSM	Least Square Mean
m	Metre
mg	Milligram
mL	Milliliter
mm	Millimeter
mmol	Millimole
mM	Millimolar
µg	Microgram
µL	Microlitre
µm	Micrometer
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin-concentration
MSV	Missing Sample Values
ng	Nanogram
No.	Number
NRV	Not-reportable Values
OTC	Over The Counter
PBS	Pharmacokinetic and Biostatistics
PCV	Packed Cell Volume
pg	Picogram
PK	Pharmacokinetic
PROC GLM	Procedure General Linear Model
QA	Quality Assurance
QAU	Quality Assurance Unit
RBC	Red Blood Cell
RPM	Rotations per minute
SAE(s)	Serious Adverse Event(s)
SAS	Statistical Analysis System
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SLIMS	Study Labels and Instruments Data Management Software

SOP(s)	Standard Operating Procedure(s)
$t_{1/2}$	Elimination Half-Life
T_{max}	Time To Observed Maximum Drug Concentration In Plasma
U/L	Units per litre
WBC	White Blood Cell
WMA	World Medical Association

TABLE OF CONTENTS

1.0 TITLE OF THE PROJECT:

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2.0 NUMBER AND DATE OF PROTOCOL:

Study code: ARL/16/560
Draft Version No:
Date:
Superseded Version: None
Date: Not Applicable

3.0 PRINCIPAL INVESTIGATOR:

Dr. Alpesh Patel, M.D. (Pharmacology)
Principal Investigator

4.0 CLINICAL INVESTIGATORS AND OTHER KEY PERSONNEL INVOLVED IN THE STUDY:

4.1 Sub-Investigator/Co-Investigator:

Dr. Darshan Koyani
Dr. Shardul Doctor, M.B.B.S.
Dr. Kaushik Chavda, B.H.M.S.
Dr. Mehulkumar Patel, B.H.M.S.

4.2 Medical Officer:

Dr. Alpesh Patel, M.D. (Pharmacology)
Dr. Darshan Koyani
Dr. Shardul Doctor, M.B.B.S.
Dr. Kaushik Chavda, B.H.M.S.
Dr. Mehulkumar Patel, B.H.M.S.

4.3 Pathologist:

Dr. Umang Gandhi, M.D. (Pathology)

4.4 Head – Quality Assurance:

Dr. Paresh Mistry, Ph.D. (Chemistry), PGDEIM-IF

5.0 PERSON IN-CHARGE FOR THE ANALYTICAL PHASE:

Dr. Arvind Jangid, Ph. D.(Chemistry)

6.0 PERSON IN-CHARGE FOR THE STATISTICAL PHASE:

Ms. Aashita Ajmera, M. Phil (Statistics)

7.0 FACILITY:

7.1	**Screening Facility:**		
	Accutest Research Lab (I) Pvt. Ltd. (Unit-I) 4th Floor, The Grand Monarch, Near Seema Hall, Anand Nagar Road, Satellite, Ahmedabad-380015, INDIA. Tel.: +91 79- 4023 1700	**OR**	**Accutest Research Lab (I) Pvt. Ltd. (Unit-II)** Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad -380059, INDIA. Tel.: +91 79-4023 1600 Fax: +91 79-40029317
7.2	**Clinical Phase:**		
	Accutest Research Lab (I) Pvt. Ltd. (Unit-II) Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad -380059, INDIA. Tel.: +91 79-4023 1600 Fax: +91 79-40029317		
7.3	**Clinical Assessment:**		
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7.4	**Analytical and Statistical Phase:**		
	Accutest Research Lab (I) Pvt. Ltd.(Unit-II) Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad -380059, INDIA. Tel.: +91 79- 40231600 Fax: +91 79-40029317		
7.5	**Clinical Laboratory Facility:**		
	SYMMERS PATH CARE 8, 9 Ground Floor Narayan Chambers, B/H Patang Hotel, NR. Nehrubridge, Ahmedabad 380009 , Gujarat, India Tel.: +91 79-26578364		
7.6	**X-Ray Facility:**		
	Shachi X-Ray, Sonography & Colour Doppler Clinic F-2, 3 Balaji Center, Opposite Gurukul, Drive-in-Road, Memnagar, Ahmedabad-380052, INDIA. Tel.: +(91)-(79)-27491622, 26754759		

7.7	**Emergency Facility:**
	SAL Hospital and Medical Institute Opp. Doordarshan, Drive-in-road, Ahmedabad – 380 052, Gujarat, India Tel: +91-79-2684 5600 Fax: +91-79-2684 5675
7.8	**Biomedical waste Management:**
	Medicare Environmental Management Pvt. Ltd. 28, Ashwamegh Industrial Estate, Changodar, GIDC, Ta.: Sanand, Dist.: Ahmedabad-382213 Tel.: +91 79-26304248

8.0 STUDY OBJECTIVE:

Primary Objective: To demonstrate the bioequivalence between **Test Product (T):** Levanix (Levofloxacin) 500mg Coated Tablets and **Reference Product (R):** Levaquin (Levofloxacin) 500mg Coated Tablets, in normal, healthy, adult, male and female human subjects, under fasting conditions.

Secondary Objective:
To monitor the safety and tolerability of a single oral dose of investigational medicinal products (IMPs).

Purpose: The sponsor aims to market test product as similar alternative to the already existing innovator product. Hence as per the ANVISA, a bioequivalence study is being conducted in normal, healthy, adult, male and female human subjects.

8.1 Background Information:

8.1.1 Investigational Medicinal Products:

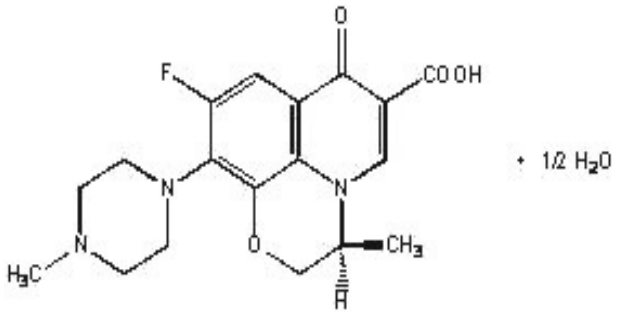
Test Product:
Levanix (Levofloxacin) 500mg Coated Tablets.

Reference Product:
Levaquin (Levofloxacin) 500mg Coated Tablets.

8.1.2 General Pharmacology: [3]

Description: Levofloxacin is a synthetic broad-spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro2,3-dihydro-3-methyl-10- (4-methyl-1-piperazinyl) -7-oxo-7H-pyrido [1,2,3-de]-1, 4benzoxazine-6- carboxylic acid hemihydrate. The empirical formula is $C_{18}H_{20}FN_3O_4$ • ½ H_2O and the molecular weight is 370.38

[Structural Formula]



8.1.3 Mechanism of Action: [4]

As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

8.1.4 Indication and Usage: [5]

Levofloxacin is indicated for the treatment of bacterial infections caused by susceptible agents to levofloxacino, such as:

- infections of the upper and lower respiratory tracts, including sinusitis, acute exacerbations of chronic bronchitis and pneumonia.
- infections of the skin and subcutaneous tissue, complicated and not complicated, such as impetigo, abscesses, furunculosis, Cellulitis and erysipelas.
- Urinary tract infections, including acute pyelonephritis
- osteomyelitis

8.1.5 Pharmacokinetics: [4]

Absorption:

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1- 2 h. The absolute bioavailability is 99- 100 %.

Food has little effect on the absorption of levofloxacin.
Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.

Distribution

Approximately 30 - 40 % of levofloxacin is bound to serum protein. The mean volume of distribution of levofloxacin is approximately 100 l after single and repeated 500 mg doses, indicating widespread distribution into body tissues.

Penetration into tissues and body fluids:

Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin *has* poor penetration intro cerebro-spinal fluid.

Biotransformation

Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for < 5 % of the dose excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t½: 6 – 8 h). Excretion is primarily by the renal route > 85 % of the administered dose).

The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/-29.2 ml/min. There are no major differences in the pharmacokinetics

of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Linearity

Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg.

8.1.6 Adverse Effects: [4]

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.

Frequencies are defined using the following convention: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known (cannot be estimated from available data)**
Infections and infestations		Fungal infection including Candida infection Pathogen resistance		
Blood and lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity	Anaphylactic shock[a] Anaphylactoid shock [a]
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients	Hyperglycaemia Hypoglycaemic coma
Psychiatric disorders	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt

Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion Paraesthesia	Peripheral sensory neuropathy Peripheral sensory motor neuropathy Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension
Eye disorders			Visual disturbances such as blurred vision	Transient vision loss
Ear and Labyrinth disorders		Vertigo	Tinnitus	Hearing loss Hearing impaired
Cardiac disorders			Tachycardia, Palpitation	Ventricular tachycardia, which may result in cardiac arrest Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged
Vascular disorders			Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence		Diarrhoea – haemorrhagic which in very rare cases may be

		Constipation		indicative of enterocolitis, including pseudomembranous colitis Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased		Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases Hepatitis
Skin and subcutaneous tissue disorders [b]		Rash Pruritus Urticaria Hyperhidrosis		Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia	Tendon disorders including tendinitis (e.g. Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) Ligament rupture Muscle rupture Arthritis
Renal and Urinary disorders		Blood creatinine increased	Renal failure acute (e.g. due to interstitial nephritis)	
General disorders and administration site conditions		Asthenia	Pyrexia	Pain (including pain in back, chest, and extremities)

[a] Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose

[b] Mucocutaneous reactions may sometimes occur even after the first dose

Other undesirable effects which have been associated with fluoroquinolone administration include:

• attacks of porphyria in patients with porphyria.

For more details on adverse effects, please see the reference literature.

8.1.7 Contraindication: [5]

Levofloxacin Tablets must not be used:

- in patients hypersensitive to levofloxacin or other quinolones or to any of the excipients
- in patients with epilepsy
- in patients with history of tendon disorders related to fluoroquinolone administration
- in children or growing adolescents
- during pregnancy
- in breast-feeding women

For more drug contraindications see the reference literature.

8.1.8 Drug Interaction: [4]

Effect of other medicinal products on levofloxacin

Iron salts, zinc salts, magnesium- or aluminium-containing antacids, didanosine
Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) are administered concomitantly with Levofloxacin Tablets. Concurrent administration of fluoroquinolones with multi-vitamins containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cations such as iron salts, zinc salts or magnesium- or aluminium-containing antacids, or didanosine (*only didanosine formulations with aluminium or magnesium containing buffering agents)* should not be taken 2 hours before or after Levofloxacin Tablets administration. Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate
The bioavailability of Levofloxacin Tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and

Levofloxacin Tablets, it is best to administer sucralfate 2 hours after the Levofloxacin Tablets administration.

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs
No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.

Levofloxacin concentrations were about 13 % higher in the presence of fenbufen than when administered alone.

Probenecid and cimetidine
Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24 %) and probenecid (34 %). This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance.

Caution should be exercised when levofloxacin is coadministered with drugs that effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Effect of levofloxacin on other medicinal products
Ciclosporin
The half-life of ciclosporin was increased by 33 % when coadministered with levofloxacin.

Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists.

Drugs known to prolong the QT interval
Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotic).

Other forms of interactions
Meals
There is no clinically relevant interaction with food. Levofloxacin Tablets may therefore be administered regardless of food intake.

For more drug interactions see the reference literature.

8.2 Rationale of Dose: [4]

Levofloxacin is indicated for the treatment of mild, moderate and severe infections caused by susceptible strains of the designated microorganism.

The following dose recommendations can be given for Levofloxacin Tablets:
Dosage in patients with normal renal function
(creatinine clearance > 50 ml/min)

Indication	Daily dose regimen (according to severity)	Duration of treatment (according to severity)
Acute bacterial sinusitis	500 mg once daily	10 - 14 days
Acute bacterial exacerbations of chronic bronchitis	500 mg once daily	7 - 10 days
Community-acquired pneumonia	500 mg once or twice daily	7 - 14 days
Pyelonephritis	500 mg once daily	7 - 10 days
Complicated urinary tract infections	500 mg once daily	7 - 14 days
Uncomplicated cystitis	250 mg once daily	3 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated Skin and soft tissue infections	500 mg once or twice daily	7 - 14 days
Inhalation Anthrax	500 mg once daily	8 weeks

The present study will be conducted under fasting condition based on the recommendation of regulatory authority.

This dose is expected to be well-tolerated and will provide sufficient plasma concentrations to measure. Based on this rationale, the current study has been designed.

8.3 Risk and Benefits:

There will not be any direct health related benefit to the subject. However, a health assessment is provided by this study free of charge. In this study subjects will receive a single dose of the IMPs as per the randomization schedule. Subjects are aware of the potential risks of administration of this drug after reading, understanding and signing Informed Consent Form (ICF).

8.4 Study Conduct:

This study will be conducted in compliance with the protocol approved by the Ethical Committee (EC) and according to Good Clinical Practice (GCP) standards. Deviation

having any impact on the safety of the subject or on study data will not be implemented without prior review and approval of the EC except where it may be necessary to eliminate an immediate risk to a study subject. In such a case, the deviation will be reported to the EC as soon as possible.

9.0 STUDY DESIGN:

9.1 Type:

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover design.

Study Duration:

Excluding screening period, the duration of clinical phase will be approximately 11 days including a washout period of at least 7 days for each study period.

9.1.1 Generation and handling of Randomization:

The randomization for this study will be generated by PBS personnel using the PROC PLAN on statistical software SAS® 9.2 or a higher version.

The handling of randomization will be done as per the SOP: Randomization of treatment.

The analyst concerned will be blinded to the sequence of administration of Test and Reference product to the individual subject.

9.2 Identification of Test and Reference Drug Products:

Test Product (T): Levanix (Levofloxacin) 500mg Coated Tablets
Label claim:
Each film-coated tablet contains Levofloxacin 500 mg, as Levofloxacin hemihydrates.
Manufactured By: Neopharma LLC.
Plot A-1 89-95, Industrial City of Abu Dhabi (ICAD),
Mussafah, P O Box 72900,
Abu Dhabi, United Arab Emirates.
Telephone: +971 2 550 1000 Fax: +971 2 550 1199
Dosage Form: Tablet
Formulation strength: 500 mg
Dose: 1 x 500 mg Tablet

Reference Product (R): Levaquin (Levofloxacin) 500mg Coated Tablets
Label claim:
Each Film coated tablet contains Levofloxacin 500 mg
Manufactured by: Janssen-Cilag Farmacêutica Ltda.
Rodovia Presidente Dutra, km 154, São José dos Campos – SP - Brasil
Distributed By: Anchieta Comercio de Medicamentos Delivery Ltda.
Dosage Form: Tablet
Formulation strength: 500 mg

Dose: 1 x 500 mg Tablet

9.2.1 Investigational Medicinal Product Accountability:

9.2.1.1 Receipt:

The study IMPs will be accepted in accordance with current version of the Standard Operating Procedure (SOP) for 'Handling of Investigational Medicinal Product'. The Pharmacist will check the IMPs for integrity and correctness of the label. The products will be accompanied by the certificate of analysis (COA). The sponsor will be responsible for the supply of IMPs in a properly labeled pack according to the requirements of Good Manufacturing Practice (GMP). The quantity of IMPs should be sufficient as per current version of the SOP for 'Handling of Investigational Medicinal Product' or as provided by the sponsor.

The assay content of the test product should not differ from that of the reference product by more than 5 percent.

9.2.1.2 Storage and Dispensing:

The IMPs will be stored in a restricted access area (pharmacy) in a storage cabinet maintained at a temperature specified on the label of the IMP. The pharmacist will prepare the labels for the IMP dispensing vials/containers in accordance with the current version of the SOP. Labels should be approved by Quality Assurance (QA) prior to dispensing. The Pharmacist will carry out dispensing as per randomization code in accordance with the current version of the SOP for 'Dispensing' in presence of QA personnel.

The label of IMP dispensing vials/containers will contain the following details:
"For Clinical Research Use Only"
Study Code:
Period:
Subject No:
Treatment Code:

9.2.1.3 Reconciliation:

The PI will not allow the study drugs to be used for the purposes other than those indicated in this protocol. At the end of last dosing, the IMPs received, the quantity used for dispensing for the concerned study, the retention quantity and the balance quantity will be recorded in accordance with the current version of SOP 'Handling of Investigational Medicinal Product'.

9.2.1.4 Retention:

The IMPs for the test and reference formulations will be retained as per the current version of the SOP for 'Handling of Investigational Medicinal Product'. The disposal of the retained samples will be done only at the end of the retention period as mentioned in the "IMP log" after obtaining written confirmation from the sponsor.

The minimum quantity of retention of test and reference drugs will be sufficient to repeat the study.

9.3 Drug Administration:

The subjects will be administered the IMPs in sitting position in each period, after an overnight fast of at least 10.00 hrs. as per the randomization schedule.

Dose: 1 x 500 mg Tablet.

Schedule: The dose will be administered at around 08:00 or 09:00 hours, in a staggered manner to maintain subsequent blood collection schedule.

Dose administration will be done with 200 mL ± 2 mL of water at ambient temperature by trained personnel, under the supervision of Principal Investigator/ authorized trained person in accordance with current version of SOP for 'Dosing'. Subjects will be instructed not to chew or crush the IMPs but to consume it as a whole. The QA person will ensure that the dosing is done as per the dosing schedule and as mentioned in the protocol.

Compliance for dosing will be assessed by a thorough check of the oral cavity by using a disposable tongue depressor and torch immediately after dosing by Principal Investigator/Authorized trained person/Medical Officer. Record of dosing for individual subject will be maintained in Case Report Form.

9.4 Housing of Subjects:

The subject will be housed from at least 10.50 hrs before dosing until 24.00 hrs post dose in the centre for each study period. Activities beyond 24.00 hrs will be conducted on ambulatory basis.

Visits: Each eligible subject is required to return to the study centre on check-in days of each study period and ambulatory blood sample (s) collection.

9.4.1 Subject data identification:

The volunteers will be identified via thumb impression/finger print using computerized software during screening. Thereafter, for every visit for the study, the volunteers will be identified via thumb impression/finger print using Computerized Software or with ID card.

All 'Fit Subjects' will be given the subject number as per the current version of SOP for 'Check-In and Check-Out of Subjects' and it will remain the same throughout the study. Data of each subject will be identified either by the volunteer registration number or subject number.

9.5 Fasting and Feeding Time Table:

Standardized meals *(Appendix G)* will be provided to the subjects as scheduled below for all the study periods:

Period	Time in Hours Pre-dose	Time in Hours Post-dose		
	Dinner on check-in night	Lunch	Snack	Dinner
I	In such a way to maintain at least 10.00 hours pre-dose fasting	04.00 hours	08.00 hours	12.00 hours
II	In such a way to maintain at least 10.00 hours pre-dose fasting	04.00 hours	08.00 hours	12.00 hours

The record of food serving will be documented in the meal consumption record.

9.6 Sampling Schedule:

As this is a bioequivalence study, no efficacy measurement will be done. Blood sample collection, handling, processing, bioanalysis and statistical analysis will be done to establish bioequivalence between the test product and reference product.

Blood sample collection:

An intravenous cannula will be inserted into the subject's arm for the collection of the blood samples before the pre-dose blood sample and up to 24.00 hrs post-dose. If difficulties occurs in blood withdrawing or if the subject is not feeling comfortable with the cannula, then the cannula will be removed before 24.00 hrs post-dose and the remaining blood samples will be collected through fresh vein puncture or by recannulation. When meals, vitals and sample collections coincide, samples will be collected first followed by vitals and then meal will be served.

Before every blood sample collection, 0.2 mL of blood present in the intravenous cannula will be discarded during the use of the intravenous cannula except for the ambulatory sample. Also after every blood sample collection, 0.2 mL of heparinised saline (by mixing 1 mL of 5000 IU/5mL of heparin with 500 mL of normal saline) will be injected into the intravenous cannula.

Twenty one (21) blood samples (5 mL) will be collected in Na- Heparin Vacutainers at pre dose (collected within 30 min. prior to dosing), 00.25, 00.50, 00.75, 01.00, 01.25, 01.50, 01.75, 02.00, 02.25, 02.50, 03.00, 03.50, 04.00, 06.00, 08.00, 10.00, 12.00, 16.00, 24.00 and 48.00 hrs post dose. The actual time of blood collection will be considered for calculation of PK parameters. Duration of 2 minutes is required for the completion of procedure of blood sample collection. Hence, the reason for deviation up to 2 minutes for the blood sample collection activity need not be documented. However, the reason for delay beyond 2 minutes will be documented in the case record form and/or other document.

Blood samples after 24.00 hrs will be collected on ambulatory basis through direct vein puncture. The actual end-point time of collection of each blood sample will be recorded in the CRF.

Ambulatory blood sample will be collected up to 04.00 hours from the scheduled time of blood sample collection. If the subject reports for blood sample collection beyond 04.00 hours, the blood sample will not be collected and the subject will be requested to come for the next ambulatory blood sample (if any).

Approximate blood loss during the study:

		Males	Females
Total blood samples (42 x 5.0 mL)	:	**210 mL**	**210 mL**
Pre study screening	:	**10 mL (up to)**	**10 mL (up to)**
Post study evaluation	:	**10 mL (up to)**	**10 mL (up to)**
Discarded heparinised blood (40 x 0.2 mL)	:	**8 mL**	**8 mL**
Serum β-hCG (2 x 2 mL)	:	-	**4 mL**
Approximate blood loss	:	**238 mL**	**242 mL**

Blood withdrawal beyond this specified blood volume in the study will be considered as an incidental blood loss.

The incidental blood loss may occur due to following reasons.

1. For performing pending laboratory tests if study subject are primarily screened for other study not having such investigations.
2. For performing pending laboratory tests on the day of check-in for period I if such investigations are not performed on the day of screening due to any reason.
3. For repeating PK sample due to any reason after check-in in the study if required in the opinion of the investigator (example: loss of blood sample due to spillage or breaking of sample container etc).

The subjects will be compensated proportionately for any incidental blood loss as per the compensation policy (*Appendix L*).

If additional blood sample is taken for safety evaluation anytime after check in for first period, no compensation will be provided for such blood loss.

9.7 Sample Handling and Processing:

Centrifugation of the samples will be done within 60 minutes after the last blood sample collection of respective time point. Following centrifugation at 3500 RPM for 10 minutes at 5°C ± 3°C, the plasma will be transferred to appropriate size biological sample storage vials (previously labeled with study code and sample code), in duplicate (one aliquot as control samples and one aliquot for analysis, the aliquot for analysis should contain approximately 1.5 mL of plasma).

Each vial will be labeled with a unique code containing subject number, nature of sample (analytical or control sample), study code, period number and sample number. The specimens of label are mentioned below. The number in the first row corresponds to the subject number. Analytical sample and control sample are denoted by AS and

CS respectively. The box next to it denotes 'study code'. The code in the last row indicates the subject number/study period/serial time point number for PK samples. The study period is denoted with X and Y for period I and II respectively. The serial time point number is denoted by T01, T02 and so on.

Example:

01	
CS	ARL/16/560
01/Y/T01	

01	
AS	ARL/16/560
01/Y/T01	

Storage: The vials containing plasma samples will be kept in the pre-labeled boxes or vial-holding racks. The boxes/vial holding racks will be stored in a deep freezer maintained at -20°C ± 5°C. The above procedures will be performed in accordance with the current version of the SOP for 'Blood sample collection, Processing and Storage'.

Transport: Transport of plasma samples from the sample storage area to analytical site will be done as per the current SOP of 'Segregation, Transfer, Retention and Disposal of Biological Samples' and 'Transport of biological samples outside the study centre' maintaining the appropriate storage condition during transportation.

10.0 STUDY POPULATION:

10.1 Detailed description:

A total of 24 (12 male and 12 female) normal, healthy, adult, human subjects with age in the range of 18- 45 years (both inclusive), Body Mass Index between 18.5-30 Kg / m^2 extremes included, fulfilling the inclusion criteria and none of the exclusion criteria will be enrolled for this study.

10.2 Subject selection:

The subjects will be evaluated for eligibility to participate in the study based on the inclusion & exclusion criteria, demographic characteristics, physical examination including vital sign as per current version of SOP for 'Vital and Physical examination of volunteer', 12-lead ECG reports, chest X-ray reports (P/A view) (if taken) and clinically acceptable laboratory reports. The ultimate decision for selection of subject will be taken by medically qualified person.

10.2.1 Pre study (screening) and during study Evaluation:

The pre study and during study evaluation procedure will include following:

10.2.1.1 Demography:

Demographic information will be captured during screening which includes volunteer registration number, date of birth, age, race, gender, height and weight of the subjects.

10.2.1.2 12-Lead Electrocardiogram:

12-lead ECG will be done during screening. The electrocardiograms will be assessed by a cardiologist from the clinical assessment team of Accutest, and will document, if the specific findings were judged as normal, abnormal clinically non-significant (CNS) or as abnormal clinically significant (CS). The ultimate decision for selection of subject will be taken by medically qualified person.

10.2.1.3 Radiological Examination:

Chest X-ray (P/A view) will be done during screening as per the discretion of the medical officer and/or PI if required based on any significant past medical history and/or positive finding in respiratory system examination.

10.3 Clinical Assessment (Medical History & Physical Examination):

Subject's past and present medical / clinical history, vital signs measurement (blood pressure, pulse rate, respiration rate and body temperature) and systemic examination will be done.

10.4 Clinical Laboratory Examination:

Laboratory tests will be done prior to the study for all subjects.

10.4.1 Blood & Urine Tests:

Pre-study blood samples will be obtained for haematology, biochemistry and serology screening (HIV, Hepatitis B, Hepatitis C and Anti HBc IgM). Pre-study routine urinalysis will also be done. The details of these laboratory tests are given in *Appendix H*.

In addition to the above tests, for female subjects, serum (β) beta- hCG (Human Chorionic Gonadotropin) test will be done on the day of check-in for each study period.

Any other test/s, if required, will be done as per the suggestion given by Principal Investigator or Sub-Investigator/Co-Investigator.

Subjects qualifying the acceptance criteria for all above examinations and tests will be called on check-in day for Period-I.

The results of the blood and urine tests will be considered as "acceptable' when they are within the normal range specified by the laboratory. For numeric results, the values out of the specified normal range might be considered as "acceptable" based on the clinical judgment of the medical officer or clinical investigator.

In case of change of laboratory or use of different test kits resulting in new normal ranges, the interpretation of such investigations will be done considering the new range and it's clinical correlation.

10.4.2 Breath Alcohol test:

A breath alcohol test will be done using breath alcohol analyzer at the time of screening, before check-in and before each ambulatory blood sample collection for each study period.

10.4.3 Urine test for drug abuse:

Urine test for drug abuse will be done before check-in for each study period.

Note: If any of the tests mentioned above is not performed on the day of screening, it will be done on the day of check-in for first period.

10.4.4 Recording of clinically non-significant (CNS) observation:

"Clinically non-significant" (CNS) observations/values will be identified with the appropriate marks in clinical laboratory report, itself by medically qualified person.

10.4.5 Screening validity:

The clinical/physical examination will be carried out in a period not more than to 21 days prior to the first drug's administration. medical / clinical history, 12-lead ECG, anthropometric data and laboratory examinations (including serological tests) will be carried out in a period not more than to 21 days prior to the first drug administration.

10.5 Inclusion Criteria:

The subjects who qualify for the study should meet the following inclusion criteria:

1. Male and non pregnant female human subjects, age in the range of 18 – 45 years both inclusive.
2. Body Mass Index between 18.5-30 Kg / m^2 extremes included.
3. Subjects with normal findings as determined by baseline history, physical examination and vital sign examination (blood pressure, pulse rate, respiration rate and body temperature).
4. Subjects with clinically acceptable findings as determined by haemogram, biochemistry, urinalysis, 12 lead ECG and chest X-ray (if done).
5. Willingness to follow the protocol requirements especially abstaining from xanthine containing food or beverages (chocolates, tea, coffee or cola drinks) or fruit juice/grapefruit juice, any alcoholic products, the use of cigarettes and the use of tobacco products for 48.00 hours prior to dosing until after the last blood sample collection in each study period and adherence to food, fluid and posture restrictions.
6. No history of significant alcoholism.
7. No history of drug abuse (benzodiazepines and barbiturates) for the last one month and other illegal drugs *(Appendix H)* for the last 06 months.
8. Non smokers as evident from the history obtained will be included.

10.6 Exclusion Criteria:

The subjects who qualify for the study should not meet the following exclusion criteria:

1. Known history of hypersensitivity to Levoflaxacin or related drugs.
2. Requiring medication for any ailment having enzyme-modifying activity in the previous 28 days, prior to dosing day.
3. Subjects who have taken prescription medications or over-the-counter products (including vitamins and minerals) within 14 days prior to administration of IMP.
4. Any medical or surgical conditions, which might significantly interfere with the functioning of gastrointestinal tract, blood–forming organs etc.
5. History of cardiovascular, renal, hepatic, ophthalmic, pulmonary, neurological, metabolic, haematological, gastrointestinal, endocrine, immunological or psychiatric diseases.
6. Participation in a clinical drug study or bioequivalence study 180 days prior to period I dosing of the present study.
7. History of malignancy or other serious diseases.
8. Blood donation 180 days prior to period I dosing of the present study.
9. Subjects with positive HIV tests, HBsAg, Hepatitis-C or Anti HBc IgM tests.
10. Found positive in breath alcohol test.
11. Found positive in urine test for drug abuse.
12. History of problem in swallowing.
13. Any contraindication to blood sampling.
14. Female subjects found positive serum (β) Beta- hCG (Human Chorionic Gonadotropin) test.
15. Lactating women (currently breast feeding).
16. Female subjects not confirming to using birth control measures, from the date of screening until the completion of the study. Abstinence, barrier methods (condom, diaphragm, etc.) are acceptable.
17. Use of hormonal contraceptives either oral or implants.

10.7 Restrictions and Prohibitions: Before and During the Study:

10.7.1 Medication:

All subjects should not take any prescription medication or over-the-counter (OTC) products including vitamins and minerals for at least 14 days prior to participation in the study and till the completion of the study.

10.7.2 Diet Restriction:

In each period, all subjects will be required to fast overnight from at least 10.00 hours (hrs) before dose administration and for at least 04.00 hrs post-dose. Subjects will be given standardized dinner on check-in day and standardized meals scheduled at time points described in *Appendix G* in each study period.

All subjects will be instructed to abstain from any xanthine-containing food or beverages (chocolates, tea, coffee or cola drinks) or fruit juice/grapefruit juice and any alcoholic products, the use of cigarettes and use of tobacco products for 48.00 hours prior to dosing until after the last blood sample collection in each study period.

10.7.3 Fluid Restriction:

Water will not be allowed from at least 01.00 hour pre-dose until at least 01.00 hours post-dose except 200 mL ± 2 mL water given during administration of the dose in each study period. At all other times drinking water will be given *ad-libitum*.

10.7.4 Physical Activity/Posture:

Subjects will remain upright (sitting) for the first 02.00 hours post-dose except for any procedural reason in each study period. In case of an AE, subject will be given appropriate (supine/semi-supine) position in each study period. The subjects will refrain from any strenuous activity during the confinement period at the testing facility.

10.8 Criteria for Subject Discontinuation or Withdrawal from the Study:

Any subject who is discontinued from the study by Principal Investigator/ Sub-investigator/Co-investigator/Medical Officer for other than personal reasons will be considered as withdrawn.

Subjects may be discontinued from the study for any of the following reasons:

1. Subjects not wishing to continue with the study, irrespective of the reason (dropped-out subjects).
2. Any significant medical occurrence (including laboratory results) which as per the discretion of the Principal Investigator could be a risk to the health of the subject.
3. Any illness requiring medication during the study.
4. Violation of the protocol requirement by the subject.
5. Subject found positive in breath alcohol test done during each visit, pregnancy test and urine drug abuse test done on check-in day for the study.
6. Any subject who had an episode of vomiting or had an episode of diarrhea at or before two times T_{max} will be discontinued from the study. Three or more consecutive watery stools irrespective of the stool-volume within 24.00 hours from the first occurrence will be considered as diarrhea.

Subject will not be evaluated for the post study assessment if he/she is discontinued from the study before dosing in period-I. Subject may be discontinued from the study for any reason beneficial to his/her well-being.

The Principal Investigator, as well as the sponsor, will decide to withdraw any subject's participation in the study if, in their judgment, continuation in the study may prove harmful to the subject. Such a decision may be precipitated by adverse events, including changes in vital signs, physical examination, significant laboratory parameters and 12-lead ECG etc. The Principal Investigator may also withdraw a subject due to poor compliance to the study protocol.

An attempt will be made by the Principal Investigator to find out the reason for drop-out.

If a subject discontinues from the study any time after being assigned a subject number, the reason will be recorded in the case report form ('withdrawal/dropped-out'), by the Principal Investigator/Authorized trained person/Medical Officer. The details of withdrawn /dropped out subjects will be reported in the clinical report.

If a subject discontinues from the study any time after being assigned a subject number and/or before serving standardized check-in dinner, then the principal investigator can replace the dropped-out subject with another eligible subject.

10.8.1 Discontinuation / Termination of the Study:

If the PI terminates or suspends the study without prior agreement of the sponsor, the PI will promptly inform the sponsor and the EC and will provide them with a detailed written explanation of the termination or suspension.

If the study is prematurely terminated or suspended by the sponsor, the sponsor will promptly inform the PI and the regulatory authority-(ies) of the termination or suspension and the reason(s) for the termination or suspension. The EC will also be informed promptly and will be provided with the reason(s) for the termination or suspension by the sponsor or by the PI.

If the EC terminates or suspends its approval/favorable opinion, the PI will promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

If the study is terminated prematurely or suspended for any reason, the PI will promptly inform the study subjects, will assure appropriate follow-up for the subjects, and where required by the applicable regulatory requirement(s) the PI will inform the regulatory authority(ies).

11.0 ADVERSE REACTIONS AND EMERGENCY PROCEDURES:

11.1 Assessment of Safety:

The PI will monitor safety data throughout the course of the study. A qualified medical officer will be available during the housing in the clinical center. Subjects will be monitored throughout the study period for occurrence of AEs. A nearby contracted hospital capable of handling emergency situations will be informed about the study. The hospital has agreed to provide the necessary treatment facilities, if required, and the physicians attached to the hospital will carry out treatment of AEs as appropriate, either at the study center or at contracted hospital. Subjects experiencing AEs will be followed up until resolution of the AE. Subjects who at least received one dose of the study medication will be included in the safety analysis.

All data from pre-study and post-study medical and clinical laboratory examinations acquired after signing of the ICF will be documented. Any clinical laboratory result outside the normal range will be evaluated by the PI against the clinical co-relation and study medication if given. The PI will determine whether the laboratory test will be repeated to establish if and when this value returns to normal. Assessments and

comments on the clinical significance of laboratory values outside the normal range will be provided by the PI in the clinical report.

The PI should ensure that adequate medical care is provided to a subject for any AE, including clinically significant laboratory values related to the study. The PI should inform a subject when medical care is needed for inter current illness(es) of which the PI becomes aware.

If possible, the PI should make a reasonable effort to follow up all AEs until an outcome is known or until the AE is determined not to be related to the study.

The AEs will be documented appropriately and described in the clinical report.

11.2 Safety Evaluation:

The subjects will be monitored for occurrence of adverse events and serious adverse events throughout the study. Safety evaluation will be done on the basis of outcomes of physical examination, vital signs measurement and clinical laboratory results which will be performed during each study period as per the details given below.

Timings	Activities
Before check-in	Physical examination, measurement of blood pressure, pulse rate, respiration rate and body temperature
Pre-dose	Well-being assessment, Measurement of blood pressure and pulse rate
Post-dose	Well-being assessment, Measurement of blood pressure and pulse rate at 02.00, 06.00 and 10.00 hrs ± 45 minutes of scheduled time.
At check-out	Well being assessment, physical examination, measurement of blood pressure, pulse rate, respiration rate and body temperature. Physical examination and vital examination can be started approximately 02.00 hours prior to the scheduled time in each study period. Intravenous cannula site will be observed by principal investigator/co-investigator /Sub-investigator /medical officer for any swelling or thrombophlebitis.
During Ambulatory sample	Well-being assessment
During Post-study evaluation	Well being assessment, physical examination (including vital signs), 12-lead ECG, serum pregnancy test for female subjects, haemogram, biochemistry and urinalysis.

Additionally, any other assessment including laboratory test(s) will be done if judged necessary by the Principal Investigator (PI) or authorized trained personnel at any time during the course of study.

Post study evaluation will be done at the time of collection of last PK sample in last study period. Physical examination and measurement of blood pressure, pulse rate, respiration rate and body temperature performed at the time of check-out will be considered for post-study evaluation if the timing of post study evaluation and check-out coincides.

If any subject fails to complete the study or is discontinued from the study, the post-study evaluation will be done either on the day of discontinuation or before/at the end of study. If the post study evaluations are not completed within this time frame due to any reason, the same can be attempted at later stage at the discretion of Principal Investigator. The reason for not completing the study will be specified in the respective CRF and the clinical report.

The subjects may also report spontaneously any inconvenience or AEs to the monitoring staff at any time during the study or after check-out within the total number of days not exceeding the washout period.

All clinically important abnormal laboratory results occurring during the study should be revaluated at adequate time intervals until they return to baseline values, to an acceptable level according to the Investigator or until a diagnosis that explains said changes are made.

11.3 Handling of Adverse Events:

Investigators are responsible for monitoring the safety and for providing appropriate medical care for all subjects from their check-in of Period-I onwards. Each subject will be carefully questioned and/or examined by the investigator or a medically qualified delegate (i.e. authorized by the investigator) to obtain information regarding AEs. All events spontaneously reported by the subject, observed by the clinical staff or elicited by general questioning will be recorded appropriately.

Appropriate treatment of any AEs will be instituted under the direction of a physician. All AEs will be followed until resolved or stabilized. The resolution of any AE will be done on the basis of appropriate medical examinations and/or laboratory investigations. Should any subject choose to withdraw early from the study, they will be informed of the safety precautions to be taken. The reason for withdrawal will be documented.

11.3.1 Definitions:

Adverse Event (AE)

An AE is any untoward medical occurrence (including a symptom/disease or an abnormal laboratory finding) during treatment with a pharmaceutical product in a

patient or a human volunteer that does not necessarily have a relationship with the treatment being given.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a (investigational) medicinal product, whether or not related to the (investigational) medicinal product. For example:

- A new sign, symptom, illness or syndrome;
- Abnormal laboratory value as well as a significant shift from baseline within normal range which the qualified investigator or medically qualified delegate considers to be clinically significant (CS).
- An AE of the Investigational Medicinal Product (IMP), including comparator or concomitant medication;
- Drug interactions.

Adverse Drug Reaction (ADR)
An ADR is any untoward and unintended response to an IMP related to any dose administered. The definition implies a reasonable possibility of a causal relationship between the AE and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship, the relationship cannot be ruled out.

Serious Adverse Event (SAE)
A SAE is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability/incapacity;
  or
- Is a congenital anomaly / birth defect.

11.3.2 Severity Assessment:

The severity of all AEs will be graded by the PI or a medical qualified delegate according to the following definitions:

TERM	DEFINITION
Mild	Causing no limitation of usual activities; the subject may experience slight discomfort.
Moderate	Causing some limitation of usual activities; the subject may experience annoying discomfort.
Severe	Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

11.3.3 Causality Assessment:

The following criteria should be used in assessing the apparent causal relationship of an AE to study medication.

Definitely - The AE follows a reasonable temporal sequence from study medication administration. Though not practically doable in BA/BE studies, this can be verified by dechallenge (abates upon discontinuation of the study medication) and rechallenge (reappearance of the reaction on repeat exposure).

Probably - The AE follows a reasonable temporal sequence from study medication administration and cannot be reasonably explained by the known characteristics of the subject's state.
Possible - The AE follows a reasonable temporal sequence from study medication administration but that could readily be produced by a number of other factors.

Unlikely - The AE follows a reasonable temporal sequence from study medication administration could have been produced by either the subject's clinical state or by study medication administration.

Not related - The AE does not have a reasonable temporal association with the administration of study medication has some other obvious explanation for the event.

11.3.4 Expectedness Assessment:

An "Unexpected Adverse Event" is an adverse event that its nature or severity is not consistent with the applicable product information. All other adverse events will be documented as "Expected Adverse Event".

11.4 Reporting of AEs and SAEs including death:

Reporting of AEs

Documentation of adverse event or serious adverse event will be done in accordance with current version of SOP for "Handling And Reporting of Adverse Event", "Handling And Reporting of Serious Adverse Event". In particular the information will include description of the event, details of the timing of the event to administration of the study medication, frequency of adverse event, description of the severity of the event, any treatment or diagnostic steps taken in relation to the event, description of the outcome of the event, judgment by the medical officer of any relationship of the event to study medication or procedures. All adverse events will be reported to the sponsor and EC within 14 calendar days by investigator(s).All AEs will be followed until resolved or stabilized.

Reporting structure of SAEs including death

Nature	By whom	To whom	Timelines
Initial report	Investigator	Chairman EC, DCGI, Sponsor	Within 24 hrs* of occurrence
Follow-up report	Investigator	Chairman EC, DCGI, Sponsor, Clinical Site Head	Within 14 calendar days of occurrence
Follow-up report	Sponsor	Chairman EC, DCGI, Clinical Site Head	Within 14 calendar days of occurrence

**Follow-up report	Ethics Committee	DCGI	Within 30 calendar days of occurrence
Notification	Investigator	ANVISA	Within 15 business days of occurrence[#]

* If delayed beyond 24 hrs, the reason for the delay to the satisfaction of the DCGI along with the report of the serious adverse event to be submitted.
**Report after due analysis along with its opinion on financial compensation to be submitted.
[#] In case of death, notification must occur within 7 days from incidence.

11.5 Additional Information:

- Subjects will be confined in a climate controlled environmental condition from their check-in till discharge from the study facility for each study period.

12.0 ETHICS:

12.1 Basic Principles:

This study will be conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (*Appendix J*). All subjects participating in the study will receive detailed information about the study, the procedures, the risks and the medication. All subjects will be required to sign ICF in the presence of the Principal Investigator/authorized trained person before participation in the study. The photocopy of signed ICF will be provided to all subjects. All signed ICF will be retained in the Trial Master File. The EC will be informed about the study dates. All adverse events will be reported to EC within a specified time.

12.2 Ethics Committee (EC):

The study will be conducted after review and obtaining written approval from the Ethics Committee (EC).

Following documents will be submitted to the EC for review and approval:

1. Study Protocol.
2. Subject Information sheet and Informed Consent Form for enrollment in BA/BE study (English and Vernacular language(s)).
3. Literature of the product under investigation.
4. Updated *Curriculum Vitae* of Investigators.
5. Investigator's Undertaking
6. Any other documents that the EC may need to fulfill its responsibilities.

Modifications, interfering with the subject's health interests and involving changes in the design of the study or its scientific significance require a new approval of the EC. Any modifications will be signed by investigator and sponsor. All such modifications or subsequent amendments to the protocol prior to commencement of the study will be implemented after written approval of the EC and the sponsor. During the course of the study, the Principal Investigator can do minor administrative or technical

modifications that do not interfere with the subject's interest. The same will be conveyed to the EC and the sponsor.

12.3 Informed Consent:

All the subjects participating in this study will receive complete details about the study, the procedures, the risks and the medication involved by verbal and written form in the Informed Consent Form in best understood language. Before they take voluntary participation, in the study, subjects will be asked to sign an Informed consent form to indicate their informed agreement to undergo the study. They will be given a copy of the form they have signed.

12.4 Subjects' Compensation:

The subjects will be adequately compensated as per the compensation policy for the subjects participating in BA/BE study. If any subject withdraws or discontinues from the study, compensation will be given as per the compensation policy of Accutest Research Laboratories (I) Pvt. Ltd.

13.0 ANALYTICAL METHOD:

13.1 Description:

A Validated LC-MS/MS method will be employed for the estimation of Levoflaxacin in plasma.

Samples from dropped-out or withdrawn subjects will not be assayed. Analysis of study drugs will be carried out from plasma samples of the subject who completes all the study periods or as per the discretion of Principal Investigator.

Whenever possible, all samples from each subject will be analyzed on the same standard curve. Quality control samples will be distributed through each batch of study samples assayed and will be analysed against calibration curve standards. Samples with drug concentrations greater than the upper limit of the validated range of the assay will be diluted with the appropriate drug-free biological fluid and reassayed.

Those which are below the lower limit of this range will be set to "BLQ" for all Pharmacokinetic and statistical calculations being below LOQ. The analysts will not have access to the randomization schedule. Any missing sample will be reported as "MSV".

If any concomitant medication occurred during the Clinical phase of the Study for those Subjects which are to be analyzed for pharmacokinetic evaluation, as per information received from Clinical department, selectivity of method shall be checked in the presence of those concomitant medications.

13.2 Validation Protocol:

Analytical method will be validated for the selectivity, linearity, accuracy and precision (reproducibility and repeatability), percent recovery and stability studies

(freeze-thaw stability, bench-top stability, auto-sampler stability, short-term and long-term stability of stock solution and internal standard, and long-term stability of analyte in plasma), carryover and matrix effect tests as per In-house SOP and current ANVISA guideline. The analytical method validation report, as well as the correspondent method description, will be provided by the time of study conclusion.

14.0 STATISTICAL TREATMENT:

Non-compartmental pharmacokinetic analysis will be performed on the observed plasma concentrations of Levoflaxacin using the statistical package SAS® 9.2 or higher version.

The analysis of Levoflaxacin will be considered for statistical analysis and for establishing bioequivalence.

All concentration values below the limit of quantification (BLQ) will be set to "zero" for the estimation of pharmacokinetic parameters.

14.1 Study design:

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover design.

14.1.1 Pharmacokinetic Parameters:

The following parameters will be calculated for each subject using the non-compartmental model by using statistical package SAS® 9.2 or higher version:

C_{max}	Maximum observed drug concentration in plasma.
AUC_{0-t}	Area Under The Concentration Versus Time Curve Calculated Using The Trapezoidal Rule Up To The Last Measurable Time Point
AUC_{0-inf}	AUC_{0-t} plus additional area extrapolated to infinity, calculated using the formula $AUC_{0-t} + C_t/K_{el}$, where C_t is the last measurable drug concentration and K_{el} is the elimination rate constant.
T_{max}	Time to observe maximum drug concentration in plasma. If the maximum value occurs at more than 1 time point, T_{max} is defined as the first time point with this value.
AUC_{0-t}/AUC_{0-inf}	Ratio of AUC_{0-t} and AUC_{0-inf}
AUC_{0-inf}/AUC_{0-t}	Ratio of AUC_{0-inf} and AUC_{0-t}
K_{el}	Apparent first – order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve, using the method of least square regression.
$t_{1/2}$	Terminal half-life as determined by quotient $0.693/K_{el}$

No value of K_{el}, $AUC_{0-inf,}$ AUC_{0-t}/AUC_{0-inf}, AUC_{0-inf}/AUC_{0-t} and $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

14.1.2 Missing samples:

Missing samples can be due to withdrawal of subject, not reported to facility for ambulatory sample and accidental spillage of samples as mentioned in current version of SOP for 'Missing samples'.

Missing sample values (MSV) or non-reportable values (NRV), of the plasma concentration data, will be represented as MSV and NRV in the plasma concentration tables and reasons for their missing will be documented. Any BLQ value occurring between two measurable concentration values will also be treated as missing sample (MS). These missing values will be treated as 'missing values' for Pharmacokinetic and statistical analysis. All the procedures will be performed in accordance with current version of SOP for 'Calculation of Pharmacokinetic Parameters'.

Data from the subjects with missing concentration values (missed blood draws, lost samples, samples unable to be quantified) may be used, if pharmacokinetic parameters can be estimated using the remaining data points. Otherwise, concentration data from these subjects will be excluded from the final analysis.

14.1.3 Statistical Analysis:

The data of subjects, completing all the study periods successfully or as per the discretion of Principal Investigator, will be subjected to statistical analysis.

Calculation of pharmacokinetic parameters and statistical analysis for establishing bioequivalence will be performed using the statistical package SAS® 9.2 or higher version.

PROC GLM procedure will be used for analysis of variance and the estimation of least square mean differences (Test-Reference) of the test and reference formulations on the log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} and on un-transformed pharmacokinetic parameter T_{max} for Levoflaxacin, and the corresponding standard errors of the differences will also be computed.

Based on these parameters, the 90% confidence intervals will be constructed for the least square mean differences of log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} for Levoflaxacin.

The antilog (or exponential) of the limits obtained from the log-transformed data will give the 90% confidence interval for the ratio of geometric means of test and reference formulations.

Difference of T_{max} between the products will be analyzed by nonparametric Wilcoxon test.

All the pharmacokinetic parameters will be reported for each subject-product combination and descriptive statistics (mean, median, standard deviation, coefficient

of variation, minimum and maximum) will be computed for each pharmacokinetic parameter for each product.

In graphical presentation individual and mean plasma concentration versus time curves will be performed using SAS® 9.2 or higher version for both untransformed and ln-transformed data.

14.1.4 Analysis of Variance (ANOVA):

ANOVA will be performed on log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} at the α level of 0.05. ANOVA will also be performed on un-transformed pharmacokinetic parameter T_{max} for Levoflaxacin.

The analysis of variance model will include sequences, subjects nested within sequence, period and treatment as factors. A separate ANOVA model will be used to analyze each of the parameters. The significance of the sequence effect will be tested using the subjects nested within the sequence as the error term at the α level of 0.10. All other main effects will be tested against the residual error (mean square error) from the ANOVA model as the error term.

Each analysis of variance will also include calculation of least-square means, adjusted differences between formulation means and the standard error associated with these differences.

14.1.5 90% Confidence Intervals and Ratio Analysis:

A 90% confidence interval for the ratio of the test product (T) and reference product (R) averages (least square means) will be calculated for Levoflaxacin by first calculating the 90% confidence interval for the differences in the averages (arithmetic means) of the log-transformed data and then taking the antilogs of the obtained confidence limits.

The comparison of interest is T vs R, so the ratios will be of the form: - T/R. Ratio of means will be calculated using the LSM for log-transformed C_{max}, AUC_{0-t} and AUC_{0-inf} Ratio of means will be expressed as a percentage of the LSM for the reference formulations. T_{max} will be analyzed as an individual difference (Test-Reference) building a 90% confidence interval, using a non-parametric test.

14.1.6 Power:

The power (i.e. probability of detecting a 20% difference relative to the reference treatment LSM at the 5% significance level using a t-test under the null hypothesis of zero difference) will be calculated for log transformed C_{max}, AUC_{0-t} and AUC_{0-inf}.

14.2 Sample Size Justification:[6]

```
The POWER Procedure
Equivalence Test for Mean Ratio

Fixed Scenario Elements
```

Distribution	Lognormal
Method	Exact
Lower Equivalence Bound	0.8
Upper Equivalence Bound	1.25
Alpha	0.05
Coefficient of Variation	0.17

Computed N Per Group

Index	Mean Ratio	Nominal Power	Actual Power	N Per Group
1	0.95	0.8	0.801	13
2	0.95	0.9	0.910	18

Considering actual Test / Reference ratio of approximately 95 % and intra-subject CV of approximately 17%, 18 subjects would yield a probability of 90% to meet bioequivalence criteria for a two way two period crossover study, under bioequivalence assumptions. However a larger sample size of 24 subjects was chosen in order to be conservative and to take care of likely dropouts and withdrawals.

14.3 Definition of Acceptance Interval for Pharmacokinetic Parameters to be tested in the Study:

The following acceptance interval for pharmacokinetic parameters for bioequivalence will be applied for Levoflaxacin:

The 90% confidence interval of geometric mean ratio of log transformed pharmacokinetic parameters C_{max} and AUC_{0-t} between test and reference products falls within the range of 80.00% to 125.00% for Levoflaxacin.

Summary statistics, ANOVA, 90% Confidence Intervals, Ratio analyses will be calculated using SAS® 9.2 or higher version.

14.4 Treatment of Time Point Deviation:

Time deviation for any subject at any time point will be taken care, while calculation of pharmacokinetic parameters.

Pharmacokinetic and Statistical analysis will be performed using scheduled time and actual time using statistical package SAS® 9.2 or higher version. However, the analysis using scheduled time point will be considered as final.

15.0 PROTOCOL DEVIATION ACCEPTANCE:

Any deviation from the procedures given in the protocol will be documented in the Protocol deviation form and accepted as per the discretion of the Principal Investigator.

15.1 Changes in the Protocol:

Any change or addition to this protocol after its approval, but prior to the initiation of the study, will require a written protocol amendment, which must be approved by Principal Investigator, sponsor and the EC before implementation. Any deviation from the approved protocol, during the conduct of the study will be documented as a 'Protocol Deviations'.

16.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION:

A monitor or auditor for the sponsor may visit the study facilities at any time in order to maintain current knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and the progress of the study. The Investigator(s)/institution(s) provide direct access to source data/documents for study related procedures, audits, EC review, and regulatory inspection. Prior to the start of the study, the Principal Investigator/authorized trained person will be contacted and informed of any impending visits and the frequency of such visits. At each visit the Principal Investigator will assist the study monitor in terms of reviewing and verifying those records associated with the study.

17.0 QUALITY CONTROL AND QUALITY ASSURANCE:

The Quality Control and Quality Assurance department will confirm that the study is conducted in adherence to the protocol and SOPs for each activity and bioanalysis is performed according to the principles of GLP.

In process quality checks and review procedures carried out by the Quality Control and Quality Assurance department. They will ensure that the activities and the documentation of the data for clinical, bioanalytical and statistical stages are done as per the protocol and / or respective SOP, ICH GCP Guidelines, applicable regulatory requirements. Deviation from the protocol or SOP observed during the quality checks/review will be verified.

18.0 DATA HANDLING AND RECORD KEEPING:

The CRF will be identified by the volunteer registration number, subject number and the study code. Data collected on CRFs during the study will be documented in accordance with current version of SOP for "Recording of Data/Reporting of Results and correcting mistake in documents."

Any error in recording will be struck out with a single line; so as to leave the original data legible, and the new data will be inserted legibly alongside. The correction will be dated and signed. All information on CRFs will be traceable to source documents, which will be archived in Accutest Research Laboratories (I) Pvt. Ltd. The source documents will contain all demographic and medical information, including laboratory data, ECGs, chest X-ray (if done) etc., and also a copy of the signed informed consent which will indicate the study code and title of the study. The completed CRFs will be checked by the Principal Investigator/authorized trained person for completeness, accuracy and legibility, for conformance to the source documents.

The documents to be archived will include all essential documents which individually and collectively permit evaluation of the conduct of the study and the quality of data produced in the Trial master file. These documents will be archived after the completion or discontinuation of the study for a period specified in the master service agreement. Prior to destruction of study documents, the sponsor will be notified and consent will be obtained in writing.

19.0 FINANCE AND INSURANCE:

The subjects will be insured with the Oriental Insurance Company for any compensation in case of study related injury/death according to existing insurance policy.

20.0 REPORT:

Final report containing the clinical, analytical and statistical sections will be as per ANVISA guidelines unless specified. The Study report will also contain the supporting tables for the various pharmacokinetic parameters, adverse events and safety conclusion. It will also include 100% (Photocopies) case record forms of the subjects and 20% (Photocopies) subject chromatograms serially.

21.0 PUBLICATION POLICY:

Publication of the results is at the sole discretion of the study sponsor.

22.0 REFERENCES:

1. ICH Harmonized Tripartite Guideline for GCP 1996.

2. Manual for Good Bioavailability and Bioequivalence Practices.Volume I, Brazillian Sanitary Survellience Agency.Brasilia 2002.
Resolução - RE nº 894, de 29 de maio de 2003.
Resolução - RE nº 895, de 29 de maio de 2003.
Resolução - RE nº 898, de 29 de maio de 2003.
Resolução - RE nº 1170, de 19 de abril de 2006.
Resolução Da Diretoria Colegiada – RDC Nº 27, DE 17 DE MAIO DE 2012.
Resolução Da Diretoria Colegiada - RDC Nº 56, DE 8 DE OUTUBRO DE 2014.
Nota técnica nº 04 de 2015

3. Prescribing information of LEVOFLOXACIN tablets, for oral use; Initial U.S. Appro val: 1996; Revised: 11/2016.

4. Summary of Product Characteristics of Levofloxacin 500 mg Film-coated Tablets; Updated 15/10/2014
https://www.medicines.org.uk/emc/medicine/25986

5. http://www.medicinanet.com.br/bula/3056/levaquin.htm

6. NO:LV01006, Bioequivalence study of two levofloxacin 500 mg tablet formulations from eurofarma laboratorios Ltda. versus Aventis Pharma S.A. in healthy volunteers; ESTUDO DE BIOEQUIVALENCIA DE DUAS FORMULAC(cedil)O(tilde)ES DE LEVOFLOXACINA (COMPRIMIDOS DE 500 MG) DE EUROFARMA LABORATORIOS LTDA. VERSUS AVENTIS PHARMA S.A. EM VOLUNTARIOS SADIOS

APPENDIX A
FORMAT OF IMP RECONCILIATION AND RETENTION RECORD FORM

SOP No. CLI/018/00

	IMP RECONCILIATION AND RETENTION RECORD		
accutest	FORM NO.:CLI/018/00/FM03	Accutest Research Laboratories (I) Pvt. Ltd.	Page 1 of 1

Study Code(s):	Type of IMP:	Randomization code:	Date:
IMP DETAILS			
Brand Name/ Name of Product (with dosage form & strength):			Batch#/ Lot#:
Mfg. By / Mkt. By / Dist. By / Developed By / PL holder/ Mfg.for /MA holder/:			Mfg. Date: Expiry / Retest Date:
Unit(s) of IMP dispensed for every subject:		Light condition: Normal/Sodium vapour	Date of completion of study (last period dosing date):

RECONCILATION AND RETENTION DETAILS

SOLID / SEMI SOLID DOSAGE FORM IMP	
Total quantity received for dispensing (A):	
Total quantity dispensed for subject in complete study (B):	
Extra quantity dispensed in complete study (C):	
Un dosed dispensed quantity restored details (Sub. No. and/ or extra unit) in complete study (D):	
Total quantity restored which used for training purpose(If applicable) (E):	
Total quantity used for appearance check (F):	
Total quantity found damaged i.e. .broken, cracked (G):	
Total retention quantity = (A-B-C):	
Total balance Quantity = [(A-B-C) + (D+E+F+G)]:	

POWDER FOR RECONSTITUTION/LIQUID DOSAGE FORM IMP	
Total quantity received for dispensing (A):	
Total quantity of IMP reconstituted (received for dispensing) for dispensing in complete study (B):	
Total quantity of reconstituted IMP dispensed for subject in complete study (received for dispensing) (C):	
Total quantity of reconstituted IMP dispensed (received for dispensing) as EXTRA in complete study (D):	
Total quantity of reconstituted (received for dispensing) IMP remained = (B-C-D):	
Total quantity of un reconstituted IMP remained (received for dispensing) = (A-B):	
Total quantity used for appearance check (E):	
Total balance Quantity =	
Total retention quantity =	

POWDER DOSAGE FORM IMP	
Total quantity received for dispensing (A):	
Total quantity dispensed for subject in complete study (B):	
Extra quantitydispensed in complete study (C):	
Un dosed dispensed quantity restored details (Sub. No. and/ or extra unit) in complete study (D):	
Total quantity restored which used for training purpose(If applicable) (E):	
Total quantity used for appearance check (F):	
Total retention quantity = (A-B-C):	
Total balance Quantity = [(A-B-C) +(D+E+F)]:	

Retention Period:	**Expiry date of retention period:**
Comment:	
Reconciled and retained by:	

REFERENCE COPY

APPENDIX B
FORMAT OF IMP ACCEPTANCE RECORD FORM

SOP No. CLI/018/00

	IMP ACCEPTANCE RECORD		
accutest	FORM NO.:CLI/018/00/FM02	Accutest Research Laboratories (I) Pvt. Ltd.	Page 1 of 1

Study Code(s):		**IMP acceptance Date:**	
Note: Encircle wherever applicable			
Sponsor:			
Light condition: Normal/Sodium vapour		Packing condition: Sealed / Unsealed	
Type of Investigational Product: Test /Reference			
Brand Name/ Name of Product (with dosage form & strength):			
Generic Name of Product:			
Label Claim:			
Dosage Form: Tab/Cap/syrup/suspension/powder/Liquid/granules/Gel/ other		Strength:	
Batch / Lot No.:		Mfg. Date:	
Expiry/Retest Date:		Storage condition:	
Mfg. By / Mkt. By / Dist. By / Developed By / PL holder//Mfg.for /MA holder :			
Discrepancies noted during IMP receipt resolved: (Yes/No). If not confirmation for IMP acceptance obtained from PI: (Yes/No/NA).			
Quantity Details	**As per IMP receipt**	**As per counted**	**Remarks**
Total packs received			
Units of IMP / pack			
Total units of IMP			
Container s/pack selected for IMP description :			
Primary container (blister, strip, and bottle) opened for IMP description: (Yes/No).			
Comments:			
Recorded by:		Verified by:	

REFERENCE COPY

APPENDIX C

FORMAT OF IMP RECEIPT RECORD

SOP No. CLI/018/00

	IMP RECEIPT RECORD		
accutest	FORM NO.:CLI/018/00/FM01	Accutest Research Laboratories (I) Pvt. Ltd.	Page 1 of 1

Study Code(s):		**IMP Receipt Date:**	
Note: Encircle wherever applicable			
Sponsor:		Light condition: Normal/Sodium vapour	
Mode of Receipt: Courier/Hand Delivery		Packing condition: Sealed / Unsealed	
Type of Investigational Product: Test /Reference			
Brand Name/ Name of Product (with dosage form & strength):			
Generic Name of Product:			
Label Claim:			
Dosage Form: Tab/Cap/syrup/suspension/powder/Liquid/granules/Gel/ other		Strength:	
Batch / Lot No.:		Mfg. Date:	
Expiry/Retest Date:		Storage condition:	
Mfg. By / Mkt. By / Dist. By / Developed By / PL holder//Mfg.for /MA holder :			
Regulatory of study submission :		Quantity required for study(s) : Sufficient/Insufficient Quantity required for Retention:	
Description of pack:			

Quantity Details	As per sponsor communications	Remarks
Total packs received		
Units of IMP / pack		
Total units of IMP		

COA details				
Receipt date	**Information provided in**			
Check	**COA**		**Label**	
	YES	**NO**	**YES**	**NO**
Name of IMP				
Batch# or Lot#				
Expiry date or retest date				
Mfg. date				
Mfg. By/ Mkt. By/ Dist. By/ Developed By/ PL holder /Mfg.for /MA holder				
Storage conditions				
Description				
Dissolution			Not Applicable	Not Applicable
Assay		Not Applicable	Not Applicable	Not Applicable
Total units of IMP / pack				

Any other documents received:		
Data logger accompanied: Yes/No	Print of data logger obtained: Yes/No	Temp. exertion acceptable: Yes/No
Allotted serially pharmacy ID no.:	Quarantine instrument ID. No.:	
Comments:		
Recorded by:		

REFERENCE COPY

APPENDIX D
FORMAT OF ADVERSE/MEDICAL (OHE) EVENT RECORD

SOP No. CLI/022/00/N

accutest	**ADVERSE/MEDICAL (OHE) EVENT FORM**		
FORM No. CLI/022/00/N/FM01	**Accutest Research Laboratories (I) Pvt. Ltd.**	**Page 1 of 1**	

Type of event	□ Adverse Event	□ Medical (OHE)		
Subject No.:	**Study code:**	**Period:**	□ **Pre Dose** □ **Post Dose**	**Last Dose** Date: Time: NA □
Onset time:	**Date:**	**Serious**	**Report Method**	**Severity**
Symptoms/Sign:		□ Yes □ No	□ Spontaneous □ Observed	□ Mild □ Moderate □ Severe
Reporting time:			**Date:**	
Comment:				
Resolution Time :		**Date:**	**Recorded By:**	

Medicines used to treat event:

Drug name (Brand name)	Dosage Form	Strength	Frequency	Start date (dd/mm/yy)	End Date (dd/mm/yy)	Recorded By
Concomitant medication detail:						

To be filled by Principal investigator/ Authorized trained person

Seriousness	**Relationship**	**Action**	**Outcome**
□ Serious □ Not Serious **Likelihood** □ Expected □ Unexpected □ NA	□ Definite □ Probable □ Possible □ Unlikely □ NA	□ Assurance given □ Under observation □ Required Non pharmacological treatment □ Treatment □ Discontinued from the study □ None	□ Resolved □ Ongoing □ Unchanged □ Not known
Reviewed by:			**Date:**

REFERENCE COPY

APPENDIX E
FORMAT OF SERIOUS ADVERSE EVENT REPORT

SOP NO. CLI/023/00/N

	SERIOUS ADVERSE EVENT REPORTING FORM		
accutest	FORM NO.: CLI/023/00/N/FM01	Accutest Research Laboratories (I) Pvt. Ltd.	Page 1 of 2

A. Type of report: ☐ Initial ☐ Follow-up

B. Study Information

Study code		Investigational product	
Type of study	☐ Open ☐ Blinded	If blinded, code opened, please record details in section F	☐ Yes ☐ No

C. Subject Information:

Subject initials/ Registration No			Date of birth/Age		
Sex	☐ Male ☐ Female	Weight	kg	Height	cms

D. Details of Serious Adverse event:

Serious Adverse Event Symptom/Sign: _____

Study Period	☐ P-I ☐ P-II or _____	Report method	☐ Spontaneous ☐ Observed
Onset of Event	Time: _____ Date:_____		
IP administration	☐ Pre Dose ☐ Post-dose	Last dose	
Severity of Event	☐ Mild ☐ Moderate ☐ Severe	Serious	☐ Yes ☐ No
Reporting time	Time (Hrs): _____ Date: _____		

E. Type of Serious Adverse Event:

☐ results in death	☐ life-threatening	☐ congenital anomaly/birth defect
☐ inpatient hospitalization or prolongation of existing hospitalization		
☐ persistent or significant disability/incapacity		

Additional Comments: _____

_____

_____

_____

_____

_____

_____

SAE Resolution time (Hrs) : _____ Date: _____ Total Duration of SAE: _____

Recorded By: _____ **Date:** _____

REFERENCE COPY

SOP NO. CLI/023/00/N

	SERIOUS ADVERSE EVENT REPORTING FORM		
accutest	FORM NO.: CLI/023/00/N/FM01	Accutest Research Laboratories (I) Pvt. Ltd.	Page 2 of 2

F. Investigation Product Treatment details:

IP start date and time	Time (Hrs): _____	Date: _____
Treatment type	☐ Test	☐ Reference
Route of administration		
Brand name		
Mfg date		
Expiry date		
Batch/Lot no.		

G. Concomitant Medications/Treatment details:

Drug name/Brand name	Dosage Form	Strength	Frequency	Start Date	End Date	Recorded by

To be filled by Principal investigator/Authorized trained person

H. Serious Adverse Event Outcome:

Relationship:	Action Taken	Likelihood	Outcome
☐ Definite ☐ Probable ☐ Possible ☐ Unlikely	☐ None ☐ Under observation ☐ Under treatment ☐ Study drug discontinued	☐ Expected ☐ Un-expected	☐ Resolved with Sequel ☐ Resolved without Sequel ☐ On-going ☐ Unknown

I. Reviewed by: _____ **Date :** _____
Principal Investigator/Authorized trained person

REFERENCE COPY

APPENDIX F
RANDOMIZATION SCHEDULE

Will be incorporated at protocol finalization stage

APPENDIX G
MEALS FOR EACH STUDY PERIOD

Food-item	Amount	Ingredients		CHO (g)	Protein (g)	Fat (g)	Energy (Kcal)
DINNER ON CHECK-IN DAY (WILL BE GIVEN IN SUCH A WAY TO MAINTAIN THE 10.00 HRS PRE DOSE FASTING)							
01) Chapati	150g	Wheat Flour	100g	69.4	12.1	1.7	341
		Oil	5g	--	--	5	45
02) Onion-Potato Veg	120g	Potato	50g	11.3	0.8	0.05	49
		Onion	50g	5.6	0.6	0.05	25
		Tomato, green chili and garlic to taste only					
		Oil	10g	--	--	10	90
03) Cabbage Capsicum Veg	100g	Cabbage	80g	3.7	1.44	0.08	22
		Capsicum	30g	1.3	0.39	0.09	7
		Tomato	20g	0.7	0.18	0.04	4
		Garlic for taste only.					
		Oil	10g	--	--	10	90
04) Plain Rice	100g	Rice	30g	23.5	2.04	0.15	104
05) Dal Gujarati	150g	Tur Dal	30g	17.3	6.69	0.51	101
		Tomato	5 g	0.2	0.05	0.01	1
		Jaggery to taste only					
		Oil	7g	--	--	7	63
Total				**133.0**	**24.29**	**34.68**	**942**

Abbreviations:- CHO: carbohydrates, g: grams , ml: milliliter, Kcal: Kilo calories , HRS: Hours.

Nutritive Value of the Check In Day's Menu				
Description	**CHO (g)**	**Protein (g)**	**Fat (g)**	**Energy(Kcal)**
DINNER	**133.0**	**24.29**	**34.68**	**942**
TOTAL	**133.0**	**24.29**	**34.68**	**942**
KCAL	**532**	**97**	**312**	**NA**
PERCENT	**56.52**	**10.32**	**33.16**	**NA**

MEALS FOR DOSING DAY OF EACH STUDY PERIOD

Food-item	Amount	Ingredients		CHO (g)	Protein (g)	Fat (g)	Energy (Kcal)
LUNCH 04.00 HRS AFTER DOSING							
01) Chapati	150g	Wheat Flour	100g	69.4	12.10	1.70	341
		Oil	5g	--	--	5	45
02) Mixed Vegetable	120g	Potato	20g	4.5	0.32	0.02	19
		Green peas	20g	3.2	1.44	0.02	19
		Tomato	10g	0.4	0.09	0.02	2
		Capsicum	20g	0.5	0.30	0.06	3
		French bean	20g	1.0	0.34	0.02	5
		Oil	8g	--	--	8.00	72
		Coriander leaves chopped, garlic paste to taste only					
03) Chhole	100g	Kabuli chana	30g	18.3	5.13	1.59	108
		Onion	20g	2.2	0.24	0.02	10
		Tomato	20g	0.7	0.18	0.04	4
		Garlic, Ginger, Coconut and Coriander leaves for flavor only					
		Oil	10g	--	--	10	90
04) Jeera Rice	100g	Rice	30g	23.5	2	0.20	104
		Cumin seeds for taste purpose					
		Ghee for Sautee.					
05) Dal Fry	150g	Tur dal	30g	17.3	6.70	0.50	101
		Onion	20g	2.2	0.30	0.0	10
		Tomato	20g	0.7	0.20	0.0	4
		Oil	5g	--	--	5	45
		Garlic & Ginger for flavor only					
06) Buttermilk	200ml	Curd	80g	2.4	2.50	3.20	48
Total				**146.3**	**31.84**	**35.39**	**1030**

SNACKS 08.00 HRS AFTER DOSING							
01)patra	200g	Besan	100g	59.8	20.8	5.6	372
		Colocasia leaves	50g	3.4	1.95	0.75	28
		Oil	10g	--	--	10	90
Total				**63.2**	**22.75**	**16.35**	**490**

DINNER 12.00 HRS AFTER DOSING							
01) Chapati	150g	Wheat Flour	100g	69.4	12.10	1.70	341
		Oil	5g	--	--	5	45
02)Aloo methi	100g	Aloo	50g	11.3	0.8	0.05	49
		Fenugreek leaves	30g	1.8	1.32	0.27	15
		Onion	20g	2.2	0.24	0.02	10
		Oil	8g	--	--	8	72
		Coriander leaves chopped, garlic paste to taste only					
03) Fried Khichadi	150g	Rice	30g	23.5	2.04	0.15	104
		Tur dal	10g	5.8	2.23	0.17	34
		Tomato, onion, garlic, and green chopped chili for taste only					
		Oil	5g	-	-	5	45
04) Gujarati Kadhi	200g	Curd	50g	1.5	1.55	2	30
		Sugar	10g	9.9	0.01	--	40

		Oil	4g	--	--	4	36
		Besan	20g	12.0	4.16	1.12	74
		for taste purpose					
05) Dal na Khaman	200g	Channa dal	50g	29.9	10.4	2.8	186
		Curd	10g	0.3	0.31	0.4	6
		Oil	5g	-	-	5	45
Total				**167.6**	**35.16**	**35.68**	**1132**

Abbreviations:- CHO: carbohydrates, g: grams , ml: milliliter, Kcal: Kilo calories , HRS: Hours.

Nutritive Value of the Dosing Day's Menu				
Description	**CHO (g)**	**Protein (g)**	**Fat (g)**	**Energy(Kcal)**
LUNCH	**146.3**	**31.84**	**35.39**	**1030**
SNACKS	**63.2**	**22.75**	**16.35**	**490**
DINNER	**167.6**	**35.16**	**35.68**	**1132**
TOTAL	**377.1**	**89.75**	**87.42**	**2652**
KCAL	**1508**	**359**	**787**	**NA**
PERCENT	**56.83**	**13.53**	**29.64**	**NA**

Please note: Food items mentioned in the menu plan may be altered, subject to availability and within limitations of the 'Food Exchange List' being currently followed for 'menu planning' at Accutest Research Laboratories (I) Pvt. Ltd. Alterations are as per the solitary discretion of the Dietitian and consent of the Principal Investigator present at Accutest Research Laboratories (I) Pvt. Ltd.

Exchange-list Resources:

1. Nutritive value of Indian Foods by C. Gopalan *et al*, 2002.

APPENDIX H
CLINICAL LABORATORY TESTS

Test Description	Reference range[#]	
Haemogram	**Normal Value**	**Clinically Accepted Value**
Hemoglobin	13.5-18.0 g/dL- Male 12.5-16.0 g/dL- Female	≥ 13.0 g/dL- Male ≥ 11.0 g/dL- Female
Erythrocyte Count	4.70-6.00 x 10^6/ µl - Male 4.20-5.40 x 10^6/ µl - Female	**To be correlate with hemoglobin value**.
PCV (Packed Cell Volume, Hematocrit)	42.0-52.0 %- Male 37.0-47.0 %- Female	
MCV (Mean Corpuscular Volume)	78.0-100.0 fL	
MCH (Mean Corpuscular Hemoglobin)	27.0-31.0 pg	
MCHC (Mean Corpuscular Hemoglobin-concentration)	32.0-36.0 g/dL	
WBC Count	4.0-10.50 x 10^3/ µl	3.6-11.50 x 10^3/ µl
Differential Count:		
Neutrophils	50.0-80.0 %	**To be correlate with WBC Count.**
Eosinophils	0.0-5.0 %	
Basophils	0.0 – 2.0 %	
Lymphocytes	25.0-50.0 %	
Monocytes	2.0- 10.0 %	
Platelets:		
Platelet Count	150 - 450 x 10^3/ µl	135 - 495 x 10^3/ µl
RBC Morphology	Normal/Abnormal	Clinically correlation
WBC Morphology	Normal/Abnormal	Clinically correlation
	Biochemistry Tests	
Blood urea	16.6 – 48.5 mg/dL	≤ 53.3 mg/dL
Blood Glucose (Random)	70-130 mg/dL	63-143mg/dL
Blood Urea Nitrogen	6.0 – 20.0 mg/dL	0.0 – 22.0 mg/dL
Serum Creatinine	0.70 – 1.20 mg/dL- Male 0.50 – 0.90 mg/dL- Female	0.00 – 1.30 mg/dL - Male 0.00 – 1.00 mg/dL- Female
Serum Bilirubin;		
Serum Bilirubin – Total	0.10-1.20 mg/dL	0.10-1.47 mg/dL
Serum Bilirubin – Direct	< 0.30 mg/dL	Clinically correlation
Serum Bilirubin – Indirect	0.10 – 1.00 mg/dL	Clinically correlation
SGOT	Up to 40 U/L- Male Up to 32 U/L- Female	0-70 U/L- Male 0-70 U/L- Female
SGPT	Up to 41 U/L- Male Up to 33 U/L- Female	0-72 U/L- Male 0-72 U/L- Female
S. Alkaline Phosphatase	40-129 U/L- Male 35-104 U/L- Female	32-155 U/L- Male 28-125 U/L- Female
Total Cholesterol	Desirable : < 200 Borderline High : 200-239 High : ≥ 240	≤ 239 mg/dL
Triglyceride	Desirable : < 150 Borderline High : 150-199 High : 200-499 Very High : ≥ 500	≤ 199 mg/dL
Serum Uric Acid	3.40 – 7.00 mg/dL - Male 2.40 – 5.70 mg/dL - Female	≤ 7.7 mg/dL - Male ≤ 6.2mg/dL - Female

Total Protein	6.60 -8.70 g/dL	6.0-9.50 g/dL
Albumin	3.97 – 4.95 g/dL	3.6-5.4 g/dL
Serological Tests		
HIV test – ELISA method	Non Reactive	Non Reactive
Anti HBc IgM test – ELISA method	Non Reactive	Non Reactive
HBsAg test – ELISA method	Negative	Negative
HCV test – ELISA method	Non Reactive	Non Reactive
Serum (β) Beta- hCG Test		
Serum (β) Beta- hCG (Human Chorionic Gonadotropin) level	Absent, Non Pregnant level: Less than 10 mIU/ml- Female	Absent
Urinalysis		
Physical Examination:		
Colour		
Reaction (Ph)	5.0 to 9.0	Clinically correlation
Specific gravity	1.000-1.030	Clinically correlation
Transparency		
Volume		
Chemical Examination:		
Protein	Negative	Trace (+)
Glucose	Negative	Trace (+)
Ketone	Negative	Trace (+)
Blood	Negative	Trace (+)
Bilirubin	Negative	Trace (+)
Urobilinogen	0.2-1.0 mg/dL	0.2-1.0 mg/dL
Leukocytes	Negative	Negative
Nitrite	Negative	Negative
Microscopic Examination		
Leucocytes	0-10/hpf	0-10/hpf
Red Blood Cells	0-10/hpf	0-10/hpf
Epithelial Cells	Absent / Present	0-10/hpf
Casts	Nil	(+)
Crystals	Nil	(+)
Bacteria	Nil	Nil
Other Findings		
Comment		
Urine Examination For Drugs Abuse		
Benzodiazepines	Negative=Below300 ng/mL	Negative
Marijuana	Negative= Below 50 ng/mL	Negative
Barbiturates	Negative=Below300 ng/mL	Negative
Cocaine	Negative=Below300 ng/mL	Negative
Morphine	Negative=Below300 ng/mL	Negative
Amphetamine	Negative=Below1000ng/mL	Negative

#Applicable, as per the study population

*Urine microscopic will be done only if reagent strip found positive for Protein, Leukocytes and Blood.

Reference:

1. Todd. Sanford. Davidson. Clinical Diagnosis and Management by Laboratory Methods. 20th Edition. W.B. Saunders Company, Philadelphia, U.S.A.
2. According to manufacturer's kit reference.

3. ABX Pentra XL 80 User manual.
4. M.sibille, D.Vital Durand et al "Laboratory screening method for selection of healthy volunteer." Eur J Clin Pharmacol. (1990) 39 475-479.
5. Tester F Ashavaid, Seema P Todour et al "Health status of Indian population" JAPI Vol. 52 MAY 2004, 363-369.
6. American Diabetes Association (ADA) 2013 Guideline.
7. Interpretation of diagnostics test, Jacques Wallach, MD, Seventh edition.
8. Internal Laboratory reference.

APPENDIX I
SCHEDULE OF STUDY EVENTS

Procedure	Screening (within 21 days prior to dosing of period-I)	Check-in Day for each study period	During confinement for each study period	Ambulatory sample visit	Post Study OR Discontinuation of Subject
Issue of Subject information sheet and informed consent form	√				
Breath Alcohol test	√	√		√	
Weight	√				
Height	√				
Vital Signs measurement	√	√	√		√
Well being assessment			√	√	√
Physical examination	√	√	√		√
12 Lead ECG	√				√
Serology	√				
Haemogram	√				√
Biochemistry	√				√
Urinalysis	√				√
Serum pregnancy test for female		√			√
Urine examination for drugs of abuse		√			
Admit to Clinical Research Center		√			
Meals		√	√		
Study medication administration			√		
PK Samples			√	√	

Note: Additionally, any other assessment including laboratory test(s) will be done if judged necessary by the Principal Investigator (PI) or medical officer at any time during the course of study.

APPENDIX J
WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven

interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.
Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.
All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.
The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.
In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher,

the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the

physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.
Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX K
FORMAT OF IMP DISPENSING RECORD FORM

SOP NO. CLI/017/00/N

	IMP DISPENSING RECORD		
accutest	FORM No. CLI/017/00/N/FM01	Accutest Research Laboratories (I) Pvt. Ltd.	Page 1 of 2

Study Code:	Type of IMP:	Randomization code:	Light Condition: Sodium/Normal
INVESTIGATIONAL MEDICINAL PRODUCT DETAILS:			
Name of IMP(with dosage form & strength)/ Brand Name:			Batch#/ Lot#:
Mfg. By / Mkt. By/ Dist. By/ Developed By / PL holder/ Mfg.for/ MA holder/ Reg. By/Sup. By/Imp. By:			Mfg. Date:
			Expiry / Retest Date:
Unit(s) of IMP to be dispensed for every subject:			
*Method of Reconstitution:			

Dispensing Details	Period			
Labeled Dispensing containers separated treatment-wise:	Yes / No	Yes / No	Yes / No	Yes / No
Time of separation (hours):				
Date				
Total quantity of IMP available for dispensing				
IMP Container /pack no. used for dispensing				
IMP Quantity per Container /pack				
Total IMP quantity removed from Container /pack				
*Quantity of reconstituting solvent added per Container /pack				
*Quantity of reconstituted IMP per Container /pack				
Recorded by				
Checked by				

* indicates wherever applicable

REFERENCE COPY

SOP NO. CLI/017/00/N

	IMP DISPENSING RECORD		
accutest	FORM No. CLI/017/00/N/FM01	Accutest Research Laboratories (I) Pvt. Ltd.	Page 2 of 2

Study Code:	Type of IMP:	Randomization code:

DISPENSING DETAILS

Details	Period			
	Date:	Date:	Date:	Date:
Dispensing Start Time(Hours):				
IMP dispensed for Subject Nos.				
Dispensing End Time (Hours)				
Total No. of Units Dispensed for subjects:				
Extra Unit Dispensed:				
Total Unit Dispensed:				
Quantity of IMP remained and Container /pack no. (used for dispensing):				
Dispensed by:				
Checked by:				
Un dosed dispensed quantity returned details (sub. No. and/ or extra unit)				
Un dosed dispensed quantity disposed details (sub. No. and/ or extra unit)				
Returned by/ Disposed By:				

REFERENCE COPY

APPENDIX L
COMPENSATION POLICY

Head	Rupees	Multiplier (Male)	Multiplier (Female)	Total amount (₹)(male)	Total amount (₹)(female)
Screening visit	300*	-	-	-	-
Per mL blood loss	18	238	242	4284	4356
Night stay	225	4		900	900
Day stay	150	4		600	600
Ambulatory visit (each)	200	2		400	400
Additional/follow-up visit (if required)	200	0		0	0
Others (if any like multiple dosing, multiple drug intake, pharmacodynamics of the drug(s) etc.)	0	0		0	0
Total amount				6184	6256
Compensation after rounding off the total amount to next figure in the multiple of ₹ 10/-				6190	6260

* ₹ 300 will be given at the time of screening.

Explanation of Key Heads	
Compensation Head	**Comments**
Blood loss	This will take into account the total blood loss incurred due to all study related activities including the incidental blood loss.
Night stay	The night time when the subject is housed/present in the clinical centre for study related activities. The night time will be considered as a period of approximately 12.00 hours (example: from 08 pm to 08 am). The subject should be present in the centre for at least 2/3 rd of the required duration in the centre. The night stay on the enrollment day of each period and the post dosing night stay(s) will be taken into account for the compensation calculation.
Day stay	The day time period when the subject is housed/present in the clinical centre for study related activities. The day time will be considered as a period of approximately 12.00 hours (example: from 08 am to 08 pm). The subject should be present in the centre for at least 2/3 rd of the required duration in the centre. The enrollment day, dosing day and subsequent days till discharge of the subject in each period will be taken into account for the compensation calculation.

Incidental blood loss	Blood withdrawal beyond the specified blood loss in the study will be considered as an incidental. If the incidental blood loss is due to blood withdrawal to assess the eligibility of the subject during screening or due to repeat pharmacokinetic withdrawals, the subject will be compensated additionally for it. However, if the blood withdrawal is due to safety assessment of the subject after his/her admission in the study, he will not be compensated for it.

Terms and Conditions for Compensation:

Sr. No.	Terms and Conditions	Compensation
1.	Subject withdrawal due to adverse event or on medical ground by Principal Investigator/ Designee.	Full compensation.
2.	Subject withdraws voluntarily after his/her enrollment in the study, dropped out due to personal reason	Proportionate compensation till the time of withdrawal/drop-out.
3.	Subject withdrawal due to misbehavior or protocol violation.	A deduction of up to fifteen percent of the proportionate compensation till the time of withdrawal/drop-out may be done at the discretion of Principal Investigator.
4.	Subject does not turn up for the ambulatory sample	Deduct amount for the number of missing ambulatory samples and visits.
5.	Termination/ Suspension of Study	Full compensation.

APPENDIX M

Subject Information Sheet and Informed Consent Form

Will be incorporated after finalization of protocol