GTC-45-803: A Study to Determine the Effect of Sevelamer HCl (Renagel®) on Single Dose Metoprolol Tartrate (Lopressor®) Pharmacokinetics in Healthy Subjects.

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Prescribing decisions should be made based on the approved package insert in the country of prescription.

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 was a single-center study conducted in Ireland.

Studied Period

First patient dosed: 08 April 1999
Last patient dosed: 15 April 1999

Phase of Development

Phase I

Objectives

To determine the effect of a single 2418 mg (6 x 403 mg capsules) dose of sevelamer on the pharmacokinetics of a single 100 mg dose of metoprolol tartrate in healthy subjects.

Methodology

This was an open-label, randomized, 2-period crossover, drug interaction study. Subjects were admitted to the study unit in the evening approximately 12 hours prior to each scheduled dosing and remained in the unit until the completion of events 24 hours following dosing. For the first study period, the subjects were randomly assigned to receive a single 100 mg dose of metoprolol or a single 100 mg dose of metoprolol administered with 2418 mg (6 x 403 mg capsules) of sevelamer. The alternate treatment was administered during the subsequent study period. A 48-hour metoprolol pharmacokinetic profile was performed following each dose. Dosing for each study period was separated by a seven-day washout interval.

Number of Patients (Planned and Analyzed)

A sample size of 36 subjects was planned. Thirty-two subjects were enrolled and 31 subjects completed the study. One subject was dropped from the study because of a toothache that required extraction.

Diagnosis and Main Criteria For Inclusion:

Healthy male and female volunteers between 18 and 50 years of age.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride (Renagel®) 2418 mg (6 x 403 mg capsules) plus metoprolol (Lopressor®) 100 mg tablet; both drugs were administered orally

Reference Therapy, Dose and Mode of Administration

Metoprolol (Lopressor®) 100 mg tablet administered orally

Duration of Treatment

The total study duration for a subject was 1.5 weeks including two dosing sessions separated by 7 days.

CRITERIA FOR EVALUATION

Criteria for Evaluation – Pharmacokinetics

The effect of sevelamer on the pharmacokinetics of metoprolol was assessed by measuring serial plasma metoprolol concentrations (predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 hours) after single administrations of metoprolol alone or co-administered with sevelamer.

Criteria for Evaluation – Safety

Adverse events, laboratory results (chemistry, hematology, urinalysis), vital signs (temperature, pulse, blood pressure, and respirations), electrocardiogram (ECG), and physical examination.

STATISTICAL METHODS

Statistical Methods – Pharmacokinetics

A parametric general linear model was applied to the logarithmic transformation of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}. The analysis of variance (ANOVA) model included sequence, subject within sequence, period, and treatment. The two one-sided hypotheses were tested at the 5% level for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} by constructing 90% confidence intervals for the ratio of the sevelamer/metoprolol to metoprolol alone geometric mean. Sevelamer was considered to have no significant effect on the bioavailability of metoprolol if the 90% confidence intervals for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were within the range of 80% to 125%.

Statistical Methods – Safety

Adverse events, laboratory results, vital signs, and findings from ECGs and physical examinations were listed.

SUMMARY – CONCLUSIONS

Summary – Conclusions (Patients)

Seventeen of the subjects enrolled were male and 15 were female. The mean age was 26 years, the mean height was 170 cm, and the mean weight was 67.7 kg.

Summary – Conclusions (Pharmacokinetics)

All subjects who completed the study were included in the analyses (n=31).

The overall shape of the mean metoprolol concentration–time profiles resulting from co-administration of metoprolol with sevelamer is similar to that resulting from the administration of metoprolol alone. Individual C_{max} concentrations were observed within 0.5 to 3.0 hours for metoprolol alone (C_{max} range 60.85 to 438.62 ng/mL) and within 0.5 to 2.5 hours for metoprolol with sevelamer (C_{max} range 45.27 to 399.12 ng/mL). The mean ratios of log-transformed C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ for the comparison of the two treatments were 100%, 98.3%, and 98.9%, respectively. The 90% confidence intervals for log-transformed C_{max}, $AUC_{(0-t)}$ and $AUC_{(0\infty)}$ were all within the 80-125% range, indicating that sevelamer had no detectable effect on the rate and extent of metoprolol absorption.

Summary – Conclusions (Safety)

A total of 15 adverse events occurred in 9 patients. Ten adverse events occurred in 6 patients following metoprolol alone and 5 events occurred in 3 patients following co-administration of sevelamer and metoprolol. All events were mild to moderate in intensity. Six adverse events (2 events of lightheadedness, 1 event of stomach cramps, 2 events of vomiting, and 1 event of headache) were assessed as related to metoprolol. No adverse events were assessed as related to sevelamer/metoprolol treatment. No serious adverse events were reported. There were no clinically significant findings for laboratory parameters, vital signs, ECGs, or physical examinations.

Based on Report Prepared on: June 1999
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