DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-673

Genzyme Corporation
4545 Horizon Hill Blvd.
San Antonio, TX 78229-2263

Attention: Mike Bernstein, MPH
Senior Director, Regulatory Affairs

Dear Mr. Bernstein:

Please refer to your new drug application (NDA) dated March 29, 2004, received March 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CLOLAR™ (clofarabine) Intravenous Infusion.

We acknowledge receipt of your submissions dated April 22, July 7, August 2 and 5, September 15, October 6, November 18, and December 15, 21, and 28, 2004.

This new drug application provides for the use of CLOLAR™ (clofarabine) Intravenous Infusion for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-673**." Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study commitments specified in your facsimile submission dated December 28, 2004. These commitments, along with any completion dates agreed upon, are listed below.

1. Completion of study CLO-216: This is a Phase 1/2 Dose-Escalation Study of Clofarabine Plus Cytarabine and L-Asparaginase in Pediatric Patients with Refractory or Relapsed Acute Lymphoblastic Leukemia, showing that an acceptable and potentially useful regimen has been developed for study in a Phase 3 study. We expect the Phase 1 part of this study to be completed by March 1, 2006, and the Phase 2 part of the study, assuming a tolerated regimen is found in Phase 1, by October 1, 2006. If either the Phase 1 or 2 components fail to identify a useful and tolerated regimen, you have agreed to promptly develop an alternative plan to verify and describe clinical benefit.

	Phase 1	Phase 2
Protocol Submission:	Done	Done
Study Start:	June 1, 2005	June 1, 2006
Trial Completion:	March 1, 2006	October 1, 2006
Final Report Submission:	June 1, 2006 (interim report)	April 13, 2007

2. Completion of a controlled clinical study to verify and describe the clinical benefit of clofarabine in pediatric ALL. Your proposed Phase 3 study to be possibly conducted by the COG does not appear to have a realistic chance of showing a clinical benefit of clofarabine in children with ALL in first relapse. Please submit a new protocol for a study to show clofarabine clinical benefit in children with ALL within 2 months of the date of this letter. Timelines for study start, completion and submission of the study report will also be submitted. Please request a meeting to discuss this protocol within 30 days of receipt of this letter, so that a meeting can be scheduled to occur about one month after receipt of the protocol.

The Division will monitor your progress closely with regard to these post marketing commitments to ensure due diligence.

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing study commitments must be clearly designated "**Subpart H Postmarketing Study Commitments**."

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

Immediately submit all promotional materials (both promotional labeling and advertisements) to be used within the first 120 days after approval. Send one copy to this Division and two copies of the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

In addition, as required by 21 CFR 314.550, submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of the promotional materials and the package insert to the address above.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Christy Cottrell, Consumer Safety Officer, at (301) 594-5761.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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

/s/

Robert Temple

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