DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125103/0

DEC 15 2004

Amgen, Incorporated
Attention: Ross Lobell
Director, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Lobell:

We have approved your biologics license application for Palifermin effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Palifermin, under your existing Department of Health and Human Services U.S. License No. 1080. Palifermin is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.

Under this license, you are approved to manufacture Palifermin drug substance at Amgen, Incorporated (LakeCentre Facility) in Boulder, Colorado. The final formulated product will be manufactured, filled, labeled, and packaged at (b)(4) . You may label your product with the proprietary name Kepivance™ and will market it in 6.25 mg vials.

The dating period for Palifermin drug product shall be 18 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of (b)(4) of the formulated drug product. The dating period for your drug substance shall be (b)(4) when stored at (b)(4) . Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your Palifermin drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Palifermin to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Palifermin, or in the manufacturing facilities.

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 are waiving the pediatric study requirement for ages 0 to less than 3 years and deferring submission of your pediatric studies for ages 3 to 16 years until February 28, 2008.

We acknowledge your written commitments as described in your letter of December 14, 2004, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. Your deferred pediatric study required under section 2 of the Pediatric Research Equity Act (PREA) is considered a required postmarketing study commitment. The status of this postmarketing study shall be reported annually according to 21 CFR 601.70. This commitment is listed below.

   To conduct a deferred pediatric study under PREA to determine whether, compared to placebo, administration of Palifermin decreases the incidence and duration of severe oral mucositis and related sequelae experienced by patients age 3-16 with hematologic malignancies who are receiving myelotoxic therapy. Study protocol 20010133, a 174 patient, multicenter, dose escalation study to evaluate the safety, pharmacokinetics and efficacy of Palifermin in children and adolescents with stage 1 (unresected) and stage 2 B-cell Non Hodgkin's Lymphoma (B-NHL) undergoing multi-agent chemotherapy will be submitted by April 30, 2005. The study will be initiated by May 31, 2005, patient accrual will be completed by November 30, 2007, the study will be completed by January 31, 2008, and the final study report, with revised labeling if applicable, will be submitted by April 30, 2008.

   Submit final study reports to this BLA. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "Required Pediatric Study Commitments."

2 To complete and submit data from study protocol 960226, a long-term observational follow-up study of subjects previously enrolled in any Palifermin study conducted in the myelotoxic therapy setting. Interim results of the study will be reported to the BLA annually, with revised labeling if applicable, beginning December 15, 2005, for a period of 10 years. The final study report, with revised labeling if applicable, will be submitted by June 30, 2015.

3. To complete and submit data from study protocol 990123, a long-term observational follow-up study of subjects with head and neck cancer previously enrolled in Palifermin studies in the fractionated chemoradiotherapy setting.

Interim results of the study will be reported to the BLA annually, with revised labeling if applicable, beginning December 15, 2005, for a period of 10 years. The final study report, with revised labeling if applicable, will be submitted by June 30, 2015.

4. To submit the final study report for protocol 20030142, a Phase 1 study to evaluate the pharmacokinetics of Palifermin in subjects with renal impairment. This study was completed in May 2004 and the final study report will be submitted by January 31, 2005.

5. To conduct an *in vivo* study in healthy volunteers to evaluate the drug-drug interaction of Palifermin with heparin. The study protocol will be submitted by September 1, 2005, will be initiated by November 1, 2005, will be completed by September 30, 2006, and the final study report submitted by March 30, 2007.

6. To conduct an *in vitro* study to evaluate the drug-drug interaction of Palifermin with low molecular weight heparins. The study protocol will be submitted by July 1, 2005, will be initiated by October 1, 2005, will be completed by April 30, 2006, and the final study report submitted by October 30, 2006.

7. To conduct an *in vivo* study in healthy volunteers, contingent on the results of the *in vitro* study, to evaluate the drug-drug interaction of Palifermin with low molecular weight heparin. If required, the study protocol will be submitted by September 30, 2006, will be initiated by November 30, 2006, will be completed by September 30, 2007, and the final study report submitted by March 30, 2008.

8. To conduct a study to determine the incidence of cataracts and decreased visual acuity associated with Palifermin administration. This study will be a component of the clinical study 20040253 conducted in patients with metastatic breast cancer receiving multi-cycle chemotherapy. The final protocol will be submitted by September 30, 2005, will be initiated by January 30, 2006, will be completed by July 30, 2008, and the final study report submitted by December 31, 2008.

9. To evaluate the incidence and characteristics (severity, duration, reversibility, and clinical sequelae) of proteinuria in patients receiving Palifermin. Appropriate testing will be conducted in a controlled clinical study of adequate size. The study protocol will be submitted by September 30, 2005, will be initiated by February 28, 2006, will be completed by June 30, 2008, and the final study report will be submitted by December 31, 2008.

10. To complete study 103599 to evaluate the potential of Palifermin to enhance the incidence of spontaneous tumors in the Tg.rasH2 transgenic mouse model. This study was initiated in July 2004. An audited draft report will be submitted by June 30, 2005. The final report will be submitted by December 31, 2005.

11. To conduct a prospective cohort study using the available International Bone Marrow Transplant Registry (IBMTR) and Autologous Blood and Bone Marrow Registry (ABMTR) databases to evaluate the incidence of secondary malignancies, cancer relapse rates, and survival in patients who receive Palifermin compared to a matched patient control group who have not received Palifermin. The study protocol will be submitted by July 30, 2005, and will be initiated by January 31, 2006. Interim data will be submitted at 2 year intervals for a period of 10 years, beginning July 31, 2008 and the final study report will be submitted by July 31, 2016.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70

12. To re-evaluate the following:

    a. action and acceptance limits for Palifermin drug substance yields after manufacture of (b)(4) lots;

    b. in-process controls, release, and stability specifications based on data from all drug product lots manufactured through the end of 2007; and,

    c. in-process controls, release, and stability specifications based on data from all drug substance lots manufactured through the end of 2008.

    Results of these re-evaluations will be submitted by March 31, 2008, for drug product and March 31, 2009, for drug substance.

13. To evaluate the photostability of Palifermin drug product under conditions that are representative of the conditions for use of the lyophilized and reconstituted Palifermin drug product, and to submit the results of the study with revised labeling, if necessary, by September 30, 2005.

14. To evaluate the specificity of the ELISA (b)(4) method as an identity test for the Palifermin drug product, by a quantitative comparison of cross-reactivity to a series of FGF-related growth factors that are highly homologous in amino acid sequence to Palifermin, and report the results of this study by December 31, 2005.

15. To establish an in-process control test (b)(4) in the manufacture of Palifermin drug substance by (b)(4) September 30, 2005.

16. To submit ED50 control limits for the reference standard used in the bioassay (b)(4) by September 30, 2005.

17. To evaluate, using the (b)(4) test, (b)(4) in Palifermin drug product vials exposed to accelerated storage conditions, including heat and light, and to submit the final study report by September 30, 2005.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125103. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125103. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publically disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

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.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Division of Drug Marketing, Advertising and Communication (HFD-42), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Sincerely,

(b)(6)

Karen D. Weiss, M.D.
Director
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Enclosures: Package Insert
Vial and Package Labeling