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Bioequivalence Study of Two Etoricoxib 90 mg Film-Coated Tablet Formulations

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Research Article

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Abstract

The present study was conducted to compare the bioavailability of two etoricoxib 90 mg film-coated tablet formulations (test formulation and reference formulation). This study was an open-label, randomized, single-dose, two-periods, two-treatments, and crossover study which included 24 healthy adult male and female subjects under fasting conditions. Each of the two study periods was separated by a 7 days washout. A single dose of test or reference drug was administered to the subject in each period based on the randomization scheme.

Plasma concentrations of the drug were determined by LC-MS/MS method. The pharmacokinetic parameters assessed in this study were the area under the plasma concentration-time curve from time zero to 96 h (AUC_{0-96h}), area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), the peak plasma concentration of the drug (C_{max}), time needed to achieve the peak plasma concentration (T_{max}), and the elimination half-life ($T_{1/2}$). The geometric mean ratios (90% CI) of the test drug/reference drug for etoricoxib were 102.39% (97.63% – 107.38%) for AUC_{0-96h} and 93.23% (86.54% – 100.43%) for C_{max}. The 90% Confidence Intervals (CI) calculated for AUC_{0-96h} and C_{max} of etoricoxib were within the standard bioequivalence range (80.00– 125.00% for AUC_{0-t} and C_{max}). It was concluded that the two etoricoxib film-coated tablets (test and reference drug) were bioequivalent in terms of the rate and extent of absorption.

Keywords: Analgesic; Anti-inflammatory; Bioequivalence; Etoricoxib

Abbreviations: BMI: Body Mass Index; CI: Confidence Intervals; CRF: Case Report Form; EMA: European Medicines Agency; ECG: Electrocardiogram; FERCAP: Forum for Ethical Review Committee in the Asia and Western Pacific Region; GCP: Good Clinical Practice; ICH: International Council for Harmonization; LLOQ: Lower Limit of Quantification.

Introduction

Over the past three decades, the global regulatory requirement for bioequivalence of generic pharmaceutical drugs has grown significantly [1]. Studies on bioequivalence are widely acknowledged and play a significant part in the approval and marketing of both new and generic medicinal products [2]. Therefore, in this study, we compared two formulations of etoricoxib film-coated tablets i.e. the reference and test drugs.

Etoricoxib is a potent selective cyclo-oxygenase 2 inhibitor with anti-inflammatory and analgesic properties. The therapeutic indications of etoricoxib in different countries include treatment for osteoarthritis, rheumatoid

arthritis, ankylosing spondylitis, acute gouty arthritis, chronic low back pain, acute pain, chronic musculoskeletal pain, and primary dysmenorrhea. Etoricoxib is available at the strengths of 30, 60, 90, and 120 mg [3].

The various doses of etoricoxib are indicated for certain diagnostic conditions. For osteoarthritis, the recommended dose is 60 mg once daily, for rheumatoid arthritis and ankylosing spondylitis is 90 mg once daily, and short-term relief of acute pain is 90 mg or up to 120 mg once daily limited to a maximum of 8 days of treatment, Postoperative dental pain is 90 mg once daily, and for primary dysmenorrhea is 120 mg once daily [4].

Etoricoxib (CAS 202409-33-4) is 5-chloro-2-(6-methylpyridine-3-yl)-3-(4-methylsulfonyl phenyl) pyridine with the empirical formula $C_{18}H_{15}ClN_2O_2S$ [5]. The molecular weight of Etoricoxib is 358.8 g/mol. The solubility of Etoricoxib in water is 0.0033 g/L in water [6].

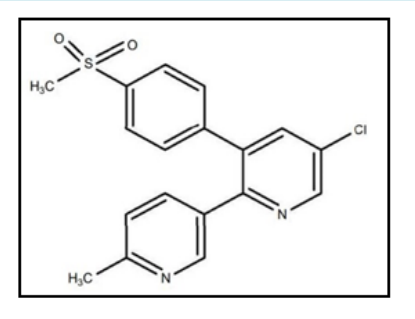

Figure 1: Chemical Structure of Etoricoxib.

Orally administered etoricoxib is well absorbed. The mean oral bioavailability is approximately 100%. Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 mcg/mL. The volume of distribution at steady state (Vdss) is approximately 120 L in humans. Etoricoxib is extensively metabolized with < 1 % of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'- hydroxymethyl derivative is catalyzed by CYP3A4. Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion [7]. The elimination half-life of etoricoxib 90 mg is approximately 22 hours [8].

This study was conducted to investigate the bioequivalence of Etoricoxib 90 mg film-coated tablet manufactured by PT Otto Pharmaceutical Industries to the reference drug, Etoricoxib 90 mg film-coated tablet, Arcoxia™ manufactured by Frosst Iberica, S.A., registered and packed by PT Merck Sharp Dohme Pharma Tbk Pasuruan, East Java.

Subjects, Materials, and Methods

Subjects and Study Design

Twenty-four (24) healthy subjects, which consist of twenty-one (21) male subjects and three (3) female subjects, 24-52 years old, and Body Mass Index (BMI) between 18.95 kg/m2 – 25.64 kg/m^2 were enrolled in the study. All subjects should pass the screening and selection phase with inclusion and exclusion criteria based on Covid- 19 testing, physical examination, vital signs (blood pressure, pulse/heart rate, respiratory rate, and body temperature), electrocardiogram (ECG), blood biochemistry including glucose, liver function (AP, SGPT, SGOT, and total/direct bilirubin), renal function (serum creatinine and urea), sero-immunology (HBsAg, anti-HCV, and anti-HIV), routine hematology (hemoglobin and leucocyte), blood glucose, and urinalysis (specific gravity, pH, leukocyte esterase, nitrite, albumin, glucose, ketones, urobilinogen, bilirubin, occult blood, tubular and sediment). A pregnancy test (for women) was performed for female subjects in the screening phase and before taking the drug in each period.

This study was an open-label, randomized, single- dose, two-periods, two-treatments, cross-over study in fasting conditions with 7 days washout between each period. The study was performed in accordance with The International Council for Harmonization (ICH) guidelines for Good Clinical Practice (GCP) and the declaration of Helsinki provisions [9,10]. This study was approved by the Indonesian Food and Drug Regulatory Authority and the Ethics Committee of the Medical Faculty University of Indonesia which was certified by the Forum for Ethical Review Committee in the Asia and Western Pacific Region (FERCAP).

Treatment Phase and Blood Sampling

Subjects attended PT Biometrik Riset Indonesia a night before drug administration and conducted rapid test antigen for Covid-19 in each period, only the subject with a negative result of Covid-19 was allowed to continue in this study. The subjects were requested to fast from any food and drink except mineral water from 9 p.m. In the next morning (approximately 6 a.m.) of the dosing day, after an overnight fast, a pre-dose blood sample amount of 5 mL was taken one hour before drug administration for each period. The study drug (one film-coated tablet of the test or the reference drug) was given at 7 a.m. with 250 mL of water.

After drug administration, a 5 mL blood samples were taken at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72, and 96 hours for each period. Seven days after the first drug administration (washout period), the same procedure was

repeated with the alternate drug to complete the crossover design. Plasma was separated from the blood samples by centrifuging at 4000 rpm for 10 minutes in a room with a temperature range of 20 - 30°C and humidity range of 35 - 70%. Samples for analysis were stored at (-20)°C and the retained samples were stored at (-80)°C. The date and the time of drug administration (dosing) and taking of each blood sample (sampling) were recorded in the Case Report Form (CRF) for each subject.

Statistical Analysis

EquivTestPK software was used to perform the statistical analysis of $AUC_{0\text{-}96h}$, $AUC_{0\text{-}\infty}$, and C_{max} using analysis of variance (ANOVA) after the transformation of the data to their logarithmic (ln) values. Using the error variance (S2) obtained from the ANOVA; the 90% CI with α = 5.00% was calculated from the following equation:

$$90\%CI=(\bar{X}_T-\bar{X}_R)\pm t_{0.1(v)}\sqrt{S^2\left(\frac{1}{n_{TR}}+\frac{1}{n_{RT}}\right)}$$

- $\bar{X}_T$, $\bar{X}_R$: the means of in transformed values for the test drug [T] and the reference drug [R].
- S^2: the error variance obtained from the ANOVA.
- n_{TR}, n_{RT}: the number of subjects of sequence TR and RT.
- $t_{0.1}$: the t-value for 90% CI with α = 5.00%.
- v: the degree of freedom of the error variance from ANOVA.

The anti (ln) of the above confidence intervals (CIs) are the 90% CIs with α = 5.00% of the ratios of the test/the reference geometric means. The power of the study should be 80% with α = 5.00%. The acceptance criterion of the bioequivalence study is the value of a 90% confidence interval with α = 5.00% of the test/reference geometric means ratio must be in the range of 80.00-125.00% for $AUC_{0\text{-}96h}$ and C_{max} [11,12,13].

The differences between drugs (T/R) in T_{max} and $T_{1/2}$ parameters were analyzed nonparametric ally on the original data using Wilcoxon Test.

Assay Methodology and Validation

Prior to the assay of Etoricoxib in the sample, bioanalytical method validation was evaluated for anticoagulant effect (i.e. comparing the effect of CPDA anticoagulant used in blank plasma bought from Indonesian Red Cross for method validation towards anticoagulant used in K3EDTA anticoagulant used in blood collection tube to collect blood samples); selectivity; carry- over effect; calibration curve and Lower Limit of Quantification (LLOQ); precision and accuracy; matrix effect; dilution integrity; and stabilities (i.e. short term stability at room temperature and post-preparative/auto- sampler batch integrity, freeze-thawed stability, also long term stability). An assay of Etoricoxib concentration in plasma was carried out by a fully validated LC-MS/MS with LLOQ 5.00 ng/mL. During the bioanalytical phase of the plasma samples, the analysis was monitored by the quality control process including system suitability test, linearity of a calibration curve, and quality control samples (Low QC, Medium QC, and High QC) referred to requirements described in European Medicinal Agency (EMA) guideline 2011 [14].

Result and Discussion

There were 24 subjects who finished the study, consisting of 21 male and 3 female subjects. There were no adverse events reported in this study. The demographic data of the subjects enrolled in this study are tabulated in Table 1.

	MIN	MAX
Age (year)	24	52
BMI (kg/m2)	18.95	25.64
Pulse (bpm)	60	90
Respiratory Rate (x/minute)	16	18
Blood Pressure (mm/Hg)	101/62	130/90

Table 1: Demographic Data of the Subject.

Pharmacokinetic Analysis

The blood samples from 24 subjects were analyzed for plasma concentrations of Etoricoxib. Mean plasma concentrations versus time profiles of etoricoxib in human subjects (n = 24) after oral administration of 90 mg etoricoxib film-coated tablet of test drug and reference drug are shown in Figure 2.

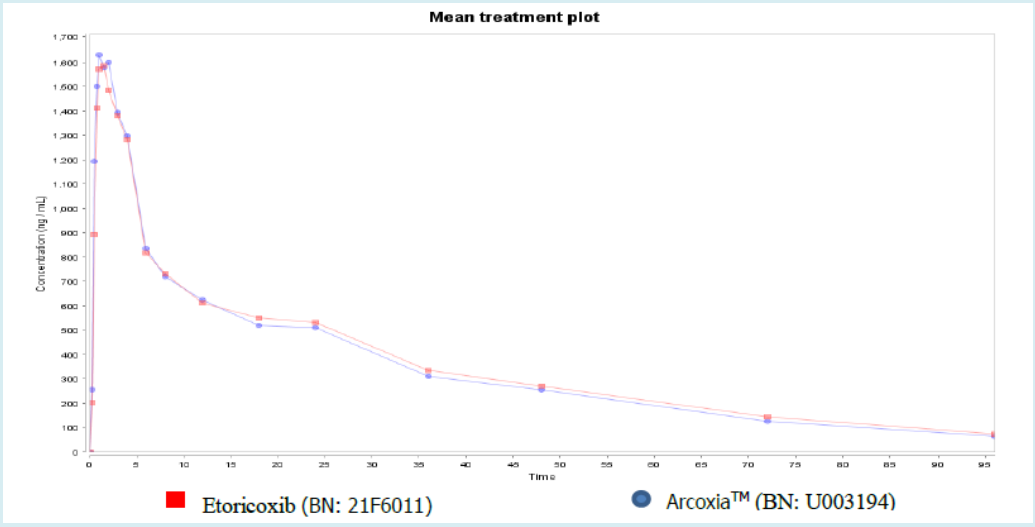

Figure 2: Geometric Means of Plasma Concentration vs. Time Profiles after Dosing of Test Drug [T]:Etoricoxib and Reference Drug [R]: Arcoxia™.

The pharmacokinetic parameters ($AUC_{0\text{-}96h}$, $AUC_{0\text{-}\infty}$, C_{max}) of the test drug (T) and reference drug (R) were calculated and compared to assess bioequivalence. The calculated 90% CI with α = 5.00% for the geometric mean of individual and the ratios of $AUC_{0\text{-}96h}$ and $AUC_{0\text{-}\infty}$ as well as C_{max} for the test drug: Etoricoxib (BN: 21F6011) and reference drug: Arcoxia™ (BN: U003194) were all within 80.00 - 125.00% interval. This was in accordance with the standard guideline for bioequivalence study [13]. The main pharmacokinetic parameters drug of study Etoricoxib was obtained from 24 subjects after oral administration of the test drug and the reference drug is shown in Table 2. Meanwhile, the result of T_{max} and $T_{1/2}$ is shown in Table 3.

	Mean (SD)				
Parameter	**Test**	**Reference**	**Geometric Mean Ratio of T/R (90% CI)**	**% Intrasubject CV**	**Statistical Power (%)**
$AUC_{0\text{-}96h}$(ng.h/mL)	34,497.48 (12,409.05)	33,359.65 (11,295.36)	102.39% (97.63% – 107.38%)	9.59%	100%
C_{max} (ng/mL)	1,816.3 (447.24)	1,925.97 (404.79)	93.23% (86.54% – 100.43%)	15.00%	100%
$AUC_{0\text{-}\infty}$ (ng.h/mL)	37,346.34 (15,175.45)	35,528.75 (13,451.49)	103.73% (98.53% – 109.20%)	10.34%	100%

Table 2: Pharmacokinetic Parameters of Etoricoxib after a Single-Dose Oral Administration of Test & Reference Drug.

Parameter	Test	Reference
T_{max} (hours)	1.50 (0.75 –4.00)	1.00 (0.50 - 3.00)
$T_{1/2}$ (hours)	21.57 ± 7.97	19.89 ± 7.22

Table 3: The Result of T_{max} and $T_{1/2}$.

Bioanalytical Result

Result of applying the bioanalytical method validation of the bioequivalence study of Etoricoxib (BN: 21F6011) manufactured by PT Otto Pharmaceutical Industries in twenty-four (24) healthy subjects were all calibration curves of the subject showed good linearity within the range of 5-5000 ng/mL with the coefficient of correlation (R2) ≥ 0.9900. For accuracy and precision of three levels (low, medium and high) of concentration QC samples and LLOQ were provided in Table 4.

	QC			LLOQ
	Low	Medium	High	
Concentration (ng/mL)	15.06	2,509.98	3,764.97	4.99
Precision (% CV)	9.93%	7.82%	7.57%	0.58%
Accuracy (% deviation)	0.20%	5.71%	7.13%	0.99%

Table 4: Accuracy and Precision.

After all study phases are completed, remaining samples and data management should be maintained. The rest of the plasma samples analysis was destroyed following the stability long-term validated method, while retain samples were destroyed for at least 1 (one) year after the final reports had been sent to the Sponsor.

A copy of CRF and all source data were retained in the investigator's files. Other copies were given to the Sponsor as needed. Copies of all pertinent information including raw data of bioanalysis were retained by the Responsible Investigator until the study drug is destroyed. Additional consideration was made about complying with applicable local laws, guidelines, etc. Study document binders were provided for all required study documents.

Conclusion

Based on pharmacokinetics and results of this study, it is concluded that the test drug Etoricoxib (BN: 21F6011) manufactured by PT Otto Pharmaceutical Industries has a similar pharmacokinetic profile in terms of both rate and extent of absorption with the reference drug Arcoxia™ (BN: U003194) manufactured by Frosst Iberica, S.A., registered and packed by PT Merck Sharp Dohme Pharma Tbk Pasuruan, East Java with geometric mean ratio and 90% confidence interval for AUC_{0-96} and C_{max} parameters were 102.39% (97.63% – 107.38%) and 93.23% (86.54% –100.43%) respectively (requirement 80.00 – 125.00% for AUC_{0-t} and C_{max}) and the intra-subject coefficient of variation is 9.59% and 15.00%. Therefore, it can be concluded that the two formulations of etoricoxib are pharmacokinetically equivalent and interchangeable.

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