DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Martha J. Carter
Vice President, Regulatory Affairs
GelTex Pharmaceuticals, Inc.
153 Second Avenue
Waltham, MA 02451

RE: NDA# 20-926
NDA# 21-179
Renagel Capsules (sevelamer hydrochloride)
Renagel Tablets (sevelamer hydrochloride)
MACMIS ID # 10194

Dear Ms. Carter:

This letter concerns dissemination of promotional materials for Renagel Capsules and Tablets (sevelamer hydrochloride). As part of its routine monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a press release entitled "Genzyme Study Demonstrates Significant Impact of Renagel On Cardiac Calcification" submitted under cover of Form FDA 2253 by GelTex Pharmaceuticals, Inc. (GelTex). The press release promotes Renagel in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Specifically, we have the following objections:

Unsubstantiated Outcomes Claims

Several statements in the press release misleadingly state or imply outcomes of Renagel therapy that have not been demonstrated by substantial evidence. For example, the press release includes conclusory statements relating to preliminary, interim data derived from an ongoing study of cardiac calcification:

> The title of the press release – "**Genzyme Study Demonstrates Significant Impact of Renagel On Cardiac Calcification**"
>
> "In a powerful way, the 'Treat to Goal' study has begun to **clarify and confirm** the vital clinical role Renagel can play in allowing patients to avoid the progression of cardiovascular calcification." (emphasis added)

These statements imply that Renagel is effective in reducing the risk of cardiac calcification when, in fact, substantial evidence of that effect has not been established. Until the "Treat to Goal" study is completed, conclusions regarding treatment outcomes, based on interim data, are misleading because the final results may not support these claims.

In addition, the press release misleadingly implies that treatment with Renagel will decrease morbidity or mortality. For example:

> "Patients on dialysis are at high risk for elevated phosphorus levels, which can lead to cardiac complications, bone disease, and increased mortality rates. Nearly all patients on dialysis take a phosphate binder to control the level of phosphorus in their blood. Before the introduction of Renagel, the majority of patients were treated with calcium-based binders. Independent studies have associated excessive calcium intake with increased morbidity in dialysis patients. Renagel is the only calcium-free, aluminum free phosphate binder on the market."

The approved product labeling (PI) for Renagel does not report an effect on either cardiac calcification or overall morbidity and mortality because the trials that formed the basis for Renagel's approval did not measure these outcomes. Therefore, the press release misleadingly overstates the benefits of Renagel therapy because substantial evidence of the impact of Renagel treatment on these outcomes has not been established.

Unsubstantiated Superiority Claims

In addition, the press release contains unsubstantiated claims regarding the superiority of Renagel over unspecified calcium-based phosphate binders. These claims are also misleading conclusions based on preliminary, interim results of an ongoing study. The unsubstantiated superiority claims include:

> "The findings from this trial reveal a clear difference between the two groups in the progression of cardiovascular disease"

> "Despite this similar degree of phosphorus control, the study's investigators found a clear, highly significant difference between the two patient groups in the progression of cardiac calcification."

Until the study is completed, conclusions regarding the superiority of Renagel over other therapies in the progression of either cardiac calcification or general cardiovascular disease are misleading because the final results may not support these claims. Furthermore, other factors may be responsible for the disparity in results. These factors may not be evident until the final analysis of the completed study.

The PI for Renagel includes the statements that "the risk of developing hypercalcemia is less with Renagel Capsules compared to calcium acetate" and that "Renagel decreases the incidence of hypercalcemic episodes relative to patients on calcium acetate treatment." The PI does not extrapolate these findings to conclude that Renagel has a superior effect on the relative risk of either cardiac calcification or the broader risk of cardiovascular disease progression. Therefore, presentation of these conclusions misleadingly overstates the comparative safety of Renagel therapy.

Broadening of Approved Indication

The claim that "Renagel offers long-term phosphorus **control** in patients with end-stage renal disease on hemodialysis, without adding excess calcium or aluminum" (emphasis added) is misleading because it implies a higher degree of efficacy than has been demonstrated for Renagel. According to the PI, Renagel is only approved for **reduction** of serum phosphorus in patients with end-stage renal disease on hemodialysis. Therefore, this claim misleadingly broadens the approved indication of Renagel because patients may experience a reduction in serum phosphorus levels while still remaining hyperphosphatemic.

In addition, references throughout the press release to "dialysis" patients are misleading because they imply that Renagel is useful in a broader population than has been demonstrated by substantial evidence. Dialysis procedures include both hemodialysis and peritoneal dialysis. Renagel is approved for use in hemodialysis patients only. It is not approved for use in peritoneal dialysis patients.

DDMAC requests that GelTex immediately discontinue the dissemination, including posting on the internet, of this violative press release. All other promotional materials that contain the same or similar violative claims or representations should be discontinued. DDMAC requests that GelTex submit a written response to this letter no later than August 31, 2001, including your plan to comply with DDMAC's request. Your written response should include a list of all materials that you have discontinued and the date that they were discontinued.

If you have any questions or comments, please contact me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #10194 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Margaret M. Kober, R. Ph.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Margaret Kober
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For Immediate Release
June 26, 2001

Media Contact:
Dan Quinn
617-591-5849

Investor Contact:
Sally Curley
617-591-7140

Genzyme Study Demonstrates Significant Impact of Renagel® On Cardiac Calcification

CAMBRIDGE, Mass.—Genzyme General (Nasdaq:GENZ) today reported first-year results from its three-year "Treat to Goal" clinical trial at the European Dialysis and Transplantation Association meeting being held in Vienna. The study results demonstrate that patients with end-stage renal disease taking calcium-based phosphate binders to control serum phosphorus levels experienced a dramatic progression of cardiac calcification, a type of cardiovascular disease in which calcium deposits form within the blood vessels of the heart. Conversely, patients taking Renagel® (sevelamer hydrochloride) experienced no significant progression of calcification.

Specifically, patients taking calcium-based binders who had cardiovascular calcification at baseline showed a significant median increase of 25 percent in their coronary artery calcification scores at one year. Renagel patients showed a non-significant median increase of only 6 percent in these scores compared to baseline. Similarly, the calcium patients showed a significant median increase of 28 percent in aortic calcification scores, while Renagel patients experienced a non-significant increase of 5 percent from baseline. The study's investigators used electron beam

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tomography scanning to measure the volume and density of calcification within the heart.

"The findings from this trial reveal a clear difference between the two groups in the progression of cardiovascular disease," said Glenn Chertow, M.D., assistant professor at the University of California at San Francisco and the study's principal investigator. "Renagel appears to have arrested the progression of cardiovascular calcification. These results support the growing body of published evidence linking excessive use of calcium-containing phosphate binders with the alarming level of cardiovascular calcification observed in hemodialysis patients."

Renagel was approved for marketing in the United States in 1998 and in Europe in 2000, and is the only phosphate binder available that does not contain calcium or aluminum. The "Treat to Goal" clinical trial was designed to compare Renagel with standard calcium-based phosphate binders by measuring the effect of each product on cardiac calcification and evaluating the ability of each to maintain serum phosphorus, calcium, and parathyroid hormone levels in the target ranges.

The open-label, randomized study was conducted at 15 medical centers in the United States and Europe. Half of the 202 patients enrolled in the study were assigned to the Renagel group and half were assigned to the calcium group. Patients were evaluated at baseline and at one year on a variety of measures.

At the end of one year, serum phosphorus levels and calcium-phosphorus product levels had been lowered into the target range in both the Renagel patients and the calcium patients. Despite this similar degree of phosphorus control, the study's investigators found a clear, highly significant difference between the two patient groups

in the progression of cardiac calcification. They also found that patients taking Renagel experienced fewer incidences of hypercalcemia compared to the patients taking calcium-based binders, obtained superior control of their parathyroid hormone levels in the target range, and markedly reduced their LDL cholesterol levels compared to baseline. A majority of patients on calcium binders experienced oversuppression of their parathyroid hormone levels. No reduction in LDL cholesterol levels was observed among the calcium patients.

In his overview of the "Treat to Goal" results, Dr. Chertow also focused on the baseline scores for patients who enrolled in the trial. These scores revealed a striking correlation between a patient's level of cardiovascular calcification entering the trial and his or her history of cardiovascular disease.

A similar finding was presented at the EDTA meeting by Gerard London, M.D., of the Hospital Fleury-Merogis in France. In this independent study of arterial stiffening and vascular calcification in end-stage renal disease, Dr. London found that the presence of arterial calcification was strongly and independently predictive of outcome in end-stage renal disease. Dr. London concluded that the severity of a patient's calcification score is a strong independent predictor of overall and cardiovascular mortality.

Based on these and other findings, Genzyme has begun a large, prospective clinical trial designed to evaluate Renagel's impact on patient morbidity and mortality. The prospective, multi-center trial will compare outcomes for patients on Renagel and patients taking a calcium-based phosphate binder. Full enrollment in the trial is expected by the end of this year. Morbidity and hospitalization data are expected to be

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available during the second half of 2003, and mortality data should be available during the first half of 2004.

"Our goal is to improve the care of patients with end-stage renal disease," said Henri A. Termeer, chairman and chief executive officer of Genzyme Corp. "In a powerful way, the "Treat to Goal" study has begun to clarify and confirm the vital clinical role Renagel can play in allowing patients to avoid the progression of cardiovascular calcification."

Renagel offers long-term phosphorus control in patients with end-stage renal disease on hemodialysis, without adding excess calcium or aluminum. Phosphorus control is critical to the quality of care of all dialysis patients.

Patients on dialysis are at high risk for elevated phosphorus levels, which can lead to cardiac complications, bone disease and increased mortality rates, if left untreated. Nearly all patients on dialysis take a phosphate binder to control the level of phosphorus in their blood. Before the introduction of Renagel, the majority of patients were treated with calcium-based binders. Independent studies have associated excessive calcium intake with increased morbidity in dialysis patients. Renagel is the only calcium-free, aluminum-free phosphate binder on the market.

Renagel is indicated for reduction of serum phosphorus in patients with end-stage renal disease on hemodialysis. The safety and efficacy of Renagel in patients with end-stage renal disease not on hemodialysis have not been studied. Renagel is contraindicated in patients with hypophosphatemia or bowel obstruction. In a placebo-controlled study, adverse events reported for Renagel were similar to those reported for placebo. The most common treatment-emergent side effects were not dose related and

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included diarrhea (16%), infection (15%), and pain (13%). In drug interaction studies, Renagel had no effect on the bioavailability of digoxin, warfarin, enalapril, or metoprolol. When administering any other oral drug for which alteration in blood levels could have a clinically significant effect on safety and efficacy, the drug should be administered at least 1 hour before or 3 hours after Renagel, or the physician should consider monitoring blood levels of the drug. For more information about Renagel, including complete prescribing information, please visit www.renagel.com.

Genzyme General develops and markets therapeutic products and diagnostic products and services. Genzyme General has four therapeutic products on the market and a strong pipeline of products in development focused on the treatment of genetic disorders and other chronic debilitating diseases with well-defined patient populations. Genzyme General is a division of the biotechnology company Genzyme Corporation.

This press release contains forward-looking statements based on management's current expectations, including without limitation statements about: the preliminary results of the "Treat to Goal" study; the potential impact of Renagel on patient morbidity and mortality; the expected timing of a clinical trial and the availability of data from that trial. Actual results may materially differ due to numerous factors, including: the final results of the "Treat to Goal" study and other clinical trials; the enrollment rate for the morbidity and mortality clinical trial; the efficacy of Renagel; and the risks and uncertainties described in reports filed by Genzyme Corporation with the Securities and Exchange Commission under the Securities Exchange Act of 1934, as amended, including without limitation Exhibit 99.2 to Genzyme's 2000 Annual Report on Form 10-K. Genzyme General Division Common Stock is a series of common stock of Genzyme Corporation. Therefore, holders of Genzyme General Division Common Stock are subject to all of the risks and uncertainties described in the aforementioned reports.

# # #

Genzyme will host a press conference today at the EDTA meeting to discuss the "Treat to Goal" study results with reporters and financial analysts. To listen to the press

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conference live beginning at 8:00 a.m. Eastern, please call 212-231-6021. A replay of the call will be available from 11:00 a.m. Eastern on June 26 through midnight on July 3. To listen to the replay, please call 800-633-8284 from within the United States or 858-812-6440 from outside the United States. The reservation number for the replay is 19072428.

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