GTC-45-807: Effect of Sevelamer Hydrochloride and Calcium Acetate on the Oral Bioavailability of Ciprofloxacin in Healthy Volunteers

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Name of Sponsor/Company

Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142
Geltex Pharmaceuticals, Inc., Waltham, MA 02451, (Geltex Pharmaceuticals, Inc. was acquired by Genzyme Corporation December 2000)

Investigators and Study Center(s)

This study was conducted at two sites in the Unites States.

Studied Period

First subject enrolled: 09 March 2001
Last subject completed: 24 January 2002

Phase of Development

Phase I

Objectives

To determine the effect of sevelamer HCl (Renagel®) and calcium acetate on the oral bioavailability of ciprofloxacin in normal volunteers.

Methodology

This was an open-label, single-dose, randomized, 3-treatment, 3-period, crossover study. Volunteers were admitted to the clinical research unit early in the morning of each study day and were required to stay for the entire 24-hour study period. Each volunteer was randomly assigned to receive each of the following treatments: 1) ciprofloxacin alone; 2) ciprofloxacin plus sevelamer; and 3) ciprofloxacin plus calcium acetate. A washout of at least one week separated each treatment.

Number of Patients (Planned and Analyzed)

A sample size of 15 subjects was planned. Sixteen subjects were enrolled and 15 subjects completed the study.

Diagnosis and Main Criteria For Inclusion:

Healthy male and females volunteers at least 18 years of age.

Test Product, Dose, and Mode of Administration

The following test regimens were administered orally.
Sevelamer HCl/ciprofloxacin: sevelamer HCl 7 x 403 mg capsules (2821 mg) plus ciprofloxacin 1 x one 750 mg tablet (750 mg)
Calcium acetate/ciprofloxacin: calcium acetate 4 x 667 mg tablets (2668 mg) plus ciprofloxacin 1 x 750 mg tablet (750 mg)

Reference Therapy, Dose and Mode of Administration

Ciprofloxacin alone: ciprofloxacin 1 x 750 mg tablet (750 mg)

Duration of Treatment

The total study duration for a subject was six to eight weeks including three dosing sessions separated by at least one week.

Criteria for Evaluation – Pharmacokinetics

The effect of sevelamer HCl and calcium acetate on the pharmacokinetics of ciprofloxacin was assessed by measuring serial serum ciprofloxacin concentrations (predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours postdose) after a single administration of ciprofloxacin alone and after single doses of ciprofloxacin co-administered with either sevelamer HCl or calcium acetate.

Criteria for Evaluation – Safety

Safety was assessed based on adverse events.

Statistical Methods – Subjects

Demographic data were listed.

Statistical Methods – Pharmacokinetics

Since the pharmacokinetic data were not normally distributed, the data are reported as median and range, unless stated otherwise. Comparisons of the pharmacokinetic parameters among the three study phases were performed using Friedman's test and the Wilcoxon Signed Rank Test, where appropriate. C_{max} and $AUC_{0-\infty}$ values were log transformed, and the geometric least-square mean ratios for each treatment arm relative to ciprofloxacin alone were determined. The 90% confidence intervals were calculated and bioequivalence was concluded if the 90% confidence interval for the ratios were within the equivalence limits of 80-125%.

Statistical Methods – Safety

Adverse events were listed by subject.

Summary – Conclusions (Subjects)

Sixteen subjects were enrolled and 15 completed the three treatments according to the protocol. One subject was withdrawn from the study prior to dosing with any study medication. This patient was found to have a soft tissue mass along the left occipital region during the screening physical examination. The subject had a history of osteochondroma and surgery 10 years earlier.

The age of the subjects ranged from 24 to 43 years. Eight of the subjects were male. Ten subjects were Caucasian, two subjects were African-American, two subjects were Asian, and one subject was Hispanic.

Summary – Conclusions (Pharmacokinetics)

All subjects who completed the study were included in the pharmacokinetic analyses (n=15).

Co-administration of ciprofloxacin with sevelamer HCl or calcium acetate significantly decreased the C_{max}, AUC and relative bioavailability of ciprofloxacin. The median C_{max} concentrations were 3.77 µg/mL for ciprofloxacin alone, 2.49 µg/mL for ciprofloxacin with sevelamer and 1.90 µg/mL for ciprofloxacin with calcium acetate. The median ciprofloxacin AUC was 18.55, 11.27, and 10.81 µg*hr/mL when administered alone, with sevelamer, and with calcium acetate, respectively. The median relative bioavailability was 0.52 for sevelamer with ciprofloxacin and 0.49 for calcium acetate with ciprofloxacin.

Summary – Conclusions (Safety Results)

All subjects who completed the study were included in the safety analyses (n=15).

Subjects were exposed to single doses of the study drugs on three treatment occasions.

A total of seven adverse events occurred in 5 subjects. In the ciprofloxacin alone treatment arm, one subject experienced a headache and one subject experienced nausea and diarrhea. The nausea and diarrhea were considered related to ciprofloxacin. In the ciprofloxacin plus calcium acetate arm, one subject experienced nausea and diarrhea, one subject experienced nausea and one subject experienced a skin infection approximately three weeks after dosing. The events of nausea and diarrhea were considered related to calcium acetate. There were no adverse events following co-administration of sevelamer and ciprofloxacin. There were no serious adverse events.

Based on Report Prepared on: 15 August 2002
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