Pharmacokinetic Properties of Single-Dose Lamivudine/Adefovir Dipivoxil Fixed-Dose Combination in Healthy Chinese Male Volunteers

Benny S. P. Fok, PhD[1]; Stephen Gardner, MSPH[2]; Steve Piscitelli, PharmD[3]; Shuguang Chen, PhD[4]; Tanya T. W. Chu, PhD[1]; Jones C. M. Chan, MBChB[5]; and Brian Tomlinson, MD[1]

[1]Division of Clinical Pharmacology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong SAR; [2]Clinical Development Department, GlaxoSmithKline, Research Triangle Park, North Carolina; [3]Clinical Pharmacology Department, GlaxoSmithKline, Research Triangle Park, North Carolina; [4]Statistics Department, GlaxoSmithKline, Research Triangle Park, North Carolina; and the [5]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong SAR

ABSTRACT

Background: Both lamivudine and adefovir dipivoxil are approved for the treatment of chronic hepatitis B (CHB) and have established safety profiles. A fixed-dose combination (FDC) formulation of lamivudine/adefovir dipivoxil for the treatment of CHB may provide dosing convenience and improve adherence.

Objective: This study compared the pharmacokinetic profiles of an FDC capsule containing lamivudine/adefovir dipivoxil 100/10 mg and conventional lamivudine 100-mg + adefovir dipivoxil 10-mg tablets to determine bioequivalence.

Methods: This randomized, open-label, single-dose, 2-period crossover study was conducted in healthy male Chinese subjects. The study included a screening visit, 2 treatment sessions, and a follow-up visit. Subjects who met the inclusion/exclusion criteria were assigned to receive, in randomized order, 1 FDC capsule or 1 tablet each of lamivudine and adefovir dipivoxil. After a 7- to 10-day washout period, alternate treatment was given to the subjects during the second treatment session. Blood samples were collected immediately before and after dosing for 48 hours for plasma drug concentration measurement. Data on adverse events (AEs) were collected from the start of dosing until the follow-up visit. Tolerability assessments included physical examinations with vital sign measurements and clinical laboratory evaluations throughout the study.

Results: Forty subjects were enrolled into the study (mean age, 22.4 years [range, 19–28 years]; weight, 63.8 kg [range, 54–78 kg]). The pharmacokinetic profiles of lamivudine and adefovir were similar between the FDC and reference formulations. The geometric mean ratios (GMRs) for lamivudine C_{max} and AUC_{0-last} were 1.02 (90% CI, 0.92–1.12) and 0.99 (90% CI, 0.95–1.04), respectively; adefovir, 0.94 (90% CI, 0.89–0.99) and 0.95 (90% CI, 0.91–1.00). A limited number of mild AEs were reported, with no clinically significant changes in vital signs or laboratory results.

Conclusions: The FDC capsule was bioequivalent to the concurrent administration of lamivudine + adefovir dipivoxil tablets based on the 90% CIs of the GMRs for C_{max}, $AUC_{0-\infty}$, AUC_{0-last}, and $t_{1/2}$ (all were between 0.80 and 1.25). Both treatments were well-tolerated. Clinicaltrial.gov identifier: NCT01353742. (*Clin Ther*. 2013;35:68–76) © 2013 Elsevier HS Journals, Inc. All rights reserved.

Key words: adefovir dipivoxil, bioequivalence, fixed-dosed combination, lamivudine, pharmacokinetics.

INTRODUCTION

Chronic hepatitis B (CHB) is a common infection affecting > 400 million people, ~5% of the world's population.[1] Chronic hepatitis B virus (HBV) carriers are the major contributors to the spread of HBV infection and they are at a heightened risk for active liver inflam-

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mation (ie, hepatitis B) and progressive liver diseases.[2–4] The goals of therapy in CHB include suppression of HBV replication, reduction of necroinflammatory processes in the liver, and prevention of progression to serious liver diseases.

Lamivudine was the first oral nucleoside analogue approved by the US Food and Drug Administration for the treatment of CHB. The (–) enantiomer of 2′-3′dideoxy-3′-thiacytidine, lamivudine is highly soluble and rapidly absorbed when administered orally. In Phase I research in healthy adults,[5] its absorption was not reported to have been affected by food intake, and it exhibited a linear, dose-dependent pharmacokinetic profile, with a bioavailability of ~ 82% and a T_{max} of 0.5 to 1.5 hours. Approximately 5% to 10% of the ingested dose was metabolized to an inactive compound, with ~70% of the parent drug being excreted unchanged in the urine. Lamivudine had a $t_{1/2}$ of ~5 to 7 hours.

One drawback of treating CHB with lamivudine is that the prevalence of viral resistance is high. The error rate of HBV polymerase is intermediate— between those of HIV and herpes virus polymerases[6]—and studies of long-term monotherapy reported that at 1 and 4 years, lamivudine resistance had developed in up to 24% and 70% of patients, respectively,[7] and that therapeutic responses were variably diminished.[8–13]

Adefovir dipivoxil has been considered an alternative CHB treatment to lamivudine. Adefovir dipivoxil is an orally bioavailable prodrug of adefovir, a nucleotide analogue of adenosine monophosphate that has also been approved for the treatment of CHB. It is rapidly hydrolyzed to adefovir in the gastrointestinal tract. In Phase I research in healthy adults,[14] the absorption of adefovir was reported to have been unaffected by food intake, and bioavailability was ~59%. Less than 10% of the ingested dose was metabolized to inactive compound, with >90% of the parent drug being excreted unchanged in the urine. Adefovir had a reported T_{max} of 1 to 2 hours and a $t_{1/2}$ of ~6 to 7 hours. Adefovir dipivoxil has been considered an alternative treatment to lamivudine because it is effective not only in nucleoside analogue–naive patients but also in those with lamivudine resistance.[15–18] However, in patients who were switched from lamivudine to adefovir dipivoxil, markedly increased resistance to adefovir dipivoxil was reported in 18% of patients after 1 year of treatment.[4] In contrast, with lamivudine + adefovir dipivoxil combination therapy, the emergence of resistance to adefovir dipivoxil was uncommon at up to 3 years.[19] As a result, combination therapy with lamivudine + adefovir dipivoxil is preferred over switching from one monotherapy to the other. Recent studies have reported that the administration of combination therapy with lamivudine + adefovir dipivoxil might result in lower rates of resistance, a lower prevalence of viral DNA in serum, and higher rates of alanine aminotransferase normalization among patients with CHB who are nucleoside treatment naive and lamivudine resistant.[20–22] In vitro studies have reported that adefovir dipivoxil was effective in suppressing wild-type and lamivudine-resistant HBV,[23] and clinical studies have reported that patients with genotypic resistance to lamivudine experienced virologic improvement, as evidenced by lower serum HBV DNA levels, when treated with a combination of lamivudine + adefovir dipivoxil.[19,24–26]

A fixed-dosed combination (FDC) capsule of lamivudine/adefovir dipivoxil 100/10 mg is being developed to combine the established benefits of these 2 anti-HBV medications. This combination has consistently been reported as generally well tolerated in clinical practice. In previous studies, when the combination was administered to 509 patients with CHB for medians of 12 to 53 months, a small portion of patients (0%–7%) had their doses of adefovir dipivoxil reduced due to clinically significant adverse events (AEs).[19,22,24,26–29]

Although previous studies have reported that the coadministration of lamivudine + adefovir dipivoxil had no significant effect on the pharmacokinetic properties of either drug,[30] the present study aimed to determine whether the FDC is bioequivalent to the conventional tablets. This study also evaluated the single-dose tolerability of the FDC.

SUBJECTS AND METHODS

This was a randomized, open-label, single-dose, 2-period crossover study in healthy male subjects. The protocol was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee. Written informed consent was obtained from all study participants prior to any study procedures.

Study Subjects

Male Chinese volunteers aged between 18 and 55 years and having a body weight >50 kg and a body

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