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Bioequivalence study of abacavir 300 mg tablets in healthy Thai male volunteers under fasting conditions

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Abstract

Abacavir is an antiretroviral drug that can be prescribed in single dose or in fixed-dose combination formulations to make adherence easier. Due to this advantage, a generic product of abacavir of GPO has been developed with lower price and would be benefit for HIV patients. A comparative randomized, single dose, two-way crossover, open-label bioequivalence study of the generic abacavir, Abacavir GPO 300 mg tablets, and the reference, Ziagenavir™ 300 mg tablets, after oral administration to 50 healthy, Thai volunteers under fasting conditions with 7 days washout period was carried out. Blood samples were collected at predefined time points up to 12 hours. Plasma concentrations of abacavir were analyzed using a validated liquid chromatography tandem mass spectrometry. Non-compartmental model was used for pharmacokinetic analysis. The mean values (± SD) of pharmacokinetic parameters (test vs. reference) were $AUC_{0\text{-tlast}}$ (7114.645 ± 1701.7843 vs 6878.453 ± 1553.6328 ng.hr/mL), $AUC_{0\text{-}\infty}$ (7161.443 ± 1713.3557 vs 6923.175 ± 1566.9145 ng.hr/mL) and C_{max} (3238.786 ± 1075.6341 vs 3181.232 ± 1072.4422 ng/mL). The 90 % confidence intervals for the ratios of mean $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} for the test/reference were 103.1 (100.83-105.51), 103.2 (100.84-105.53) and 101.3 (94.05-109.03), respectively. These values were within the acceptable range of 80.00-125.00. Both the formulations were well tolerated. No clinically significant or serious ADRs were observed. By conclusion, two formulations of abacavir, Abacavir GPO and Ziagenavir™, were bioequivalent and can be used interchangeably.

Keywords: Abacavir, Bioequivalence, Pharmacokinetics, Liquid chromatography tandem mass spectrometry

Introduction

Antiretroviral therapy (ART) regimens which use to treat Human Immunodeficiency Virus (HIV) infection usually consist of three or more different drugs used in combination include Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs) and Integrase Strand Inhibitors (InSTIs). Abacavir is a synthetic carbocyclic 2′-deoxyguanosine nucleoside reverse transcriptase inhibitor analogue as shown in Figure 1 [1]. Abacavir is available in a single-agent formulation that can be prescribed once or twice daily and in fixed-dose combination formulations containing Lamivudine or Zidovudine allowing regimens with the fewest number of pills to make adherence easier [2]. Abacavir is rapidly absorbed after single oral dose

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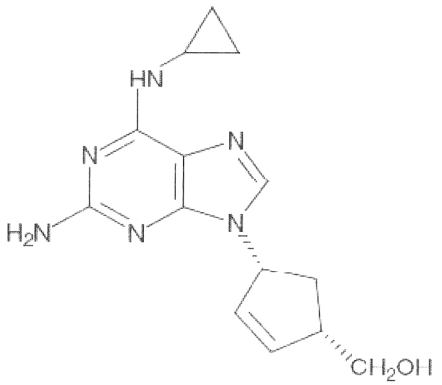

Figure 1 Chemical structure of abacavir

administration with absolute bioavailability in excess of 80 % [3]. A time to maximum plasma concentration (t_{max}) occurring around 0.63 - 1 hour after dosing and C_{max} are 4.10 - 5.46 μg/mL after single 600 mg tablets and 2.39 - 3.11 μg/mL after single 300 mg tablets [1]. Abacavir can be administered with or without food because the total amount of absorbed in the fed state is same as in the fasting state [1]. The apparent volume of distribution (Vd) is 0.86 ± 0.15 L/kg after intravenous administration and almost 50 % is bound to plasma proteins [1]. Abacavir is extensively metabolized by the liver via 2 pathways, by Uridine diphosphate glucuronyltransferase (UGT) and Alcohol dehydrogenase (ADH) enzymes, less than 2 % is excreted as unchanged in the urine, therefore no dosage adjustments are required for patients with renal dysfunction.

Due to the advantages of abacavir in formulation and dosing regimen, a generic product of abacavir of The Government Pharmaceutical Organization (GPO) has been developed with lower price and would be benefit for HIV patients. Consequently, the bioequivalence study is conducted to demonstrate the interchangeability between the generic abacavir and the reference product.

Materials and Methods

Drugs: The test product (Abacavir GPO 300 mg tablets) was manufactured from GPO (Batch number S540417, Manufactured on 13 Dec 2011, Expiry date 13 Dec 2013). The reference product (Ziagenavir™ 300 mg tablets) was manufactured by Glaxo Wellcome Operations, Ware, UK (Batch number R544339, Manufactured on 20 Apr 2011, Expiry date 19 Apr 2014).

Study design: This study was designed as comparative randomized, single dose, two-way crossover, open-label study to determine the bioequivalence of abacavir formulation, Abacavir GPO 300 mg tablets, and Ziagenavir™ 300 mg tablets, after oral administration to healthy, Thai volunteers under fasting conditions. Washout period was at least 7 days between treatments. The study protocol was approved by Institute for the Development of Human Research Protections (IHRP).

Study subjects: 50 subjects, randomly selected from healthy adult Thai male volunteers were participated in this study. Subjects must satisfy the inclusion criteria to be enrolled in the study such as age between 18-55 years and Body Mass Index (BMI) between 18-25 kg/m^2. All subjects were determined healthy judged from medical history, physical examination and laboratory examination (complete blood count, hematocrit, hemoglobin, fasting blood sugar, blood urea nitrogen (BUN), serum creatinine, alkaline phosphatase, ALT, AST, total bilirubin, total protein, albumin, hepatitis B test, urine analysis and ECG). The exclusion criteria included history of hypersensitivity to abacavir or any of the excipients, history of medical sickness (like gastrointestinal, hepatic, renal, cardiovascular, diabetes mellitus, and gallstone disease), clinically significant illness within 4 weeks before the start of the study, asthma, urticaria or other allergic type reactions, alcohol dependence or drug abuse, participation in any other clinical trial involving drug administration and collection of blood samples or donation blood in the preceding 1 month prior to the start of the study, and positive HLA-B*5701 allele. The subjects were informed about risks and benefits of the study and signed informed consent before participating into the study.

Blood sampling: Blood samples were collected through the indwelling intravenous cannula for 21 sampling times (0, 0.083, 0.167, 0.250, 0.333, 0.500, 0.667, 0.833, 1.000, 1.250, 1.500, 1.750, 2.000, 2.500, 3.000, 4.000, 5.000, 6.000, 8.000, 10.000, and 12.000 hours). The blood samples were centrifuged at 3000 ± 100 rcf for 5 minutes below 10 °C to separate plasma. All plasma samples were transferred to pre-labeled polypropylene tubes and stored upright frozen at -65 ± 10 °C until analysis.

Table 1 Mean pharmacokinetic parameters of abacavir of the test and the reference product

Parameters	Test product (Mean ± SD)	Reference product (Mean ± SD)
$AUC_{0\text{-}tlast}$ (ng.hr/mL)	7114.645 ± 1701.7843	6878.453 ± 1553.6328
$AUC_{0\text{-}\infty}$ (ng.hr/mL)	7161.443 ± 1713.3557	6923.175 ± 1566.9145
C_{max} (ng/mL)	3238.786 ± 1075.6341	3181.232 ± 1072.4422
t_{max} (hr)	0.708 ± 0.4051	0.631 ± 0.4048
λ_z (1/hr)	0.454 ± 0.0677	0.447 ± 0.0731
$t_{1/2}$ (hr)	1.570 ± 0.3136	1.600 ± 0.3306

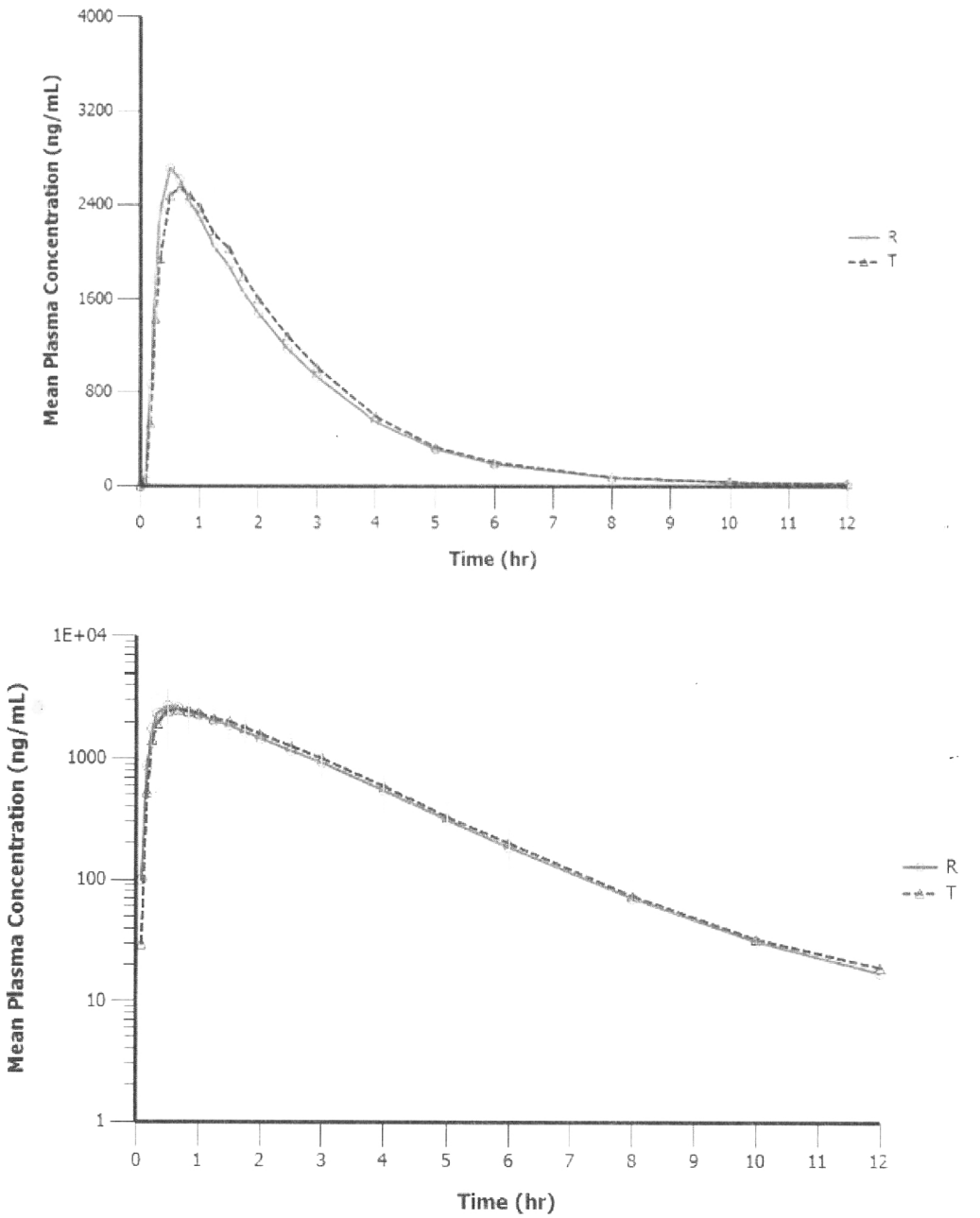

Figure 2 The mean plasma concentration-time profiles of abacavir and their semi-log scale plots

Analytical procedure: The plasma-concentrations of abacavir in study samples were determined by a validated LC-MS/MS method using abacavir-d4 as the internal standard. The analyte and internal standard were extracted from plasma using protein precipitation method which validated follow The US FDA guidance for industry, bioanalytical method validation and the European Medicines Agency guideline and monitored in the positive ion mode by applying ESI probe using the MRM transitions of m/z 287.090→191.090 for abacavir and m/z 291.114→195.090 for internal standard. The chromatographic system consisted of ACE 5 Phenyl 150 x 4.6 mm column maintained at 40 °C using an isocratic mobile phase system composed of 70 % acetonitrile and 30 % of 2 mM ammonium formate buffer (pH 4.5).

Pharmacokinetic analysis: The pharmacokinetic parameters ($AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, λ_z and $t_{1/2}$) were determined by non-compartmental model using Phoenix WinNonlin Software Version 6.3. Values below lower limit of quantification (5.090 ng/mL) were set as zero for calculation purposes.

Statistical analysis: The statistical analysis was conducted using PROC GLM of SAS® Version 9.3. The primary pharmacokinetic parameters ($AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max}) were transformed to natural logarithm scale (ln) before statistical analysis. Bioequivalence of Test product - T vs. Reference product - R was concluded, if the 90 % confidence interval of ratio of geometric least square means fell within the acceptance range of

Table 2 90 % Confidence interval for the ratios of mean $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max}

Parameters	Ratio of Geometric Least Square Mean	90 % Confidence Interval
$AUC_{0\text{-tlast}}$	103.1	100.83 - 105.51
$AUC_{0\text{-}\infty}$	103.2	100.84 - 105.53
C_{max}	101.3	94.05 - 109.03

80.00 - 125.00 % for ln-transformed pharmacokinetic parameters $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} of abacavir.

Results and Discussion

Fifty healthy, adult, male human subjects with a mean age (± SD) of 29.20 ± 7.44 years with a range of 18 to 49 years and a mean body mass index (BMI) of 21.78 ± 1.81 kg/m^2 with a range of 18 to 24 kg/m^2 were enrolled in the study. Forty-six subjects were used for pharmacokinetic and statistical analysis. Both the test and the reference products were well tolerated. No clinically significant or serious ADRs were observed.

The linear and semi-logarithmic plots of mean plasma concentration versus time after administration of test and reference products of abacavir are shown in Figure 2. The pharmacokinetic parameters including $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max}, λ_z and $t_{1/2}$ of both the test and the reference products are shown in Table 1. The extent of absorption reported as $AUC_{0\text{-tlast}}$ was 7114.645 ± 1701.7843 and 6878.453 ± 1553.6328 ng.hr/mL for the test and the reference products, respectively. $AUC_{0\text{-}\infty}$ was 7161.443 ± 1713.3557 and 6923.175 ± 1566.9145 ng.hr/mL for the test and the reference products, respectively. The rate of absorption reported as C_{max} was 3238.786 ± 1075.6341 and 3181.232 ± 1072.4422 ng/mL for the test and the reference products, respectively. The 90 % confidence intervals for the ratios of mean $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} for the Test/Reference were 103.1 (100.83 - 105.51), 103.2 (100.84 - 105.53) and 101.3 (94.05 - 109.03), respectively as shown in table 2. The 90 % Confidence Interval of $AUC_{0\text{-tlast}}$, $AUC_{0\text{-}\infty}$ and C_{max} were within the bioequivalence range of 80.00 - 125.00, indicating that the test product and the reference product were bioequivalent.

Conclusions

In summary, this study has demonstrated that the test product (Abacavir GPO 300 mg tablets) when compared with the reference product (Ziagenavir™ 300 mg tablets) met the bioequivalence criteria with respect to the rate and extent of absorption of abacavir. Both the test and the reference products were well tolerated. Thus, interchangeability between the generic abacavir and the reference product is confirmed.

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