Pharma Metric Labs

BIOEQUIVALENCE STUDY PROTOCOL

BIOEQUIVALENCE STUDY OF FUROSEMIDE 40 MG TABLET MANUFACTURED BY PT. KIMIA FARMA (PERSERO) TBK IN COMPARISON WITH LASIX® 40 MG TABLET MANUFACTURED BY PT. AVENTIS PHARMA, INDONESIA

Protocol No. : 447/STD/PML/2019

Drug Substance	:	**Furosemide 40 mg**
Sponsor	:	**PT. Kimia Farma (Persero) Tbk** Jl. Pajajaran No. 29 - 31 Bandung, Indonesia Tel : +62 22 4204043 Fax : +62 22 4237079
Study Centre	:	**PT. Pharma Metric Labs** Gedung Indra Sentral Cempaka Putih Unit R-T Jalan Letjen Suprapto Kav. 60 Central Jakarta, 10520 Indonesia Tel : +62 21 4265310 Fax : +62 21 4210302
Principal Investigator	:	**FD Suyatna MD, PhD, SpFK**
Study Director	:	**I Gusti Putu Bagus Diana Virgo, Pharm**
Protocol Author	:	**Olivia Valencia, Pharm**
Issue date	:	**08 February 2019**
Version	:	**00**

1. TITLE PAGE

1.1. Study Title

Bioequivalence study of Furosemide 40 mg tablet manufactured by PT. Kimia Farma (Persero) Tbk in comparison with Lasix® 40 mg tablet manufactured by PT. Aventis Pharma, Indonesia.

1.2. Name, person in charge and address of Sponsor

Dra. Dyah Yuliana P., M.Kes., Apt.
Regulatory Manager
PT. Kimia Farma (Persero) Tbk
Jl. Veteran No. 9
Jakarta, Indonesia
Tel : +62 21 3847709 ext 212; 214
Fax : +62 21 3440720

1.3. Name, person in charge and address of Institution

I Gusti Putu Bagus Diana Virgo, Pharm
PT. Pharma Metric Labs
Gedung Indra Sentral Cempaka Putih Unit R-T
Jalan Letjen Suprapto Kav. 60
Central Jakarta, 10520
Indonesia
Tel : +62 21 4265310
Fax : +62 21 4210302
Email : gusti.virgo@pharmametriclabs.com

1.4. Name and address of Principal Investigator

FD Suyatna, MD, PhD, SpFK
University of Indonesia
Jalan Salemba Raya No.6, Jakarta Pusat
Jakarta 10430

1.5. Name of Study Physician

Hendi Tri Ariatmoko, MD

1.6. Name and address of clinical laboratory

Tri Handayani
Pramita Clinical Laboratory
Jalan Matraman Raya, No. 26, East Jakarta, Indonesia.
Tel : +62 21 85908530
Fax : +62 21 8502039

1.7. Name, person in charge and address of analytical laboratory

Seriyati Naibaho, Chem
PT. Pharma Metric Labs
Gedung Indra Sentral Cempaka Putih Unit R-T
Jalan Letjen Suprapto Kav. 60
Central Jakarta, 10520
Indonesia
Tel : +62 21 4265310
Fax : +62 21 4210302

1.8. Name, person in charge and address for pharmacokinetics and statistical analysis

Niken Pratiwi, Pharm
PT. Pharma Metric Labs
Gedung Indra Sentral Cempaka Putih Unit R-T
Jalan Letjen Suprapto Kav. 60
Central Jakarta, 10520
Indonesia
Tel : +62 21 4265310
Fax : +62 21 4210302

1.9. Name and address of other study personnel

Study Director	:	I Gusti Putu Bagus Diana Virgo, Pharm
Clinical	:	Uluk Suharsi Putra, Chem
Quality Assurance	:	Hanoum Kayasa Swasti, Chem. Eng

1.10. Start and end date of clinical and analytical study

Dates of Clinical Portion:

Screening	: After protocol approval from NADFC
Period 1	: After completion of screening process
Period 2	: One week after Period 1

Dates of Analytical Portion :

Method Validation	: July 2014
Sample Analysis	: After completion of Period 2

INVESTIGATOR SIGNATURE PAGE

The undersigned hereby confirmed that the protocol had been read and understood, and agreed to abide by the procedures as stipulated. We agreed to conduct the study with reference to The Indonesian Good Clinical Practice Guideline 2016; The Indonesian Bioequivalence Study Guideline BPOM 2015; ASEAN Guidelines for The Conduct of Bioavailability and Bioequivalence Study 2015; EMA Guideline on the Investigation of Bioequivalence 2010; USFDA Guidance for Industry on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products 2003; Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guideline.

Responsibility	Name	Signature and date
Principal Investigator	FD Suyatna MD, PhD, SpFK	April 8, 2019
Study Director	I Gusti Putu Bagus Diana Virgo, Pharm	04 Apr 2019
Study Physician	Hendi Tri Ariatmoko, MD	01 APR 2019
Clinical	Uluk Suharsi Putra, Chem	02 Apr 2019
Analytical	Seriyati Naibaho, Chem	01 Apr 2019
Quality Assurance	Hanoum Kayasa Swasti, Chem.Eng	01 Apr 2019
Statistician	Niken Pratiwi, Pharm	01 Apr 2019
Sponsor	Dra. Dyah Yuliana P., M.Kes, Apt.	12 April 2019

2. PROTOCOL SYNOPSIS

Title of Study	Bioequivalence study of Furosemide 40 mg tablet manufactured by PT. Kimia Farma (Persero) Tbk in comparison with Lasix® 40 mg tablet manufactured by PT. Aventis Pharma, Indonesia.
Objectives	The objective of this study is to investigate whether Furosemide 40 mg tablet manufactured by PT. Kimia Farma (Persero) Tbk is bioequivalent to its reference product, Lasix® 40 mg tablet manufactured by PT. Aventis Pharma, Indonesia.
Study Design	Randomized, single-blind, single-dose, 2-period, cross-over study in healthy subjects under fasting condition.
Test Product	Name : Furosemide 40 mg tablet Manufacturer : PT. Kimia Farma (Persero) Tbk Reg No : GKL0012517510A1 Batch No : I72015B Mfg Date : 14 September 2017 Exp Date : *31* August 2020
Reference Product	Name : Lasix® 40 mg tablet Manufacturer : PT. Aventis Pharma, Indonesia. Reg No : DKL0121203710A1 Batch No : 245U228 Mfg Date : August 2018 Exp Date : July 2021
Number of Subjects	24 healthy subjects
Subject Population	Healthy male or female subjects aged between 18-55 years with body mass index (BMI) between 18–25 kg/m^2
Inclusion and Exclusion Criteria	<u>Inclusion Criteria</u> - have read the subject information and signed informed consent documents - age 18 – 55 years - body mass index between 18–25 kg/m^2 - have a normal electrocardiogram - blood pressure within normal range (systolic 90-120 mmHg and diastolic 60-80 mmHg) - heart rate within normal range (60-100 bpm) - with absence of significant disease or clinically significant abnormal laboratory values on laboratory evaluation, medical history or physical examination during screening

Inclusion and Exclusion Criteria	- acceptance to use protection (condom) during intercourse with their spouse throughout the study Exclusion Criteria - those who are pregnant and/or nursing women - those with a history of hypersensitivity to furosemide, or other diuretics or other ingredients in the drugs or a history of serious allergic reaction to any drug, a significant allergic disease, or allergic reaction - those with a history or presence of medical condition which might significantly influence the pharmacokinetic of the study drug, e.g. chronic gastrointestinal disease, diarrhea, gastric surgery, renal insufficiency, hepatic dysfunction or cardiovascular disease. - those with a history or presence of any coagulation disorder or clinically significant hematology abnormalities - those who are using any medication (prescription or non-prescription drug, food supplement, herbal medicine), particularly the medication known to affect the pharmacokinetic of the study drug, within one week prior to the drug administration day - those who have participated in any clinical study within 3 months prior to the study (< 90 days) - those who have donated or lost 300 ml (or more) of blood within 3 months prior to the study - those who smoke more than 10 cigarettes a day - those who are positive to HIV, HBsAg, and HCV tests (to be kept confidential) - those with a history of drug or alcohol abuse within 12 months prior to screening for this study - those who are unlikely to comply with the protocol, e.g uncooperative attitude, inability to return for follow up visits, poor venous access
Screening	Medical history, physical examination, laboratory tests (routine hematology, ***serum electrolyte (potassium)*** blood biochemistry and urinalysis), electrocardiograph, pregnancy test and HIV, HBsAg, and HCV tests are carried out to screen the subjects and to obtain eligible subjects who meet the inclusion and exclusion criteria.
Subjects' Restriction	- Abstain from taking any medication at least one week before and during study period (unless necessary) - Not permitted to smoke, consume alcohol, milk, beverages or food containing xantines (e.g., tea, coffee, chocolate, fruit juice) 24 hours prior and during study period - Instructed to avoid severe physical exertion during sampling hours
Standardization of study condition	- Subjects are instructed to stay one night before and during the sampling period - Subjects are instructed to fast from 8 hours before until 4 hours after drug administration - The menu served and meal taken by subjects are standardized and recorded

Standardization of study condition	- Water can be consumed as desired except during the period of 1 hour before until 2 hours after drug administration - Subjects are instructed to remain in a comfortable recumbent position for up to 8 hours after dosing and remain under medical surveillance for up to 12 hours after dosing. Before they are allowed to ambulate, they should sit up with legs in a dependent position for one minute prior to standing up. While standing immobile, they should be closely observed for blood pressure changes and/or orthostatic symptoms, including nausea, dizziness, or faintness for at least three minutes.
Investigational Product Administration	A single dose of the drug (either test or reference according to randomization code) will be given orally to the subjects in sitting posture. The drug will be administered with 240 mL water.
Sampling Schedule	Blood samples for furosemide assay (approximately 6 mL) are drawn into tubes containing anticoagulant (EDTA) before dosing (0 h) and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after dosing. The predose sample (0 h) is collected within an hour before the first drug dosing SN01. A total volume of 192 mL of blood will be collected from each subject (2 periods x 16 sampling points x 6 mL per sampling points) of 96 mL per period. This volume of blood was used for pharmacokinetic analysis.
Subject Monitoring	Vital signs (blood pressure, pulse, respiration rate and body temperature) are monitored and recorded prior to drug administration, and subsequently at 1, 3, 6, 12 and 24 hours after drug administration. The subjects' safety is monitored during the entire study under direct supervision by Study Physician at the study site.
Washout period	One week between each treatment
Analyte	Furosemide concentration will be measured in plasma by a validated UPLC method. The LLoQ is 4.99 ng/mL for furosemide.
Pharmacokinetics Parameter	C_{max}, AUC_t, AUC_{inf}, t_{max} and $t_{½}$ will be determined.
Statistical Analysis	Bioequivalence of the two formulations will be assessed by comparing the AUC_t and C_{max} of furosemide values after ln transformation of the concentration data. The geometric mean ratios (test/reference) of the ln-transformed data and their 90% confidence intervals will be further analyzed with a parametric method (analysis of variance/ANOVA) using Equiv Test® version 2.0 (Statistical Solution Ltd., Saugus. MA, USA) or manual calculation which has been validated to Equiv Test®.
Bioequivalence Criteria	The two products are considered bioequivalent when the 90% confidence intervals of the furosemide geometric mean ratio between test and reference products fall within the range of 80.00-125.00% for AUC_t and C_{max}.