Protocol GTC-10-801: Absorption of ^{14}C-Renagel® (Sevelamer Hydrochloride) (500 µCi) in Healthy Young and Old Male and Female Volunteers

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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 the United States.

Studied Period

First subject enrolled: 23 July 1996
Last subject completed: 01 November 1996

Phase of Development

Phase I

Objectives

To assess the non-absorbability of sevelamer in healthy young and old, male and female subjects

Methodology

This was an open-label study. As outpatients, subjects received sevelamer 2.325 g three times daily (t.i.d.) for 28 days. On Day -1, the subjects were admitted to a clinical research unit. Following an overnight fast, each subject received a single 2.325 g dose of ^{14}C-labelled sevelamer. The subjects then continued to receive non-radiolabeled sevelamer, 2.325 g per dose, three times daily through the evening of study Day 5. All subjects were required to return to the clinical for a follow-up visit approximately 2 weeks after the last sevelamer dose.

Number of Patients (Planned and Analyzed)

As planned, 20 subjects [5 young females (19-40 yrs), 5 young males (19-40 yrs), 5 old males (65+ yrs), and 5 old females (65+ yrs)] were enrolled. At the end of the outpatient portion of the study one subject from each group was released from the study. Sixteen patients entered and completed the inpatient portion of the study.

Diagnosis and Main Criteria For Inclusion:

Healthy male and female volunteers in the age groups described above.

Test Product, Dose, and Mode of Administration

Sevelamer hydrochloride 5 x 465 mg capsules administered orally t.i.d.

^{14}C-Sevelamer hydrochloride 5 x 465 mg capsules (each containing 100 µCi) administered orally once

Reference Therapy, Dose and Mode of Administration

Not applicable

Duration of Treatment

The total study duration for a subject was approximately 2 months including 28 days of outpatient dosing, a 5-day inpatient dosing period and a follow-up visit.

CRITERIA FOR EVALUATION

Criteria for Evaluation – Pharmacokinetics

Serial blood samples for radioactivity counting were collected predose, 4, 8, 12, 24, 48, 72, and 96 hours. All urine and feces voided during the confinement period were collected and radioactivity was counted for the following intervals: predose, 0-24, 24-48, 48-72, and 72-96 hours post dose.

Criteria for Evaluation – Safety

Safety was assessed based on adverse events, changes in laboratory results (hematology, chemistry, and urinalysis) and physical examination.

STATISTICAL METHODS

Statistical Methods – Subjects

The subjects' demographic characteristics were tabulated.

Statistical Methods – Pharmacokinetics

If there were detectable plasma concentrations of ^{14}C sevelamer, standard non-compartmental pharmacokinetic parameters were to be calculated. If there were detectable urinary concentrations of ^{14}C sevelamer, the total amount excreted, excretion rate, and renal clearance were to be calculated. Whole blood, urine, and fecal radioactivity data were to be summarized by age and sex using descriptive statistics. If whole blood and/or urine concentrations were detectable, a summary and an analysis of variance were to be conducted for the plasma non-compartmental pharmacokinetic parameters and/or urine total amount excreted, excretion rate, and renal clearance. A level of significance of 0.05 was to be used for all statistical analyses.

Statistical Methods – Safety

All adverse events and laboratory values were listed.

SUMMARY – CONCLUSIONS

Summary – Conclusions (Subjects)

The mean age of the young females was 31 years; the young males were 25 years; the old males were 67 years; and the old females were 69 years.

Summary – Conclusions (Pharmacokinetics)

All subjects who received ^{14}C-sevelamer were included in the radioactivity analyses (n=16).

There was no detectable ^{14}C-sevelamer in the whole blood of any subject at any time point. A small amount (0.02% or less) of the administered dose was recovered in the urine of 7 subjects. Within 7 days of administration, 90% of the dose was recovered in the feces of all but 1 subject; more than 80% was recovered in the feces of the remaining subject. The mean percent of the dose eliminated in the feces for all subjects was 99.36%.

Summary – Conclusions (Safety Results)

All enrolled subjects were included in the safety analyses (n=20).

Each subject received study drug as specified in the protocol.

A total of 125 adverse events occurred in 17 subjects. Most adverse events were mild to moderate in intensity; three events were severe (dry heaves, pain right side, headache). Thirty adverse events were classified as related to study medication. The majority of related adverse events were gastrointestinal in nature. Two (2) subjects experienced elevated liver enzyme tests during the study. One of these subjects had a positive Epstein-Barr titer; both events of elevated liver enzyme tests resolved.

There were no serious adverse events during the confinement period. One subject had pain in his right side 7 days after the last dose of study drug. He was hospitalized for an appendectomy; however the appendix was not inflamed. Subsequently, he had a colonoscopy, was diagnosed with colon cancer, and underwent a colectomy. These events were judged by the investigator to be unrelated to study drug.

There were no clinically significant changes in laboratory results.

Based on Report Prepared on: May 1997
Synopsis Prepared on: 23 May 2006