GTC-45-804: A Study to Determine the Effect of Sevelamer (Renagel®) on Single Dose Enalapril Maleate (Innovace®) Pharmacokinetics in Healthy Subjects

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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 was a single-center study conducted in Ireland.

Studied Period

First subject enrolled 12 April 1999
Last subject completed: 23 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 hydrochloride on the pharmacokinetics of a single 20 mg dose of enalapril maleate 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, remained in the unit until the completion of events at 24 hours following dosing and returned at 36, 48, and 72 hours following dosing for blood collection. For the first study period, the subjects were randomly assigned to receive a single 20 mg dose of enalapril maleate or a single dose of enalapril maleate administered with sevelamer 2418 mg (6 x 403 mg capsules). The alternate treatment was administered during the subsequent study period. A 72-hour enalapril and enalaprilat pharmacokinetic profile was performed after each enalapril maleate dose. Dosing for each study period was separated by a seven-day washout interval.

Number of Patients (Planned and Analyzed)

A sample size of 24 was planned. Twenty-eight subjects were enrolled and completed the study.

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 enalapril maleate (Innovace®) 20 mg tablet; both drugs were administered orally

Reference Therapy, Dose and Mode of Administration

Enalapril maleate (Innovace®) 20 mg tablet administered orally

Duration of Treatment

The total study duration for a subject was approximately 2 weeks with two dosing sessions separated by a 7-day washout period.

CRITERIA FOR EVALUATION

Criteria for Evaluation – Pharmacokinetics

Enalapril maleate is a prodrug that undergoes biotransformation in the liver to enalaprilat (the active moiety). Pharmacokinetic analyses were conducted for both enalapril and enalaprilat.

The effect of sevelamer on the pharmacokinetics of enalapril and enalaprilat was assessed by measuring the serial plasma concentrations (predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 72 hours postdose) after single administrations of enalapril alone or co-administered with sevelamer.

Criteria for Evaluation – Safety

Adverse events, laboratory results (chemistry, hematology, urinalysis), vital signs (temperature, pulse, blood pressure, and respiratory rate), 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 (CIs) for the ratio of the enalapril co-administered with sevelamer to enalapril alone geometric mean. Sevelamer was considered to have no significant effect on the bioavailability of enalapril and enalaprilat if the 90% confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{(0-\infty)}$ 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)

Nineteen of the subjects enrolled were male and 9 were female. The mean age was 29 years, the mean height was 171 cm, and the mean weight was 67.4 kg.

Summary – Conclusions (Pharmacokinetics)

All subjects who completed the study were included in the analyses (n=28).

The enalapril plasma concentration versus time curves show that the overall shape of the mean enalapril concentration-time profile resulting from co-administration of enalapril maleate with sevelamer is similar to that resulting from the administration of enalapril alone. However, enalapril co-administered with sevelamer resulted in higher mean peak enalapril concentration compared with enalapril alone. C_{max} concentrations were observed within 0.5 to 1.0 hours for both enalapril alone (C_{max} range 37.96 to 173.35 ng/mL) and enalapril with sevelamer (C_{max} ranged 59.67 to 341.99 ng/mL). The mean ratios of log-transformed C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ (111. 4%, 97.8%, and 97.4 %, respectively) indicate increased rate of enalapril absorption in the presence of sevelamer, but similar overall extent of absorption between the two treatments. The 90% confidence intervals for log-transformed $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ were within the 80-125% range indicating that sevelamer had no effect on the extent of bioavailability of enalapril. However, the upper boundary of the 90% confidence interval for log-transformed C_{max} (125.4%) was marginally above the 125% upper limit of the 80-125% range, indicating a moderately increased maximum concentration of enalapril absorption in the presence of sevelamer.

The enalaprilat plasma concentration versus time curves show that the overall shape of the mean enalaprilat concentration-time profile resulting from co-administration of enalapril with sevelamer is very similar to that resulting from administration of enalapril alone. C_{max} concentrations were observed within 3.0 to 5.0 hours for both enalapril alone (C_{max} range 25.7 to 106.0 ng/mL) and enalapril with sevelamer (C_{max} range 27.3 to 121.7 ng/mL). The mean ratios of log-transformed C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ (102.7%, 96.2%, and 96.0%, respectively) indicate acceptable relative rate and extent of enalaprilat availability in the presence of sevelamer. The 90% confidence intervals for C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ were all within the 80-125% range.

Summary – Conclusions (Safety)

A total of 21 adverse events occurred in 11 patients. Ten events occurred in 7 patients following enalapril maleate alone and 11 events occurred in 8 patients following co-administration of sevelamer and enalapril maleate. All events were mild to moderate in intensity. Nine adverse events (1 event of fainting, 1 event of vomiting, 2 events of headache, 1 event of frequent micturition, 2 events of lightheadedness, 1 event of weakness in legs, and 1 event of nausea) were assessed as related to enalapril maleate alone. Six adverse events (1 event of vomiting, 2 events of stomach cramps, 1 event of frequent micturition, 1 event of heartburn and 1 event of headache) were assessed as related to sevelamer co-administered with enalapril maleate. There were no serious adverse events. There were no clinically significant findings for laboratory parameters, vital signs, ECGs, or physical examinations.

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