Comparison of Pharmacokinetics of Two Fenofibrate Tablet Formulations in Healthy Human Subjects

Siddharth S. Chachad[1]; Milind Gole[1]; Geena Malhotra[1]; and Raghu Naidu[2]

[1]Department of Clinical and Bioequivalence Research, Cipla Limited, Mumbai, India; and [2]Contract Research Organisation, Sitec Labs Pvt Ltd, Mumbai, India

ABSTRACT

Background: Fenofibrate is a serum lipid-lowering agent used as an adjunct to diet in patients with hypercholesterolemia and hypertriglyceridemia. The new fenofibrate tablet formulation was developed as a pharmaceutical equivalent to the marketed tablet formulation containing 145 mg.

Objective: The objective of this study was to compare the pharmacokinetics and safety of 2 tablet formulations containing 145 mg of fenofibrate (CAS number 49562-28-9) in healthy human subjects.

Methods: The study was a randomized, 2-treatment, 3-period, 3-sequence, single-dose, 3-way crossover, partial replicate bioequivalence study in healthy human subjects under fasting conditions. Eligible subjects received each treatment in a crossover manner according to the randomization schedule. Replicate dosing was conducted for the reference formulation to determine its intrasubject variability. The predose blood sample was taken within 1 hour before dosing, and serial blood sampling was performed up to 72.0 hours' postdose. The analysis of plasma samples for concentrations of fenofibric acid, the active metabolite of fenofibrate, was conducted by using a validated LC-MS/MS method. Bioequivalence was to be concluded if the 90% CIs as constructed were within the range of 80% to 125% for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for fenofibric acid. Subjects were monitored for safety and tolerability throughout the study.

Results: 15 healthy human subjects between 18 and 45 years of age and having body mass index between 18.5 and 30 kg/m^2 were recruited into the study. The 90% CIs for the test/reference mean ratios of the ln-transformed pharmacokinetic variables C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the conventional bioequivalence range of 80% to 125%. Both formulations were well tolerated after a single oral dose in these healthy male subjects.

Conclusions: Both fenofibrate tablet formulations demonstrated equivalent rates and extent of systemic absorption, and hence were considered bioequivalent. (*Clin Ther*. 2014;▮:▮▮▮–▮▮▮) © 2014 Elsevier HS Journals, Inc. All rights reserved.

Key words: bioequivalence, fenofibrate, pharmacokinetics.

INTRODUCTION

According to the World Health Organization fact sheet No. 317 (updated March 2013), cardiovascular diseases are the number one cause of death globally: more people die annually of cardiovascular diseases than of any other cause.[1] Most cardiovascular diseases can be prevented by addressing risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity, high blood pressure, diabetes, and increased lipid levels. Elevated serum cholesterol is a modifiable risk factor that is associated with an estimated 4.4 million deaths each year and accounts for a considerable proportion of ischemic strokes and heart disease worldwide.[2] Therapeutic lifestyle changes (reduced dietary intake of saturated fats and cholesterol, weight control, and increased physical activity) form the core of all cholesterol-lowering initiatives. Supplemental therapy with lipid-lowering medications has been shown to safely reduce the long-term incidence of major cardiovascular events in secondary prevention trials and in high-risk primary prevention trials, and this therapy is universally recommended in patients with established or at high predicted risk of cardiovascular disease.[3,4]

Fenofibrate is marketed in 86 countries and is one of the most commonly used fibrates worldwide, with >6 million patient-years of experience.[5] More than

Accepted for publication April 14, 2014.
http://dx.doi.org/10.1016/j.clinthera.2014.04.017
0149-2918/$ - see front matter

80 clinical trials of fenofibrate have been conducted, involving >9000 patients and >31,000 patient-years of drug exposure.[6,7] Fenofibrate's indications include hypercholesterolemia, combined dyslipidemia, remnant hyperlipidemia, endogenous hyperlipemia (hypertriglyceridemia), and mixed hyperlipemia (Fredrickson types IIa, IIb, III, IV, and V dyslipidemia, respectively).[8]

Fenofibrate is a prodrug of the active chemical moiety fenofibric acid. Fenofibrate is converted by ester hydrolysis in the liver to fenofibric acid, which is the active constituent measurable in the circulation. After oral administration in healthy volunteers, peak plasma levels of fenofibric acid occur within 6 to 8 hours after administration. After absorption, ~60% of a single dose of radiolabeled fenofibrate is excreted in the urine, primarily as fenofibric acid and its glucuronate conjugate, and 25% is excreted in the feces.[9]

Several reformulations of fenofibrate dominate the market, although generic fenofibrate has been available for almost a decade. This continued use of branded formulations, which cost twice as much as generic versions of fenofibrate, imposes a high cost on the health care system. It is hence essential that low-cost yet equally effective and safe drug formulations are made available. In anticipation of the patent expiry, a pharmaceutical equivalent to the marketed fenofibrate 145-mg tablets was developed (by Cipla Limited, Mumbai, India). The objective of the present study was to compare the pharmacokinetics and safety of 2 tablet formulations containing 145 mg of fenofibrate (CAS number 49562-28-9) in healthy human subjects.

SUBJECTS AND METHODS

This study was conducted at Sitec Labs Pvt Ltd (Mumbai, India) in accordance with the ethical standards presented in the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Before the start of the study, written informed consent was obtained from all patients, and the protocol was approved by the local ethical review boards.

Subjects

This research was conducted as a pilot study with a minimum number of 12 evaluable subjects. Thus, to obtain data in at least 12 subjects completing the study and considering dropout and discontinued subjects, 15 subjects were recruited. Healthy human subjects between 18 and 45 years of age and having a body mass index between 18.5 and 30 kg/m^2 were included. Eligible subjects were considered healthy, as demonstrated by no medical history of significant diseases and no clinically significant abnormal findings during the prestudy screening, physical examination, and laboratory evaluations. Results of a breath alcohol test, test for drugs of abuse, and a urine pregnancy test (for female subjects) were negative at the time of screening. Hepatitis A, B, and C and antibodies to HIV I and II, Venereal Disease Research Laboratory test were negative or nonreactive. Subjects were excluded if they were allergic to fenofibrate; had a history of or current cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, metabolic, immunologic, dermatologic, neurologic, or psychiatric disease; had participated in any other clinical investigation using an investigational product; or had donated >350 mL of blood within 90 days before the first dose of study drug.

Subjects were excluded from the study if they had taken any prescription medication (eg, coumarin anticoagulant, cyclosporine, tacrolimus, bile acid resins), over-the-counter products (eg, vitamins, products of natural origin [including St. John's wort]), or topical medications meant for systemic absorption within 7 days before administration of the investigational product. All subjects were instructed to abstain from consuming grapefruit or its products and alcohol/alcoholic products for at least 48 hours before dosing until the last blood sampling in each study period. They were also instructed to abstain from consuming citrus fruits or their products and xanthine-containing products (chocolate, tea, coffee, or cola drink); they were prohibited from smoking and consuming tobacco or tobacco-containing products for at least 24 hours before dosing.

Study Design

The pharmacokinetics of 2 fenofibrate tablet formulations were compared in this randomized, 2-treatment, 3-period, 3-sequence, single-dose, 3-way crossover, partial replicate bioequivalence study. All 15 recruited subjects were administered treatment in a crossover manner under fasting conditions according to the randomization schedule. Replicate dosing was conducted for the reference formulation to determine its intrasubject variability. Because this was a