INFORMED CONSENT FORM

PROTOCOL NO: Pro/0408/006 ICF VERSION: 01 SERIAL NO.
Protocol Version: 01 SUBJECT NO:
SUBJECT ID:
DATE:

THIS IS A RESEARCH STUDY
THE FOLLOWING INFORMATION IS IMPORTANT FOR YOU TO READ
CAREFULLY AND ASK QUESTIONS IF ANY INFORMATION IS UNECLEAR.

GENERIC TEST DRUG : Enalapril Maleate sustained release 20 mg
FAMILIAR TRADE NAME : Enalapril Maleate sustained release 20 mg tablet
REFERENCE DRUG : Enalapril Maleate 10 mg
FAMILIAR TRADE NAME : Envas 10 mg tablet

1. DRUG DESCRIPTION

WHAT IS THIS DRUGS YOU WILL BE TAKING

Enalapril is given by mouth and is indicated for the treatment of Hypertension, Heart Failure, and Asymptomatic Left Ventricular Dysfunction.

The recommended initial dose in patients not on diuretics is 5 mg once a day. Dosage should be adjusted according to blood pressure response. The usual dosage range is 10 to 40 mg per day administered in a single dose or two divided doses.

Dosage Form: Tablet
Therapeutic Class: Antihypertensive

2. STUDY OBJECTIVE

1. To study comparative pharmacokinetic profile of immediate release Enalapril Maleate tablet 20mg with sustained release Enalapril Maleate Tablet 20mg
2. To estimate the duration of time of the plasma concentration of enalapril and enalaprilat above minimum effective concentration (for Enalaprilate: 10ng/ml to 50ng/ml) by single dose of Enalapril Maleate Sustained Release Tablet 20 mg
3. To study the food effect in Enalapril Maleate Sustained Release Tablet 20mg
4. To study the plasma levels of enalapril and enalaprilat in sustained release formulation and immediate release formulation during early morning hours (between 2:00 AM to 8:00AM)

5. To study the IVIVC of Enalapril Maleate Sustained Release Tablets 20mg

Secondary objective will be to monitor the safety of subjects.

3. STUDY DESCRIPTION

The duration of this study is 03 days. After you undergo a screening process and are found to be eligible as per the study requirement, you will be enrolled into the study.

In this study you will receive one of the test or reference preparation. The order in which you will receive each of the formulation will be randomly determined.

Test Product: Enalapril Maleate sustained release 20 mg
(Containing Enalapril Maleate 20 mg)
Cadila Pharmaceuticals Ltd. Ahmedabad

Reference Product: Envas 10 mg tablet
(Containing Enalapril Maleate 10 mg)
Cadila Pharmaceuticals Ltd. Ahmedabad

4. SCREENING

The following tests will be conducted to assess your eligibility to participate in the study:
- Physical examination, ECG
- Urine analysis
- Urine examination
- Chest X-Ray
- Urine drug abuse test

5. ADMISSIONS AND STAY

Subjects will be housed in the Clinical Pharmacology and Pharmacokinetic Unit (CPPU) from at least 11 hrs before drug administration to 24 hrs after drug administration. Subjects will return to CPPU for ambulatory sampling at 36.0 and 48.0 hrs post-dose with a variation of ±60 minutes being accepted.
6. STUDY REQUIREMENTS

You should abstain from alcohol and the intake of any medication other than the study drug during the entire study period.

- Report to Clinical Pharmacology and Pharmacokinetic Unit on admission days until 8 pm.
- Overnight fasting of at least 10 hrs before test meal/ breakfast. High fat and high calorific test meal/ breakfast will be provide 30 minutes before dosing allocated by randomization sheet and test meal/ breakfast has to be completed within 30 minutes.
- Be available to participate in the study as per schedule.
- Drinking water will be not allowed 1 hr before and 2 hrs after drug administration.
- Not consume any medication (either OTC or prescribed) during course of the study.
- Abstain from smoking, alcoholic grape fruit juice and other beverages, such as tea, coffee, soft drinks and chocolates 48 hrs before the study and during the study period.

7. BLOOD COLLECTION

A total of 23 blood samples (5 mL each) will be collected, prior to drug administration (0.0) and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 18, 19, 20, 21, 22, 24.0, 36.0, and 48.0 hours thereafter.

The total volume collected per subject in this study will not exceed 140 mL including 10 mL for screening, 5.0 mL for post study safety analysis and the 10 mL blood loss due to 0.5 mL discarded blood up to 24.0 hours.

HEALTH RISK OR DISCOMFORTS

It is important to note here, that we are prepared to handle all the expected, less likely ones as well as possible adverse events. If need be, we will ensure you get the required specialist care and facilities.

8. POSSIBLE COMMON SIDE EFFECTS YOU SHOULD KNOW:

The following adverse drug reactions were reported in receiving Enalapril in clinical trials were Dry Mouth, Dizziness, Blurred Vision, Nausea, Headache, Drowsiness,
Nervousness, Fatigue, Cough, Muscle Cramps, Orthostatic hypotension, Diarrhea, Palpitation, Back pain, Tachycardia.

**Contraindications, Special Warnings and Precautions that you should know**

Enalapril is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

**9. BENEFITS TO YOU AND TO HUMANITY IN GENERAL**

This is research-oriented study. If the test formulation is approved for marketing, society shall benefit from having this generic product available for its effectiveness in the treatment of hypertension and heart failure.

You will get a free medical check-up costing at least Rs.1000/- in the open market. You will also be informed about your health status.

**10. COMPENSATION**

You will be compensated in cash for your time and participation in this study. The cash payments will usually be made at the end of the last period.

In case you have to drop out for any reason, Ethics committee guidelines will govern compensation due to you. This means that if you were withdrawn from the study due to any study drug related effects you will be compensated in full. If you are dropped because of protocol violations/disciplines problems, you will be compensated to the extent of your participation.

**11. SUBJECT RIGHTS**

If you have any questions regarding the study procedure, you may contact:

- **Dr. BHASWAT S. CHAKRABORTY, B.Pharm, Ph.D.**
  Phone No. (O) 02714-220312/221481/83/84 Ext No: 107
  (R) 02717-238221

- **Dr. ANIL PATEL, M.B.B.S., M.D.**
  Phone No. (O) 02714-221481/83/84 Ext No: 266
  (M) 09374069202.
12. CONFIDENTIALITY

Your records will identify you as a subject in this study and may be examined by the Sponsor, Independent Ethics Committee and other regulatory bodies. Otherwise your records will be kept confidential.

14. CONSENT FORM FOR THE SUBJECT PARTICIPATION IN THE STUDY

Protocol title: A randomized, three-treatment, three-sequence, single dose, parallel pharmacokinetics study on Enalapril Maleate sustained release 20 mg tablet (containing Enalapril Maleate 20 mg) of Cadila Pharmaceuticals Ltd., India, compared with Envas 10 mg tablet (2 tablets) (containing Enalapril Maleate 10 mg) of Cadila Pharmaceuticals Ltd., India in 18 healthy, adult, male, human subjects under fasting and fed condition allocated by randomization sheet.

Protocol No: Pro/0408/006
Protocol Version: 01
ICF Version: 01

I have been informed to my satisfaction that:

My participation in this study is voluntary.
This study provides me no medical benefits other than a free medical check.
I have the right to be provided with answers to questions arising during the course of the study.
I can withdraw from the study at any time without prejudice to future medical care or selection for further studies.
I can be dropped from the study at any time if I violate the study protocol or to protect my health.
I will receive a copy of this signed consent form.
Further more:

- My date of birth is…………….……and I am more than 18 years but less than 45 years of age.
- I currently require no medical treatment or care.
- I have withheld no information regarding my past medical history.
- I certify that during the past three months I have not participated in any experimental studies conducted at Cadila Pharmaceuticals Ltd. or elsewhere and did not bleed more than 350 mL.
- I will comply with all administrative and disciplinary requirements of Cadila Pharmaceuticals Ltd.

I ………………………………………………… received a copy of this form and read it. I also have been readout and explained by the staff of Cadila Pharmaceuticals Ltd., the information provided in this form and have understood it. I hereby willingly affix my signature in confirmation of my participation in this study. I want/ do not want to carry a copy of this form with me for my reference.

Signature or left hand thumb impression of subject
Date: Time:

Impartial witness:
I confirm that the above named subject has understood the information given in this form and has signed on his own free will after understanding the contents of what has been communicated to him.

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Name and Address of Impartial Witness Signature, Date &Time
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Consent Obtained by (Subject Recruiter) Signature & Date
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Physician / Clinical Investigator Signature & Date
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