Pharma Metric Labs

BIOEQUIVALENCE STUDY PROTOCOL

BIOEQUIVALENCE STUDY OF ACYCLOVIR 200 MG TABLET MANUFACTURED BY PT. KIMIA FARMA (PERSERO) TBK IN COMPARISON WITH ZOVIRAX® 200 MG TABLET MANUFACTURED BY GLAXO WELLCOME S.A., ARANDA, SPAIN, PACKED BY GLAXOSMITHKLINE AUSTRALIA PTY LTD, BORONIA, AUSTRALIA, IMPORTED BY PT. GLAXO WELLCOME INDONESIA, JAKARTA, INDONESIA

Protocol No. : 515/STD/PML/2019

Drug Substance	:	**Acyclovir 200 mg**
Sponsor	:	**PT. Kimia Farma (Persero) Tbk** Jl. Rawa Gelam V No. 1 Jakarta, Indonesia Tel : +62 21 4609354 Fax : +62 21 4603143
Study Centre	:	**PT. Pharma Metric Labs** Gedung Indra Sentral Cempaka Putih Unit R-U Jalan Letjen Suprapto Kav. 60 Central Jakarta, 10520 Indonesia Tel : +62 21 4265310 Fax : +62 21 4210302
Principal Investigator	:	**Metta Sinta Sari Wiria, Pharm, MS**
Study Director	:	**I Gusti Putu Bagus Diana Virgo, Pharm**
Protocol Author	:	**Olivia Valencia, Pharm**
Issue date	:	**13 December 2019**
Version	:	**00**

1. TITLE PAGE

1.1. Study Title

Bioequivalence study of Acyclovir 200 mg tablet manufactured by PT. Kimia Farma (Persero) Tbk in comparison with Zovirax® 200 mg tablet manufactured by Glaxo Wellcome S.A., Aranda, Spain, Packed by GlaxoSmithKline Australia Pty Ltd, Boronia Australia, imported by PT. Glaxo Wellcome Indonesia, Jakarta, Indonesia.

1.2. Name, person in charge and address of Sponsor

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1.3. Name, person in charge and address of Institution

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1.4. Name and address of Principal Investigator

Metta Sinta Sari Wiria, Pharm, MS
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1.5. Name of Study Physician

Jessica, MD, SpOk

1.6. Name and address of clinical laboratory

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

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

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1.9. Name 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	: January 2016
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	Metta Sinta Sari Wiria, Pharm, MS	07 JAN 2020
Study Director	I Gusti Putu Bagus Diana Virgo, Pharm	07 Jan 2020
Study Physician	Hendi Tri Ariatmoko, MD	06 JANUARI 2019
Clinical	Uluk Suharsi Putra, Chem	08 JAN 2020
Analytical	Seriyati Naibaho, Chem	06 Jan 2020 we koy SNO 06 Jan 2020
Quality Assurance	Hanoum Kayasa Swasti, Chem.Eng	6 Jan 2020
Statistician	Niken Pratiwi, Pharm	08 Jan 2020
Sponsor	Dra. Dyah Juliana Pudjiati, M.kes., Apt	09/Jan 2020

2. PROTOCOL SYNOPSIS

Title of Study	Bioequivalence study of Acyclovir 200 mg tablet manufactured by PT. Kimia Farma (Persero) Tbk in comparison with Zovirax® 200 mg tablet manufactured by Glaxo Wellcome S.A., Aranda, Spain, Packed by GlaxoSmithKline Australia Pty Ltd, Boronia Australia, imported by PT. Glaxo Wellcome Indonesia, Jakarta, Indonesia.
Objectives	The objective of this study is to investigate whether Acyclovir 200 mg tablet manufactured by PT. Kimia Farma (Persero) Tbk is bioequivalent to its reference product, Zovirax® 200 mg tablet manufactured by Glaxo Wellcome S.A., Aranda, Spain, Packed by GlaxoSmithKline Australia Pty Ltd, Boronia Australia, imported by PT. Glaxo Wellcome Indonesia, Jakarta, Indonesia.
Study Design	Randomized, single-blind, single-dose, 2-period, 2-treatment, 2-sequence, 2-way crossover study in healthy subjects under fasting condition.
Number of Subjects	28 healthy subjects
Washout period	1 week between each treatment
Test Product	Name : Acyclovir 200 mg tablet Manufacturer : PT. Kimia Farma (Persero) Tbk Reg No : GKL9812415010A1 Batch No : C90576J Mfg Date : March 2019 Exp Date : March 2024
Reference Product	Name : Zovirax® 200 mg tablet Manufacturer : Glaxo Wellcome S.A., Aranda, Spain, Packed by Glaxo-SmithKline Australia Pty Ltd, Boronia Australia, imported by PT. Glaxo Wellcome Indonesia, Jakarta, Indonesia. Reg No : DKI1691601310A1 Batch No : 243E Mfg Date : March 2018 Exp Date : March 2020
Inclusion Criteria	- have read the subject information and signed informed consent documents - healthy male and female - 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) - absence of significant disease or clinically significant abnormal laboratory values on laboratory evaluation, medical history or physical examination during screening

Exclusion Criteria	- pregnant and/or nursing women - history of contraindication or hypersensitivity to acyclovir, or other antiviral or other ingredients in the study products or a history of serious allergic reaction to any drug, a significant allergic disease, or allergic reaction - 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. - history or presence of any coagulation disorder or clinically significant hematology abnormalities - 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 - have participated in any clinical study within 3 months prior to the study (< 90 days) - have donated or lost 300 ml (or more) of blood within 3 months prior to the study - smoke more than 10 cigarettes a day - positive to HIV, HBsAg, and HCV tests (to be kept confidential) - history of drug or alcohol abuse within 12 months prior to screening for this study - 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, 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 xanthines (e.g., tea, coffee, chocolate) or 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 - Water can be consumed as desired except during the period of 1 hour before until 2 hours after drug administration

Investigational Product Administration	A single dose of 200 mg acyclovir of the test drug or 200 mg acyclovir of the reference drug (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 acyclovir assay (approximately 6 mL) are drawn into tubes containing anticoagulant (EDTA) before dosing (0 h) and at 15, 30, 45 min, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing. The pre-dose 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 point), 96 mL per period. This volume of blood will be 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, 10, 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	Acyclovir concentration will be measured in plasma by a validated LC-MS/MS method. The LLoQ is ***7.5 ng/mL*** for acyclovir.
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 acyclovir 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 acyclovir geometric mean ratio between test and reference products fall within the range of 80.00-125.00% for AUC_t and C_{max}.