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Research Article

# Bioequivalence Study of Dapagliflozin 10 mg Film Coated Tablets in Healthy Indonesian Subjects under Fasting Condition

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## ABSTRACT

**Purpose:** This study aimed to demonstrate the bioequivalence of the Dapagliflozin 10 mg film-coated tablets manufactured by PT Dexa Medica, Indonesia, in comparison with the reference formulation, Forxiga® 10 mg film-coated tablets, manufactured by AstraZeneca Pharmaceuticals.

**Patients and methods:** This was an open-label, randomized, single-dose, two-period, two-sequence, two-way crossover study under fasting conditions with a 5-day washout period. 24 enrolled healthy subjects, 22 subjects completed the study. The test or reference formulation was administered orally to the subjects in a randomized manner. A validated Ultra-Performance Liquid Chromatography with Tandem Mass Spectrometry (UPLC-MS/MS) detection method was used to assay the plasma concentration of Dapagliflozin. This study assessed the following pharmacokinetic parameters: $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$, $t_{max}$, and $t_{½}$. Bioequivalence was established in the Test/Reference Geometric Means Ratio (GMR), and the 90% Confidence Interval (CI) of GMR was between 80.00% and 125.00% with 0.05 alpha for $AUC_{0-t}$ and $C_{max}$.

**Results:** The test dapagliflozin formulation had the mean ± Standard Deviation (SD) $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, and $t_{1/2}$ values of 83.07 ± 30.34 ng/mL, 601.72 ± 174.46 ng·h/mL, 620.87 ± 180.38 ng·h/mL, and 10.50 ± 2.64 hours, respectively. For Dapagliflozin from the reference formulation, the mean ± SD for $C_{max}$, $AUC_{0-t}$, $AUC_{0-\infty}$, and $t_{1/2}$ of were 80.29 ± 17.92 ng/mL, 606.64 ± 176.24 ng·h/mL, 626.15 ± 182.05 ng·h/mL, and 10.53 ± 2.69 hours, respectively. Dapagliflozin's median (range) $t_{max}$ was 2.00 (0.5-8.00) hours for the test formulation and 2.00 (1.00-6.00) hours for the reference formulation. The GMR (90% CI) of the Test/Reference formulation for Dapagliflozin was 100.89% (89.72%-113.46%) for $C_{max}$ and 99.21% (96.47%-102.04%) for $AUC_{0-t}$. No adverse event was reported in the study.

**Conclusion:** The results demonstrated that both formulations of Dapagliflozin 10 mg film-coated tablets were bioequivalent and were well tolerated by the subjects.

**Keywords:** Anti-diabetic; Bioavailability; Bioequivalence; Dapagliflozin; Generic; Pharmacokinetics

## INTRODUCTION

Dapagliflozin is classified under the Sodium-Glucose Cotransporter-2 (SGLT2) inhibitor, a relatively new class of oral antihyperglycemic drug indicated for diabetes mellitus type 2 treatment [1,2].

The drug's initial marketing authorization was obtained almost a decade ago in Europe and the United States [3,4]. Dapagliflozin's extended indications were recently approved in the United States for the risk reduction of cardiovascular death, heart failure hospitalization, and urgent heart failure visit in adults with heart failure; risk reduction of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression; as well

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as the risk reduction of hospitalization for heart failure in type 2 diabetes mellitus patients and either established cardiovascular disease or multiple cardiovascular risk factors [4]. Dapagliflozin is demonstrated to be non-inferior to metformin as a monotherapy in decreasing the HbA1c levels and clinically efficacious as an adjunct treatment in uncontrolled type II diabetes mellitus in Phase III trials [5].

SGLT2 inhibitors lower all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and kidney failure and reduce hospital admission for heart failure [6,7]. Cardiovascular Diseases (CVDs) are a significant concern in the progression and prognosis of type 2 diabetes mellitus, as CVD is majorly accountable for mortality and disability among patients [8]. Globally, around 32.2% of type 2 diabetes mellitus patients are affected by CVDs, including ischemic heart disease, heart failure, stroke, coronary artery disease, and peripheral artery disease [9]. Besides CKD, diabetic kidney disease is also a common and morbid complication of diabetes [10]. Moreover, 25% of people with diabetes have Chronic Kidney Disease (CKD), and 40% of people with diabetes are estimated to be at risk for developing CKD throughout their lifetime [10,11]. The introduction of SGLT2 inhibitors, including Dapagliflozin, as part of diabetes mellitus treatment was deemed to provide primary and secondary prevention of cardiorenal complications associated with the disease [12]. Due to its extraglycemic effects, SGLT2 inhibitor prescriptions have been increasing throughout the years, including from cardiologists and nephrologists [13-15].

The originator brand of Dapagliflozin was recently available in Indonesia in 2022. However, the demand for generic versions of the medicine is increasing since it provides a more affordable choice for most patients in Indonesia, thereby enhancing treatment adherence. Generic drugs must establish their bioequivalence with their reference (innovator) medicine to bridge the generic drug with the biopharmaceutical quality, therapeutic efficacy, and safety of the reference product. When two drug products are pharmaceutically comparable, and the bioavailability following administration is within the permitted established limits, bioequivalence is established [16]. The purpose of this study is to evaluate the bioequivalence of the Dapagliflozin 10 mg film-coated tablets manufactured by PT Dexa Medica in comparison with the reference formulation, Forxiga® 10 mg film-coated tablets manufactured by AstraZeneca Pharmaceuticals.

## MATERIALS AND METHODS

### Study subjects and design

The study complied with the relevant versions of the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and the International Council for Harmonisation, GCP (EMA/CHMP/ICH/135/1995). The Faculty of Medicine Ethics Committee at Universitas Indonesia approved the study protocol and informed consent declaration form before the study's launch. The protocol was registered in ClinicalTrials.gov with a trial registry number of NCT06127212. All study subjects provided written informed consent before participating in the screening evaluation process.

The study was an open-label, randomized, single-dose, two-period, two-sequence, two-way crossover study under fasting conditions involving 24 healthy subjects with a 5-day washout period. The study design conformed to the Guideline on the Investigation of Bioequivalence, EMA, London, 2010; ASEAN Guideline for the Conduct of Bioequivalence Study, Lao PDR, 2015; and Indonesian guidelines, Tata Laksana Uji Bioekivalensi, Badan Pengawas Obat dan Makanan (BPOM), Jakarta, 2022.

The study subjects comprised healthy adult males and female volunteers aged 18-55 with a Body Mass Index (BMI) within 18 to 25 $kg/m^2$ who could participate, communicate well with the investigators, and provide written informed consent to participate. The subjects were absent of any significant disease or clinically significant abnormal laboratory values on laboratory evaluation, medical history, or physical examination during screening. They could be considered healthy based on the review. They were non-smokers or smoked less than ten cigarettes daily and were willing to practice abstention or contraception during the study. The subjects were included in the study if their vital signs (after 10 minutes' rest) during screening were within the ranges of Systolic Blood Pressure: 100-129 mmHg, Diastolic Blood Pressure: 60-84 mmHg, and Pulse Rate: 60-90 bpm.

Subjects were excluded if they had history of allergy or hypersensitivity or contraindication to Dapagliflozin or allied drugs; pregnant or lactating female; had any major illness in the past 90 days or clinically significant ongoing chronic medical condition; had any clinically significant abnormal values during screening; positive Hepatitis B surface antigen (HBsAg), anti-HCV, or anti-HIV; positive result for COVID-19 rapid antigen test; had clinically significant hematology and Electrocardiogram (ECG) abnormalities; had any surgical or medical condition (present or history) which might significantly alter the absorption, distribution, metabolism or excretion of the study drug; had past history of anaphylaxis or angioedema; history of drug or alcohol abuse within 12 months prior to screening for this study; participated in any clinical trial within the past 90 days; history of any bleeding or coagulation disorders; presence of difficulty in accessibility of veins in left or right arm; donated or had a significant blood loss within 90 days before this study's first dosing day; or intake of any prescription (especially Dapagliflozin or empagliflozin), non-prescription drug (including hormonal contraception), food supplements or herbal medicines within 21 days of this study's first dosing day.

The volunteers underwent the screening evaluation 21 days before the first dosing day. A pregnancy test for female subjects and a COVID-19 test were performed at screening and before drug dosing in each period.

### Study products

Each subject was administered a single oral dose of either the test formulation or the reference formulation of Dapagliflozin 10 mg film-coated tablet in each treatment period. The 10 mg Dapagliflozin film-coated tablet manufactured by PT Dexa Medica, Indonesia (batch no. K-10706-00-F-SCU-1A) was used as the test product. As for the reference drug, this study used Forxiga® 10 mg film-coated tablet manufactured by AstraZeneca Pharmaceuticals LP, USA, imported by PT AstraZeneca Indonesia (batch no. 60041884). Each subject in this crossover study received one of the Test (T) drugs and one of the Reference (R) drugs in a random sequence of TR or RT. The randomization code was based on the block randomization (block size of 4 with two sequences) and Table of Random Numbers from Dixon and Massey, 1983 [17]. Both subjects and investigators knew whether the subject received the test or reference formulation

in this open-label design study. The bioanalytical and statistical analysis department did not have access to the randomization code.

## Treatment phase and blood sampling

Eligible subjects were admitted to the clinical investigation site at least 10 hours before Day 1 dosing. Except for mineral water, all subjects fasted for 8 hours before the medication was dosed. A 5 mL pre-dose pharmacokinetic blood sample was collected one hour before drug administration on the dosing day (Day 1). The subjects were then administered with either the test or reference drug (depending on the randomization) taken with 240 mL of 20% glucose solution in water. Blood samples (5 mL) were taken from the forearm vein at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 3.00, 4.00, 6.00, 8.00, 12.00, 24.00, 36.00, and 48.00 hours following drug administration by venipuncture with a 22G needle and collected in polyethylene tubes containing $K_3$EDTA. Plasma was separated from the collected blood samples by centrifuging them at 1538 ± 10 g for 15 minutes at room temperature. All plasma samples were stored in a -20˚C ± 5˚C freezer until analyzed.

For the following four hours, 60 mL of a 20% glucose solution was given every 15 minutes to maintain blood glucose levels and prevent hypoglycemic symptoms. Except for the 20% glucose solution administered during dosing and every 15 minutes for the first 4 hours following dosing, water intake was restricted from one hour before dosing until two hours after dose administration. Xanthine-containing food or beverages, fruit juices, smoking, and consumption of alcohol-based products were prohibited for 24 hours before and during the entire sampling days. Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature) and adverse events were monitored at 2.00, 4.00, 6.00, 8.00, 12.00, 24.00, and 48.00 hours following drug administration. Subjects were required to stay for 48 hours after dosing, and after a 5-day washout period, a similar procedure will be performed in Period 2.

## Drug concentration analysis

The collected 500 µL of plasma samples were added with internal standard, empagliflozin, and acetic acid 0.1%, then extracted using liquid-liquid extraction with tert-butyl methyl ether. After being separated, the organic layer was evaporated under a nitrogen gas spray until dry and reconstituted with 0.1% (1:1) acetonitrile: acetic acid. An aliquot of 5 µL was injected into the Ultra-Performance Liquid Chromatography with Tandem Mass Spectrometry (UPLCMS/MS) (LC Waters Acquity UPLC HClass and MS/MS detector Waters XEVO TQS Micro (ANL-TQSM 1). The analysis used a Poroshell 120 EC-C18, 2.7 m; 4.6 x 50 mm analytical column. The mobile phase was acetonitrile: Acetic acid 0.2% in water (50:50) with a 0.5 mL/min flow rate. The UPLC-MS/MS system was fully validated concerning adequate sensitivity, selectivity, specificity, linearity, accuracy, and precision (both within and between days) before it was utilized to assay the Dapagliflozin concentrations in plasma. The stability of the samples under frozen conditions, at room temperature, and during the freeze-thaw cycle was also assessed. The validation data is presented in (Table 1). The concentrations of Dapagliflozin were calculated using the internal standard method.

## Pharmacokinetic analysis

The pharmacokinetic parameters assessed in this study were the maximum observed plasma concentration ($C_{max}$), area under the plasma concentration-time curve from administration to last observed quantifiable concentration at time t ($AUC_{0-t}$), Area Under the Plasma Concentration-Time Curve Extrapolated to Infinity ($AUC_{0-\infty}$), time to reach maximum observed Plasma Concentration ($t_{max}$), and Plasma Half-life ($t_{½}$), which were calculated based on the plasma concentrations of Dapagliflozin. $C_{max}$ and $t_{max}$ were calculated directly from the observed data. The linear trapezoidal method was used to determine the $AUC_{0-t}$. The $AUC_{0-inf}$ was calculated as $AUC_{0-t}+C_t/k_e$, where $C_t$ was the last quantifiable concentration; $k_e$ was the terminal elimination rate constant and was determined by least-squares regression analysis during the terminal log-linear phase of the concentration-time curve. The $t_{½}$ was calculated as $0.693/k_e$. After transforming the data to their natural logarithmic values in ln), the statistical analyses of the $AUC_{0-t}$ and $C_{max}$ parameter used the Analysis of Variance (ANOVA) using Phoenix® WinNonlin® version 8.3 (Certara L.P., St. Louis, MO, USA). The terms employed in the ANOVA model were sequence, subject within sequence, period, and formulation. The $T_{max}$ comparison between groups was assessed using a non-parametric test from the original data using the Wilcoxon matched-pairs signed-rank test. Since the data was normally distributed, the $t_{½}$ difference was analyzed using Student's paired t-test. The two formulations were concluded as bioequivalent if the 90% Confidence Intervals (CI) of the test/reference Geometric Mean Ratio (GMR) of Dapagliflozin's $AUC_{0-t}$ and $C_{max}$ were within the range of 80.00%-125.00% with 0.05 alpha.

## RESULTS

A total of 24 subjects were enrolled in the study, but only 22 subjects completed the study and were analyzed for pharmacokinetic and bioequivalence calculation of Dapagliflozin. The two dropped-out subjects did not participate in Period 2 of the study for personal reasons unrelated to adverse events. All subjects who participated were healthy Indonesians who complied with the inclusion/exclusion criteria. Several enrolled subjects had screening-time laboratory results outside the normal range. However, those participants could still be included in the study as the deviation was not clinically significant, as specified in the inclusion and exclusion criteria. Since the subjects' physical examination pulse rates were normal (60 to 90 bpm) and there were no abnormalities in the way the ECG waves appeared, there were some subjects with sinus bradycardia (heart rate during ECG recording less than 60 bpm) who could still be included in the study. The sinus bradycardia was not considered clinically significant and did not indicate myocardial infarction, dysfunction, or cardiac rhythm disturbance. The study subjects were 17 males and seven females between 19 and 44 years old, with the body mass index ranging from 18.61 to 24.98 $kg/m^2$ (Table 2).

(Table 3), presents the Dapagliflozin pharmacokinetic parameter values and 90% CI for the Test and Reference formulation's GMR. The 90% CI of the GMR for the $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ were within the 80.00%-125.00% range. The $t_{1/2}$ and $T_{max}$ of both test and reference formulation were comparable. Figure 1 illustrates the linear scale plot of the mean Dapagliflozin concentrations in twenty-two subjects following administration of the test or reference formulation in a single dosage. There were no adverse events observed during the study.

**Table 1:** Validation data of the analytical method of Dapagliflozin determination in human plasma by UPLC-MS/MS with empagliflozin as the internal standard.

| Parameters | At concentration of | | | | |
|---|---|---|---|---|---|
| | LLOQ | Low | Medium | High | ULOQ |
| | (0.50 ng/mL) | (1.51 ng/mL) | (60.21 ng/mL) | (150.53 ng/mL) | (200.51 ng/mL) |
| **Precision[a]** | | | | | |
| Intra-assay CV | 2.36%-14.09% | 4.75%-7.04% | 2.03%-4.38% | 3.41%-6.22% | 2.88%-4.11% |
| Inter-assay CV | 8.32% | 5.33% | 4.32% | 3.94% | 3.95% |
| **Accuracy[a]** | | | | | |
| Intra-assay CV | 4.00%-6.40% | -1.46%-4.11% | -6.76%-0.84% | -7.26%-5.67% | -3.87%-0.75% |
| Inter-assay CV | 4.87% | 0.75% | -2.70% | -6.00% | -2.03% |
| **Stability of plasma sample[a]** | | | | | |
| At -20°C (stable until 75 days) | - | -2.25%-12.19% | - | -7.26%-14.91% | - |
| At room temperature (≤ 30°C, stable until 23 hours) | - | 2.38%-4.11% | - | -7.26%-3.27% | - |
| Freeze and thaw (stable until 4 cycles at -20 °C ± 5°C) | - | 4.11%-12.19% | - | -7.26%-14.91% | - |
| **Linearity** | | | | | |
| The linearity of the standard calibration curves was obtained (r=0.9993 for run 1, r=0.9993 for run 2, r=0.9990 for run 3) | | | | | |
| **LLOQ** | | | | | |
| The LLOQ has been established at 0.50 ng/mL | | | | | |
| **Selectivity** | | | | | |
| The % interference in the retention time of analyte and internal standard in 8 lots blank plasma with $K_3$EDTA as the anticoagulant (comprising of 6 normal, 1 hemolysis, and 1 lipemic) were 0.00% for analyte and internal standard | | | | | |
| **Range** | | | | | |
| The range of quantification has been established from 0.50 ng/mL to 200.65 ng/mL | | | | | |

**Note:** [a]Shown by the difference between measured and actual values (% difference).

**Abbreviations:** CV: Coefficient of Variation; LLOQ: Lower Limit of Quantification; UPLC-MS/MS: Ultra-Performance Liquid Chromatography with Tandem Mass Spectrometry.

**Table 2:** Demographic characteristics data shown as mean ± SD (range), unless otherwise specified.

| Characteristics | Number of subjects (n=24) |
|---|---|
| Age (years) | 31.46 ± 7.73 (19-44) |
| **Gender** | |
| Male, n(%) | 17 (70.83%) |
| Female, n(%) | 7 (29.17%) |
| Body weight (kg) | 58.13 ± 7.71 (43-69) |
| Body height (cm) | 161.88 ± 7.13 (147-175) |
| BMI (kg/m$^2$) | 22.14 ± 2.25 (18.61–24.98) |
| **Smoke** | |
| Non-smoker, n(%) | 16 (66.67%) |
| Smoke <10 cig./day | 8 (33.33%) |

**Note:** Data shown as mean ± SD (range), unless otherwise specified.

**Table 3:** Pharmacokinetic parameters and statistical comparison of Dapagliflozin after single-dose oral administration of test or reference formulation in healthy subjects (N=22) under fasting conditions.

| Parameter | Test product mean (SD) | Reference mean (SD) | Geometric mean ratio of T/R (90% CI)[a] | % CV | Power |
|---|---|---|---|---|---|
| $C_{max}$ (ng/mL)[b] | 83.07 (30.34) | 80.29 (17.92) | 100.89% (89.72%-113.46%) | 22.87% | 93.20% |
| $AUC_{0-t}$ (ng.h/mL)[b] | 601.72 (174.46) | 606.64 (176.24) | 99.21% (96.47%-102.04%) | 5.41% | 100.00% |
| $AUC_{0-\infty}$ (ng.h/mL)[b] | 620.87 (180.38) | 626.15 (182.05) | 99.17% (96.35%-102.08%) | 5.56% | - |
| $t_{1/2}$ (h) | 10.50 (2.64) | 10.53 (2.69) | NS[d] | - | - |
| $T_{max}$ (h)[c] | 2.00 (0.50–8.00) | 2.00 (1.00–6.00) | NS[e] | - | - |

**Note:** [a]Bioequivalence criterion defined as 90% CI of the GMR of the test formulation/reference drug is between 80.00% and 125.00% for $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$; [b]Statistical calculations for AUC and $C_{max}$ were based on log-transformed data; [c]The values are expressed as median (range); d analysis was performed using the Student's paired t-test; e analysis was performed using the Wilcoxon matched-pairs test.

**Abbreviations:** AUC: Area Under the Plasma Concentration-Time Curve; $AUC_{0-t}$: AUC from Time Zero to the Last observed Quantifiable Concentration; $AUC_{0-\infty}$: AUC Time Zero to Infinity; $C_{max}$: the Maximum Plasma Concentration; CI: Confidence Interval; CV: Coefficient of Variation; NS: Not Significant; R: Reference Formulation; SD: Standard Deviation; T: Test Formulation; $t_{1/2}$: Terminal Half-life; $T_{max}$: Time to $C_{max}$.

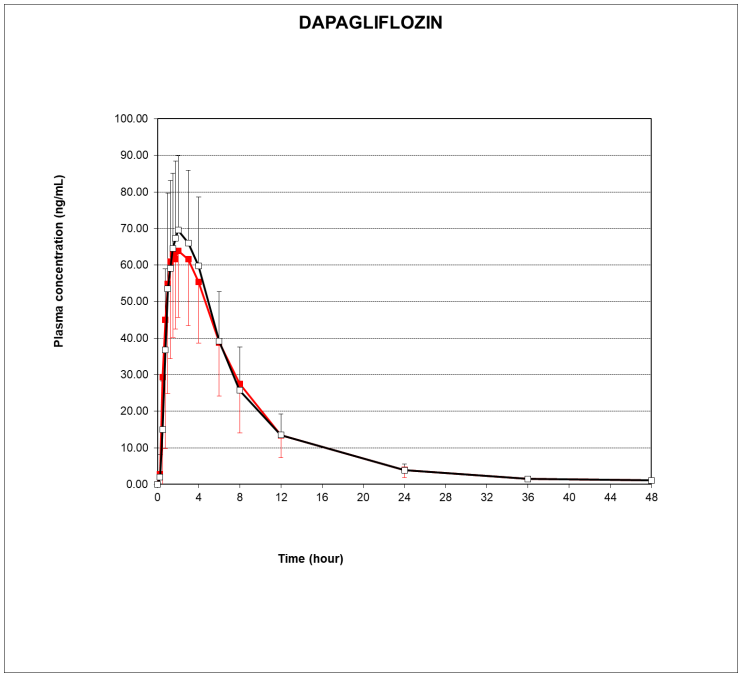


**Figure 1:** The Dapagliflozin mean plasma-time concentration profile (N=22) after a single oral dose of the test drug, Dapagliflozin film-coated tablet 10 mg (PT Dexa Medica, Palembang, Indonesia) and the reference drug, Forxiga® film-coated tablet (AstraZeneca Pharmaceuticals LP, USA for AstraZeneca Pharmaceuticals Co. Ltd., China Imported by PT AstraZeneca Indonesia, Indonesia)-linear scale. **Note:** ( ) Dapagliflozin 10 mg FC Tablet; ( ) Forxiga® 10 mg FC Tablet.TMM

## DISCUSSION

This study evaluated the pharmacokinetic profile of a generic formulation of Dapagliflozin 10 mg film-coated tablet compared with the reference drug. Confirming the bioequivalence of a generic medicine with its reference drug justifies the comparability or similarity of the generic medicinal product's quality, pharmacological properties, therapeutic efficacy, and safety profile with those of the reference. A bioequivalent result implies that the generic drug is acceptable as an alternative to the reference product with a more economical approach with the former's lower drug cost. High prescription drug cost has prompted cost-related medication non-adherence, as reported in 1 in 5 older adult patients [18]. Thus, generic medications might promote patient adherence to treatment by minimizing out-of-pocket medical treatment expenses, supporting the application of pharmacoeconomics principles. A cross-sectional survey study conducted among physicians in India further supports generic Dapagliflozin as an effective and cost-saving therapeutic option for patients with type II diabetes mellitus and its complications [19].

One generic Dapagliflozin was approved for marketing in Europe by the European Medicines Agency (EMA) in March 2023 and Canada (May 2023). As of October 2023, the United States Food and Drug Administration (USFDA) has not authorized a generic version of Dapagliflozin. In Indonesia, Dapagliflozin has just been recently introduced in 2022; thus, information on the pharmacokinetics of Dapagliflozin in Indonesian subjects is

relatively limited. A generic version of Dapagliflozin produced in India has been available in Indonesia since July 2023. This current study compared the pharmacokinetics and evaluated the bioequivalence of another generic version of Dapagliflozin 10 mg film-coated tablet formulation, which is manufactured by PT Dexa Medica, Indonesia, and the reference drug, Forxiga® 10 mg film-coated tablet (AstraZeneca Pharmaceuticals LP, USA), under fasting condition in healthy Indonesian subjects.

The study was initially planned to be conducted on 24 healthy subjects based on the intra-subject Coefficient Variation (CV) from the previous pilot study, 21.91% (report not published). The intra-subject CV result obtained from the dapagliflozin $AUC_{0-t}$ was 5.41%. Thus, the 22 subjects who completed the study were considered acceptable to ensure the study had adequate power to confirm statistical conclusions. The statistical power of $AUC_{0-t}$ obtained from the study was 100.00%, as presented in (Table 3).

Oral dapagliflozin may be administered with or without food as the pharmacokinetics are not affected by food to a clinically significant extent [4]. Therefore, according to the European Medicines Agency (EMA) Guideline on The Investigation of Bioequivalence study [16], this study was appropriate for fasting.

Our present study found that both the Test and Reference drug demonstrated highly similar pharmacokinetic profiles, resulting in a GMR and its 90% CI of both $AUC_{0-t}$ and $C_{max}$ that were within the bioequivalence acceptance range (80% to 125%). The results confirmed that both dapagliflozin formulations are bioequivalent in both rate and extent of absorption after being administered in a single-dose fashion under fasting conditions. A similar conclusion can be derived for $AUC_{0-\infty}$, as seen in our study result, even though it is unnecessary to demonstrate bioequivalence with this parameter [16].

The measurement of $C_{max}$ directly from data without interpolation represents the absorption rate of the drug investigated, while $AUC_{0-t}$ and $AUC_{0-\infty}$ are the indicators for the extent of absorption [20]. Based on the publicly available literature on the reference drug, it is known that after an oral administration of Dapagliflozin, it generally attains a maximum plasma concentration within 2 hours under a fasting state with an absolute oral bioavailability of 78% and has a dose-proportional increase in $C_{max}$ and AUC in the therapeutic dose range. Dapagliflozin is extensively metabolized into yielding its primary inactive metabolite, Dapagliflozin 3-O-glucuronide, and is mainly eliminated through the kidney [4]. Aligned with that, our present study demonstrated that the tested generic oral formulation reached the $C_{max}$ by 2.00 (0.50-8.00) hours under fasting state, similar to the reference used in the study, 2.00 (1.00-6.00) hours.

The half-life ($t_{1/2}$) of oral dapagliflozin 10 mg film-coated tablet in our study was reported to be 10.50 ± 2.65 hours and 10.53 ± 2.69 hours for the test formulation and the reference drug, respectively. The values slightly differ from the findings in the literature, which is 12.9 hours [4]. Another bioequivalence study of Dapagliflozin 10 mg reported a $t_{1/2}$ of 8.52 hours and 8.85 hours for the test and reference drug, respectively [21]. However, the $t_{1/2}$ values in our study did not differ statistically between formulations, supporting that the test and reference formulations had a comparable rate of drug elimination from the body.

None of the study subjects reported adverse events, reflecting that both formulations were well tolerated. Dapagliflozin is generally considered well tolerated, with a low risk of hypoglycemia and drug-class-related adverse events [1]. Dapagliflozin's most commonly reported adverse effects (with 5% or higher incidence) were female genital mycotic infections, nasopharyngitis, and urinary tract infections [1].

In Indonesia, our formulation of dapagliflozin 10 mg film-coated tablets was the first locally manufactured generic version. The bioequivalence result of this study serves as bridging evidence to safely perceive that the clinical benefits of our generic dapagliflozin tablets are equivalent to the reference used in the study, which is the originator dapagliflozin. Both formulations may be used interchangeably in clinical settings, with the generic formulation providing a more economical option in treating type II diabetes mellitus patients with cardiovascular or renal complications prescribed with Dapagliflozin.

## CONCLUSION

This study concluded that the formulation of Dapagliflozin film-coated tablet 10 mg (PT Dexa Medica) was bioequivalent to the reference drug, Forxiga® film-coated tablet 10 mg (AstraZeneca Pharmaceuticals LP, USA, for AstraZeneca Pharmaceuticals Co. Ltd., China Imported by PT AstraZeneca Indonesia, Indonesia) in healthy Indonesian subjects. Additionally, no adverse event was reported in the study, indicating that the subjects safely tolerated both test and reference formulations. Altogether, the results support the use of the tested Dapagliflozin film-coated tablet 10 mg as an alternative generic to the reference drug in the treatment of type II diabetes mellitus.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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PT Dexa Medica funded the whole study. The development of study protocol and design, and all technical, clinical and analytical execution of the bioequivalence studies were performed independently by PT Equilab International, Indonesia, an internationally acknowledged Bioequivalence Laboratory, without the interference of the study sponsor. RRT, LWS, CN are employees of PT Dexa Medica, and were involved in drafting and reviewing the study manuscript.

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## REFERENCES

1. Dhillon S. Dapagliflozin: A review in type 2 diabetes. Drugs. 2019;79(10):1135-1146.
2. Wilding J, Fernando K, Milne N, Evans M, Ali A, Bain S, et al. SGLT2 inhibitors in type 2 diabetes management: Key evidence and implications for clinical practice. Diabetes Ther. 2018;9:1757-1773.
3. European Medicines Agency (EMA) Forxiga. 2023.
4. FARXIGA (Dapagliflozin) tablets, for oral use. 2023
5. Nicholson MK, Ghazal Asswad R, Wilding JP. Dapagliflozin for

the treatment of type 2 diabetes mellitus-an update. Expert Opin Pharmacother. 2021;22(17):2303-2310.

6. Palmer SC, Tendal B, Mustafa RA, Vandvik PO, Li S, Hao Q, et al. Sodium-Glucose Cotransporter Protein-2 (SGLT-2) inhibitors and Glucagon-Like Peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. Bmj. 2021;372.

7. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347-357.

8. Ma CX, Ma XN, Guan CH, Li YD, Mauricio D, Fu SB. Cardiovascular disease in type 2 diabetes mellitus: Progress toward personalized management. Cardiovasc Diabetol. 2022;21(1):74.

9. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018;17(1):1-9.

10. de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes Management in Chronic Kidney Disease: A Consensus Report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). Diabetes Care. 2022;45(12):3075.

11. Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. Jama. 2016;316(6):602-610.

12. Lydia A, Suastika K, Martosuwignjo P, Sibarani RP, Nasution SA, Sulistijo SA. Early recognition of type 2 diabetes complications and use of SGLT2i in multidisciplinary approach: Indonesian perspective-an Expert opinion. Acta Med Indones. 2022;54(4):653-663.

13. Adhikari R, Jha K, Dardari Z, Heyward J, Blumenthal RS, Eckel RH, et al. National trends in use of sodium‐glucose cotransporter‐2 inhibitors and glucagon‐like peptide‐1 receptor agonists by cardiologists and other specialties, 2015 to 2020. J Am Heart Assoc. 2022;11(9):023811.

14. Alkabbani W, Gamble JM. Prescribing trends of the Sodium-Glucose Cotransporter-2 Inhibitors among different physician specialties in Canada (2015-2021). Can J Diabetes. 2023;47(2):153-161.

15. Inoue D, Nishi H, Inoue R, Nangaku M. Regional distribution of cardiologists and prescription patterns of sodium-glucose transporter-2 inhibitors in Japan. Int Heart J. 2021;62(3):592-600.

16. European Medicines Agency. Guideline on the investigation of bioequivalence. Committee for Medicinal Products for Human Use (CHMP). 2010.

17. Dixon W, Massey F. Introduction to Statistical Analysis. New York: McGraw-Hill. 1983.

18. Dusetzina SB, Besaw RJ, Whitmore CC, Mattingly TJ, Sinaiko AD, Keating NL, et al. Cost-Related medication nonadherence and desire for medication cost information among adults aged 65 Years and older in the US in 2022. JAMA Netw Open. 2023;6(5):2314211.

19. Sharma K, Chandorkar AB, Kovil R, Venkataraman S, Subrahmanyam KA, Mandal P, et al. Expert opinion about the pharmacoeconomic edge of low-cost dapagliflozin in type 2 diabetes mellitus in Indian clinical settings. Cureus. 2021;13(11).

20. Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an Abbreviated New Drug Application. 2021.

21. Kalra S, Bhattacharya S. Bioequivalence study of two different dapagliflozin tablet formulations in healthy adult Indian volunteers. J Diabetol. 2022;13(3):235-41.