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Single-Dose Bioequivalence of a New Fixed-Dose Combination Tablet Containing Tenofovir Disoproxil Fumarate and Lamivudine

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Abstract

Tenofovir Disoproxil Fumarate, CAS 147127-20-6 is a nucleotide reverse transcriptase inhibitor with potent activity against both HIV and hepatitis B infections. Lamivudine, CAS 134678-17-4 is a nucleoside analogue reverse transcriptase inhibitor developed as a treatment for HIV infection and also with activity against hepatitis B virus. The combination of tenofovir and lamivudine associated either with non-nucleoside reverse transcriptase inhibitors or with a ritonavir-boosted or unboosted protease inhibitor are recommended as preferred regimens for antiretroviral therapy-naïve patients infected with HIV, and also for the treatment of HIV-HVB coinfected patients. The objective of this study was to compare rate and extent of absorption and to assess the bioequivalence between a new pharmaceutical equivalent tablet formulation containing a fixed-dose combination of tenofovir disoproxil fumarate/ lamivudine 300/300 mg and the innovator products. A randomized, single-center, open-label, single-dose, two-way crossover bioequivalence study in 40 healthy adult subjects was conducted. Dosing was separated by a wash-out period of 14 days. All subjects signed an informed consent form. In each study period, 13 blood samples were collected in Vacutainers containing EDTA over 48 h. Plasma levels of tenofovir and lamivudine were determined by a validated HPLC/fluorescence assay and by a validated HPLC/UV assay, respectively. Rate and extent of absorption were similar between products. The 90% confidence interval(CI) of the ratio of the geometric means for log-transformed C_{max}, AUC_{last} and AUC_{inf} values were used to assess bioequivalence between the two formulations using the equivalence interval of 80 and 125%. In healthy subjects, the point estimate and 90 % C_I of the ratios of C_{max}, AUC_{last} and AUC_{inf} values for tenofovir were 100.99%(92.89-109.80%), 96.11%(90.02-102.63%) and 94.73%(88.22-101.73%), respectively; and for lamivudine were 90.37%(83.76-97.50%), 97.02%(93.27-100.93%) and 97.04%(93.41-100.82%), respectively. Both treatments exhibited similar tolerability and safety. It was concluded that the new pharmaceutical formulation was bioequivalent to the innovators.

Keywords: Bioequivalence; tenofovir; lamivudine; fixed-dose combination; healthy volunteers

Introduction

Tenofovir disoproxil fumarate (TDF) is a nucleotide analog reverse transcriptase inhibitor orally bioavailable as an ester-derived prodrug which requires diester hydrolysis for conversion to tenofovir (TFV) and subsequent intracellular phosphorylations by cellular enzymes to the active metabolite, tenofovir diphosphate, which is a competitive inhibitor of HIV-1 reverse transcriptase, leading to the prevention of DNA chain elongation and termination of viral DNA growth [1,2]. TDF was approved by the Food and Drug Administration (FDA) in October 2001 and is indicated for use in combination with other antiretroviral agents for the management of HIV-1 infection. TFV has also activity against hepatitis B infection and has been approved in 2009 as the first-line option in the treatment of hepatitis B [3,4]. The pharmacokinetic (PK) of TFV following oral administration of 300 mg has been well characterized in HIV-infected and healthy adults subjects. After oral administration of 300 mg, TFV concentrations increase over 1 to 3 h (T_{max}) with a maximum concentration (C_{max}) of approximately 300 ng/ml and a mean area under the plasma concentration-versus-time curve (AUC) at steady state of approximately 3000 ng*h/ml is observed [5,6]. When administered with a high fat meal (700-1000 calories containing 40-50% fat), TFV AUC and Cmax are increased by 40% and 14 %, respectively. TFV is primarily cleared unchanged in the urine by a combination of glomerural filtration and active tubular secretion. The once-daily dosing schedule is supported by TFV serum elimination half-life of 12 to 17 h and the long half-life of the intracellular metabolite between 10 to 50 h [7].

Lamivudine (3TC) is a nucleoside analogue developed as a treatment for HIV infection. It has also activity against hepatitis B virus (HBV). Intracellular, lamivudine is phosphorylated to its active metabolite, lamivudine 5`-triphosphate (3TC-TP) which prevents HIV-1 and HBV replication by competitively inhibiting viral reverse transcriptase via DNA chain termination after incorporation of the nucleotide analogue The pharmacokinetics of 3TC are similar in patients with HIV-1 or HVB infection, and healthy volunteers [8]. Following oral administration, 3TC is well absorbed from the gastrointestinal tract, being the bioavailability in adults between 80 and 85 %, and the mean time (T_{max}) to maximal serum concentrations (C_{max}) about an hour. Based on data derived from a study in healthy volunteers, at a therapeutic dose of 150 mg twice daily, mean steady-state C_{max} and 12h AUC in plasma are 1200 ng/ml and 4700 ng*h/ml, respectively. Lamivudine systemic exposure (based on the AUC) is not influenced when it is administered with food and is widely distributed into total body fluid being predominately eliminated

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