CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

BLA 125103/0

Administrative/Correspondence Reviews

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 15, 2004

FROM: Susan E. Giuliani, R.N., M.S.
Consumer Safety Officer
Division of Review Management and Policy, HFD-109
Office of Drug Evaluation VI

TO: STN 125103/0

SUBJECT: SBA Equivalent for:

- Product: Palifermin (Kepivance™)
- Manufacturer: Amgen, Incorporated
- License Number:

Indications and Usage
Decrease the incidence, duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support

Dosage Form, Route of Administration, and Recommended Dosage
Sterile, white, preservative–free lyophilized powder in a single-dose vial for intravenous bolus injection after reconstitution with 1.2 mL of Sterile Water for Injection, USP. Reconstitution yields a clear, colorless solution (5mg/mL).

The recommended dosage is 60 mcg/kg/day for three consecutive days before and three consecutive days after myelotoxic therapy for a total of six doses.

- **Pre-myelotoxic therapy:** The first 3 doses should be administered prior to myelotoxic therapy, with the third dose 24 to 48 hours before myelotoxic therapy.
- **Post-myelotoxic therapy:** The last 3 doses should be administered post-myelotoxic therapy; the first of these doses should be administered after, but on the same day of hematopoietic stem cell infusion and at least 4 days after the most recent administration of Palifermin

Basis for Approval

The following reviews, filed in the CDER correspondence section of the license file for STN 125103/0, comprise the SBA equivalent for this application:

Discipline	Reviewer Name	Date
Clinical (Safety and Efficacy)	Patricia Dinndorf, M.D.	December 15, 2004
Statistical	Yuan Li Shen, Ph.D. Lisa Kammerman, Ph.D.	December 2, 2004 December 1, 2004
Non clinical Pharmacology/Toxicology	Anita O'Connor, Ph.D.	November 1, 2004
Non-clinical Pharmacology/Toxicology	Barbara Wilcox, Ph.D.	December 15, 2004
Clinical Pharmacology	Hong Zhao, Ph.D.	November 23, 2004
CMC, Product	Kurt Stromberg, Ph.D. Ralph Bernstein, Ph.D.	December 14, 2004
CMC, Facility	Marlene Swider, Ph.D.	December 9, 2004
Biologics Monitoring	Jose Tavarez-Pagan	October 19, 2004
Ophthalmologic Consult	Wiley A. Chambers, M.D.	November 30, 2004
Tertiary Review	Patricia Keegan, M.D.	December 15, 2004

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 13, 2004

FROM: Patricia Keegan, M.D.
Director, Division of Biological Therapeutic Oncology Products

THROUGH: Karen Weiss, M.D.
Director, Office of Drug Evaluation VI

SUBJECT: BLA STN 125103 for Kepivance (palifermin) to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.

TO: STN 125103.0

Recommended regulatory action: Approval

Summary

The Biologic Licensing Application (BLA) for palifermin (Kepivance™), a first-in-class biological product, is the first application for systemic therapy for reduction in the incidence and duration of severe oral mucositis induced by myelotoxic, combined modality (chemotherapy and radiotherapy) employed in the course of hematopoietic stem cell transplantation. I concur with the primary reviewers' recommendations of approval of this application, based on a single major efficacy study and a supportive Phase 2 study demonstrating that six daily doses of palifermin (3 prior to and 3 following myelotoxic therapy) result in a significant reduction in both the incidence and duration of severe (WHO grade 3-4) oral mucositis. In the major efficacy study, palifermin decreased the incidence of both moderate to severe (WHO grade 2-4) and life-threatening mucositis (WHO grade 4), the median duration of moderate to severe mucositis according to multiple toxicity grading scales, and mouth and throat soreness based on patient diary reports, and reduced the requirement for opioid analgesics.

Palifermin is well-tolerated and the majority of adverse events are mild or moderate in severity. The only serious serious adverse events attributable to Palifermin are skin toxicities which occurred in <1% of patients; no fatal events have been attributed Palifermin. As compared to patients in the placebo-control arm, the following adverse events occurred at a higher incidence in palifermin-treated patients: skin toxicities (rash, erythema, pruritus, edema), oral toxicities (dysesthesias, tongue discoloration or thickness, alteration in taste), pain, arthralgias, and elevations in serum amylase and lipase. Because the KGF receptor is also present on malignant epithelial cells, there is a theoretical risk that Kepivance™ may also stimulate the proliferation of

KGF-receptor bearing malignant cells, however KGF-receptors have not been identified on cells of hematopoietic lineage, thus the theoretical risk is not likely to apply to the indicated population. There is also a theoretical risk of ocular toxicity as a result of KGF stimulation of cells on the lens of the eye, however given the high background rate of cataracts due to radiotherapy, the incremental, theoretical risk is acceptable. To date, clinical studies have not demonstrated an increase in second cancers or ocular toxicity. Additional non-clinical and clinical studies characterizing the risks of epithelial-derived tumor stimulation and ocular toxicity are ongoing or planned. Given the clinically meaningful improvements in morbidity, the benefits of palifermin outweigh the modest risks associated with this agent.

Palifermin is a non-glycosylated, truncated 16.3 kD protein derived from the genetic sequence for the endogenous paracrine growth factor, human keratinocyte growth factor (KGF). KGF, also known as FGF-7, is a member of the fibroblast growth factor family and binds to the keratinocyte growth factor receptor (FGFR2IIIb, an alternatively spliced variant of the FGFR4 receptor). Endogenous KGF is produced by mesenchymal cells and fibroblasts; binding of KGF to KGF receptors on the overlying epithelial cell tissues results in proliferation and differentiation. Proposed mechanisms by which endogenous KGF may protect epithelial cells from injury and/or hasten recovery from injury include induction of mitogenesis, tissue thickening, and induction of cellular protective mechanisms.

Regulatory History

Amgen, Inc. submitted an original IND application for palifermin (BB-IND —) on November 1, 1995. A broad development program has been conducted under this IND evaluating the safety and efficacy of palifermin for the reduction of severe oral mucositis associated with conditioning regimens (myelotoxic chemo-radiotherapy) for hematopoietic stem cell transplantation, as well as reduction in oral mucositis associated with chemo-radiotherapy for head and neck cancer and with chemotherapy for treatment of lung cancer, and for reduction in severe oral and GI mucositis associated with chemotherapy for colon cancer.

An end-of Phase 2 meeting was held in Sept 1999 to discuss general issues regarding study designs assessing the efficacy of palifermin in amelioration of the oral and gastrointestinal mucosal toxicity associated with chemotherapy with or without radiotherapy in patients with solid tumors. An additional end-of-Phase 2 meeting was held on Sept. 5, 2000, to discuss the design of efficacy studies to support approval of palifermin for reduction in the incidence and severity of severe oral mucositis in patients with hematologic malignancies undergoing hematopoietic stem cell transplantation. The proposed development plan rested primarily on the results of Study 20000162, a Phase 3 multicenter, randomized, placebo-controlled trial to be conducted in approximately 200 patients and the results of Study 980231, a Phase 2 multicenter, randomized, placebo-controlled, schedule-ranging study. In addition to these meetings, discussions were held regarding study endpoints in patients with solid tumors (Dec. 17, 1999), clinical and non-clinical studies to assess the potential impact of palifermin on tumor stimulation (Dec. 17, 1999; March 29, May 10, and Aug. 31, 2000; Mar 7, 2001; Feb 21, 2002; May 29, July 28, and Aug. 28, 2003; April 27, 2004), analytic methodology for Study 20000162 (Sept 18, and Nov. 3, 2000), role of the patient diary in support of specified labeling claims (May 24, May 25, May 31, Sept 7, 2001), and fast-track designation (July 28, 2003).

Fast track designation was granted on Dec. 31, 2003 for the following development program: "the investigation of palifermin to reduce the duration and severity of oral mucositis [redacted] in adult patients with hematologic malignancies undergoing myeloablative therapy." The proposed license application was accepted into the FDA's Continuous Marketing Application (CMA) Pilot 1 program on Jan. 31, 2004. The first reviewable unit of the BLA was the Pharmacology/Toxicology portion, which was received on May 17, 2004. The remainder of the BLA was received on June 15, 2004.

Clinical Efficacy Studies (See primary reviews by Patricia Dinndorf, M.D., Yuan-Li Shen, Ph.D)

Study 20000162, a single, randomized, placebo-controlled, multicenter trial enrolling 212 patients, provided the primary efficacy data in support of this application and confirmed the results of study 980231, a randomized, placebo-controlled, multicenter, schedule-ranging trial. Both trials were conducted in patients with hematologic malignancies undergoing myeloablative chemotherapy and total body irradiation (TBI), with hematopoietic stem cell rescue.

In the primary efficacy study, 212 patients with leukemia or lymphoma who were receiving high doses of chemotherapy and radiation therapy and bone marrow transplantation, were randomized (1:1) to receive palifermin 60 µg/kg/d or placebo by intravenous bolus injection daily for three days preceding myeloablative chemo-radiotherapy and daily for three days following completion of myeloablative chemo-radiotherapy. The randomization was stratified by underlying malignancy (NHL, Hodgkin's disease, myeloma, or leukemia) and center. The treatment schedule was as follows: investigational drug (palifermin/placebo) on study days –11, -10, and –9; 1200 cGy TBI in divided doses on study days –8, -7, -6, -5; etoposide 60 mg/kg on study day –4; cyclophosphamide 100 mg/kg on study day –2; stem cell re-infusion study day –0; investigational drug (palifermin/placebo) on study days 0, 1, and 2; and Neupogen (filgrastim) on study days 0 through 21 or until neutrophil engraftment was documented.

The primary endpoint of the study was the duration of severe (World Health Organization [WHO] toxicity severity grades 3 and 4) oral mucositis. Pre-specified secondary endpoints were the incidence of WHO grade 4 mucositis, the duration of WHO grades 2-4 mucositis, the duration of WCCNR grades 2-3 oral mucositis. Additional secondary endpoints relating to clinical symptomatology were the patient's assessment of mouth and throat soreness as captured in a daily diary (summarized as the area under the curve for mean daily scores, derived from a visual analogue scale) and the requirement for parenteral (including transdermal) opioid analgesics over the study period (study day –11 through study day 28).

The study demonstrated a significant effect on the primary efficacy endpoint, a reduction in the median duration of severe mucositis (3 vs. 9 days, $p<0.01$ CMH test). The shorter duration of severe mucositis reflects both an overall reduction in the incidence of severe mucositis and a shorter duration of severe mucositis in those who developed the condition in the palifermin-treated arm. Analysis of secondary endpoints also demonstrated a consistent effect of palifermin on reduction in the incidence and duration of severe oral mucositis. The results of the primary and secondary endpoints are summarized in Table 1.

Table 1. Primary and secondary endpoint results in Study 20000162

	Kepivance™ (60 mcg/kg/day) (n = 106)	**Placebo (n = 106)**
Median* (25th, 75th percentile) Days of WHO Grade 3/4 Oral Mucositis**	3 (0, 6)	9 (6, 13)
Incidence of WHO Grade 3/4 Oral Mucositis	63% (67/106)	98% (104/106)
Median (25th, 75th percentile) Days of WHO Grade 3/4 Oral Mucositis in Affected Patients	6 (3, 8) (n = 67)	9 (6, 13) (n = 104)
Incidence of WHO Grade 4 Oral Mucositis	20%	62%
Median (25th, 75th percentile) Days of WHO Grade 2/3/4 Oral Mucositis	8 (4, 12)	14 (11, 19)
Opioid Analgesia for Oral Mucositis: Median (25th, 75th percentile) Days	7 (1, 10)	11 (8, 14)
Median (25th, 75th percentile) Cumulative Dose (morphine mg equivalents)	212 (3, 558)	535 (269, 1429)

* $P < 0.001$ compared to placebo, using Generalized Cochran-Mantel-Haenszel (CMH) test stratified for study center. P-values presented for primary endpoint only.

** WHO Oral Mucositis Scale: Grade 1 = soreness/erythema; Grade 2 = erythema, ulcers, can eat solids; Grade 3 = ulcers, requires liquid diet only; Grade 4 = alimentation not possible.

The differences between the treatment arms with regard to relative incidence of the severity of mucositis (according to WHO Oral Mucositis Scale) are displayed in Figure 1.

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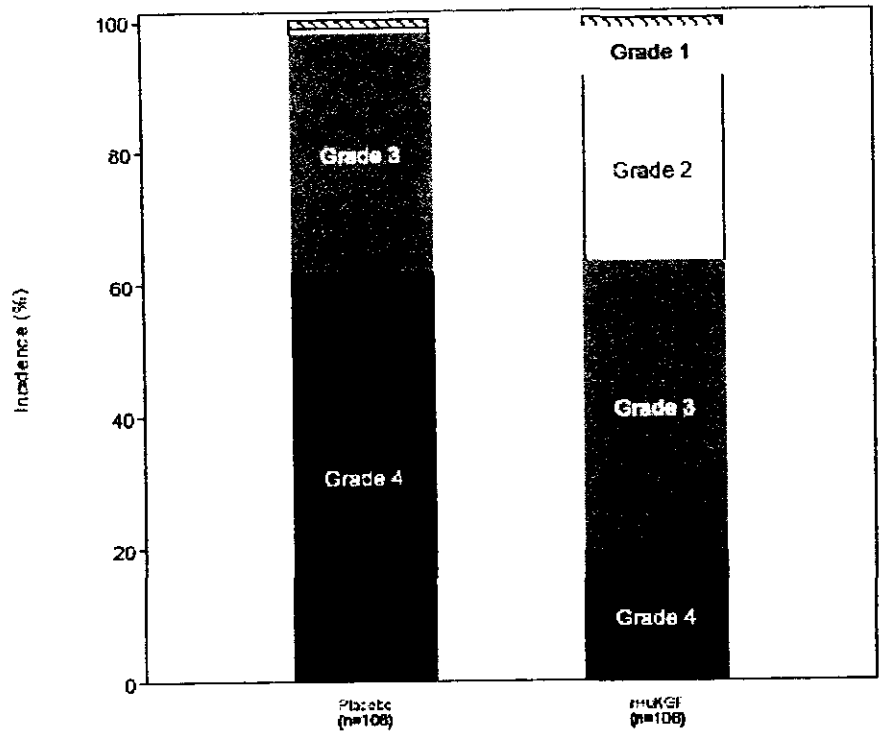

Figure 1. Incidence of mucositis in Study 20000162

Patients used a daily diary to record the severity of symptoms related to mouth and throat discomfort and diarrhea based on a 6-item questionnaire. A pre-specified analysis comparing the responses to one of these items (amount of mouth and throat soreness) revealed that palifermin-treated patients reported less mouth and throat soreness as compared with placebo-treated patients. The results of this specific question have been shown to correlate with clinical findings (mucositis score), however, based on FDA concerns regarding the development and validation of the questionnaire, analysis of other individual items or of a composite score were not performed.

The results of this study confirmed the results observed in Study 980231, a multicenter, randomized, placebo-controlled schedule-ranging study, also conducted in patients with hematologic malignancies undergoing myeloablative chemotherapy supported by hematopoietic stem cell transplantation. The treatment program was identical to that used in Study 20000162, with the exception that the dose of cyclophosphamide delivered in study day –2 could vary between 75 and 100 mg/kg. In addition, the study was initiated with a proposal to compare the effect of palifermin pre-and post-stem cell infusion and pre-infusion only with placebo controls. The initial schedule of the pre/post and pre-treatment arms were 60 µg/kg/day on study days –11, -10, -9, -5, 0, 1, and 2 (pre/post) and 60 µg/kg/day on study days –11, -10, -9, -5. After enrollment of 35 patients into the study, the Data Safety Committee monitoring the study recommended revision to the schedule to delete palifermin dosing on study day –5 (same day as TBI and less than 24 hours prior to etoposide), due to preliminary evidence of lack of efficacy and possible exacerbation of oral mucositis. The revised dosing schedule for pre/post dosing was thereafter identical to Study 20000162.

Analysis of results obtained in the 46 patients in the 6-dose palifermin arm to 40 placebo patients enrolled in the amended version of the protocol demonstrated the preliminary evidence of treatment effect that was subsequently confirmed in Study 20000162. Compared with placebo-treated patients, there was a reduction in median days of WHO Grade 3/4 oral mucositis (4 vs. 6 days), a lower incidence of WHO Grade 3/4 oral mucositis (67% vs. 80%) and a lower incidence of WHO Grade 4 oral mucositis (26% vs. 50%) for palifermin-treated patients.

As noted above, there was no evidence of improvement in the severity or duration of mucositis, and a suggestion of a detrimental effect on mucositis, when palifermin was administered in a 7-day regimen, as compared to placebo-treated patients. The additional day of dosing with the 7-day regimen (study day -5) occurred less than 24 hours after the last fractionated dose of TBI and less than 24 hours prior to etoposide dosing. A possible worsening of mucositis was also observed in animal efficacy models when palifermin was administered within 24 hours of chemotherapy/radiation therapy. Epithelial cells may be more sensitive to chemotherapy administered within 24 hours of palifermin administration due to the prolonged pharmacologic effects of palifermin, with evidence of increased cellular proliferation for 24-72 hours after dosing. Based on the findings in this treatment arm and animal studies, the labeling appropriately describes these findings in the PRECAUTIONS section and recommends a 24 hours interval between myelotoxic therapy and administration of palifermin in the DOSAGE AND ADMINISTRATION section.

Division of Scientific Investigation Review (See primary review by Jose Tavarez Pagan)

Selection of clinical study sites was based upon an evaluation of the number of subjects accrued and the consistency of findings across study sites. Because all but one study site (enrolling a single patient) demonstrated consistent results in favor of palifermin on the primary endpoint, the number of patients enrolled was used as the basis for selection of two study sites for clinical audit. These sites enrolled 40 and 29 of the total 212 patients in Study 200000162, respectively. Overall, the data from these sites were deemed to be acceptable. Protocol deviations with regard to chemotherapy dose, use of prohibited palliative medications (topical therapies for oral mucositis), and documentation of Neupogen dosing were noted. In exploratory analyses by Dr. Dinndorf, none of these deviations appeared to have an impact on the efficacy results of the study and protocol deviations were balanced between the treatment arms.

Safety (See primary reviews and consults by Patricia Dinndorf, M.D.; Ralph Bernstein, Ph.D. [Immunogenicity]; Claudia Karkowski, Pharm.D. [ODS/risk management plan] and Wiley Chambers, M.D. [ocular toxicity])

The clinical development program assessed the safety of single doses of up to 250 μg/kg of palifermin in healthy volunteers and multiple doses of up to 6- and 7-doses of palifermin over a 2 week period as a single cycle in healthy volunteers and patients with hematologic malignancy. Single doses of up to 250 μg/kg and multiple doses of up to 80 μg/kg/day were tolerable. Selection of the proposed dose and schedule is based on evidence of pharmacologic activity (epithelial cell proliferation by Ki67 immunostaining in buccal mucosa in humans) at multiple doses ≥ 40 μg/kg/d and an increase in the incidence and severity of side effects with multiple doses of 80 μg/kg/d as compared to 60 μg/kg/day. A single, multiple-dose cycle of 60μg/kg/day palifermin is the recommended dose under the proposed indication.

The application contained safety information from clinical studies of palifermin (including control subjects) conducted in healthy volunteers (6 studies), patients with hematologic malignancies receiving myeloablative therapy as conditioning prior to stem cell transplantation (5 studies), and patients with various solid tumors receiving mucotoxic chemotherapy with or without radiotherapy (6 studies). Since most adverse events were attributed to the underlying chemotherapy/radiotherapy regimen, which differs by primary cancer type, the primary assessment of palifermin toxicity was performed on safety data from 650 patients (409 palifermin, 241 placebo) enrolled in randomized, placebo-controlled studies conducted in patients with hematologic malignancies. In addition, assessment for safety signals was conducted by (1) evaluation of safety data from healthy volunteer studies, (2) within-study comparisons of toxicity in randomized, placebo-controlled studies conducted in patients with colon and head and neck cancer and (3) evaluation of all serious adverse event narratives reported for all studies, including uncontrolled, long-term follow-up studies.

The primary evaluation of safety is based upon 409 patients with hematologic malignancies (NHL, Hodgkin's disease, AML, ALL, CML, CLL, or multiple myeloma) who received palifermin and 241 patients who received placebo in 3 randomized, placebo-controlled clinical studies and a pharmacokinetic study. Patients received palifermin either before, or before and after, regimens of myelotoxic chemotherapy, with or without TBI, followed by hematopoietic stem cell support. The patients were predominantly between the ages of 41 and 60 years (median 48 yrs), male (62%), white (83%). Non-Hodgkin's lymphoma (NHL) was the most common malignancy, followed by Hodgkin's disease, multiple myeloma, and leukemia.

The most common serious adverse reaction attributed to palifermin was skin rash, which was reported in less than 1% (3/409) of palifermin-treated patients. Grade 3 skin rashes occurred in 14 patients, 9 of 409 (3%) receiving palifermin and 5 of 241 (2%) receiving placebo. In seven patients (5 palifermin, 2 placebo), study drug was discontinued due to skin rash. Other serious adverse reactions occurred at a similar rate in patients who received palifermin (20%) or placebo (21%). The most frequently reported serious adverse events in palifermin- and placebo-treated patients were fever, gastrointestinal events, and respiratory events.

The most common adverse reactions attributed to palifermin were skin toxicities (rash, erythema, edema, pruritus), oral toxicities (dysesthesia, tongue discoloration, tongue thickening, alteration of taste), pain, arthralgias, and dysesthesia. The median time to onset of cutaneous toxicity was 6 days following the first of 3 consecutive daily doses of palifermin, with a median duration of 5 days. In patients receiving palifermin, dysesthesia (including hyperesthesia, hypoesthesia, and paresthesia) was usually localized to the perioral region, whereas in patients receiving placebo dysesthesias were more likely to occur in extremities.

With regarding to laboratory abnormalities, palifermin-treated patients had a higher incidence of elevations of serum lipase and serum amylase (see Table 2), and of proteinuria. Elevations in serum lipase and amylase were observed in pre-clinical studies (see under Toxicology). The source of serum lipase and amylase elevations is not certain. Across the entire safety database, there was a single case of clinically symptomatic pancreatitis reported in a patient treated with palifermin. This patient also had multiple parasitic infections and was receiving chemo/radiotherapy for head and neck cancer.

Table 2. Incidence of Overall and Grade 3 or 4 elevations in serum lipase or amylase concentrations in the palifermin safety database		
Laboratory abnormalities	*Palifermin (n=409)*	Placebo (n=241)
Elevated serum lipase (Grade 3/4)	28% (11%)	23% (5%)
Elevated serum amylase (Grade 3/4)	62% (38%)	54% (31%)

There was no evidence of proteinuria in clinical studies of patients with hematologic malignancies; however, in these studies serial urinalyses were generally not performed. In a placebo-controlled study conducted in 145 patients with metastatic colorectal cancer receiving multi-cycle chemotherapy (5-FU/lecovorin), serial urine specimens were collected for 27 placebo-treated and 54 palifermin-treated patients. Among the 54 palifermin-treated patients, nine patients with a baseline urinalysis negative for protein subsequently developed 2+ or greater proteinuria after palifermin treatment. Among the 27 placebo-treated patients evaluated, none developed 2+ or greater proteinuria. The findings of this study are not conclusive because, by design, the number of cycles with urinalysis data collected was higher in palifermin-treated patients and risk factors for renal disease (e.g., hypertension) were not controlled for in the randomization process. However, given the findings of nephrotoxicity in rodent toxicology studies, the Applicant has agreed to the following post-marketing commitment to further assess the relationship between palifermin use and proteinuria:

- 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.

In addition, a modest increase in blood pressure was noted across studies of palifermin in patients with hematologic malignancies. In a Phase 1 placebo-controlled study in patients undergoing hematopoietic transplantation and receiving palifermin (3 doses pre-myelotoxic therapy and 3 doses post-transplant), the proportion of palifermin-treated patients reporting an adverse event of hypertension in the 60- and 80-mcg/kg/day cohorts was greater than in the placebo group (2/15 patients [13%], 2/14 [14%], and 2/23 [9%], respectively). These events were transient and did not require treatment discontinuation in any patient. In an integrated analysis of adverse events across studies in the hematology transplant setting, hypertensive events were reported in 30 of 409 (7%) palifermin-treated patients and 13 of 241 (5%) placebo-treated patients.

With regard to immunogenicity, post-treatment sera from 645 palifermin-treated patients were evaluated using a sensitive electrochemiluminescence-based binding assay. Twelve (2%) of these 645 patients tested positive for antibodies to palifermin following treatment. None of the samples had evidence of neutralizing activity in a cell-based assay.

The presence of the keratinocyte growth factor receptor on malignant epithelial cell lines and on the lens of the eye raised concerns regarding tumor promotion potential and ocular toxicities. These concerns have been discussed with the Applicant, who has developed the following risk

assessment plan for evaluation of potential stimulation of primary or secondary epithelial cancers.

- Post-marketing surveillance with special attention to new malignancies.
- Long-term follow-up of approximately 339 patients with hematologic malignancies enrolled in clinical studies of palifermin under a separate protocol (Protocol 960226). The findings in the long-term follow-up study will be evaluated against the following control groups: (1) 198 placebo-treated patients with hematologic malignancies enrolled in palifermin clinical studies; (2) historic rates on incidence of second malignancies from published literature; and (3) concurrent matched controls identified through the US International Bone Marrow Transplant Registry (IMBTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR).
- A prospective cohort study using the IBMTR and ABMTR databases.

The proposed risk management plan has also reviewed by FDA's Office of Drug Safety (see Dr. Karwoski's consult review) and found to be acceptable.

The agreed-upon post-marketing commitments include the following studies, identified as components of the proposed risk management plan for assessment of potential tumor stimulation:

- 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.

- 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.

- 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.

Assessment of ocular toxicities was attempted in a substudy nested within clinical studies of palifermin conducted in patients with hematologic malignancies undergoing hematopoietic stem cell transplantation. Although the study found no evidence of acute toxicity, the data are flawed by problems with conduct of the substudy (failure to adhere to the protocol), the short duration of

follow-up, and lack of information regarding changes in visual acuity. In order to provide additional information regarding an association between palifermin use and ocular toxicity, the Applicant has proposed to conduct the following study as a post-marketing commitment:

- To conduct a study to determine the incidence of cataracts and decreased visual acuity in 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.

Clinical and Non-clinical Pharmacology (see primary reviews by Drs. Hong Zhao [clinical pharmacology] and Anita O'Connor [non-clinical pharmacology])

The pharmacokinetic profile of palifermin was studied in rodents, wethers, non-human primates (rhesus and cynomolgus monkeys), normal volunteers, and patients. All species showed linear, dose-dependent pharmacokinetics and extravascular distribution. However, the pharmacokinetic profile in non-human primates differs from that in rodents and is more representative of that in humans.

In humans, palifermin concentrations decreased rapidly over the first 30 minutes after intravenous dosing with a plateau effect over one to four hours post-dosing. On average, total body clearance (CL) appeared to be 2- to 4-fold higher, and volume of distribution at steady state (Vss) to be 2-fold higher in cancer patients compared with healthy subjects after a 60 mcg/kg single dose of palifermin. The elimination half-life was similar between healthy subjects and cancer patients (average 4.5 hours with a range of 3.3 to 5.7 hours). No accumulation of palifermin occurred after 3 consecutive daily doses of 20 and 40 mcg/kg in healthy volunteers or 60 mcg/kg in cancer patients.

Based on the pharmacokinetic profile in patients with cancer and in healthy subjects, no gender-related differences were observed in the pharmacokinetics of palifermin at doses $\leq$ 60 mcg/kg. Clinical studies in cancer patients and healthy subjects did not include sufficient numbers of non-white healthy subjects or patients to assess potential differences in safety, activity, or pharmacokinetics as a function of ethnicity. Clinical studies of palifermin did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Among 409 patients with hematologic malignancies who received palifermin, 9 (2%) were 65 years of age or older. Clinical studies of palifermin have not been conducted in pediatric patients; studies of safety and effectiveness in children will be addressed in a required post-marketing commitment, summarized below:

- To conduct a ... pediatric study ... to determine whether administration of Palifermin decreases the incidence and duration of severe oral mucositis and related sequelae experienced by patients with hematologic malignancies who are receiving myelotoxic therapy in pediatric patients ages 3 to 16 as compared to placebo. Study protocol 20010133, a 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.

Insufficient numbers of patients with renal or hepatic dysfunction were enrolled in clinical studies to permit an assessment of the impact of these co-morbidities on efficacy, safety, or pharmacokinetics. Based on the product class (protein), the expected metabolism of palifermin is through degradation to peptides and amino acids. In non-clinical studies, there was no evidence of hepatic metabolism of palifermin. However, in ADME studies, 11% of radioactive palifermin was recovered in the urine and palifermin pharmacokinetics were altered in a bilateral nephrectomized rat model. To further assess the pharmacokinetic profile of palifermin in patients with renal impairment, the Applicant has agreed to provide the results of the following study as a post-marketing commitment:

- 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.

No formal drug-drug interactions studies were performed. However, as with the native endogenous protein, KGF, palifermin binds heparin. Based on this *ex vivo* finding, clinical studies of palifermin required that intravenous lines be flushed prior to and following intravenous administration of palifermin to remove residual heparin in the lines. Product labeling identifies the potential for interactions in the Precautions and Dosage and Administration sections of the labeling. In order to further investigate this interaction, the following post-marketing commitments have been agreed to by the Applicant:

- 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.
- 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.
- 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.

Pharmacology (see primary review by Anita O'Connor)

Palifermin has been shown to induce epithelial cell proliferation in animals and in normal volunteers, as measured by an increase in Ki67 immunostaining and BrDU uptake in epithelial cells and increased thickness of the buccal mucosa. In rodent models of chemotherapy- and radiation-therapy induced injury, administration of palifermin resulted in increased proliferation of epithelial cell, including buccal, tissues and increased tissue thickness. In some of these studies, body weight was increased and survival higher in palifermin-treated animals.

The pharmacodynamic effects of palifermin (epithelial cell proliferation) are present at 48-72 hours post-dosing, indicating that persistence of drug is not required to sustain the pharmacologic over the short-term. The persistence of the pharmacologic effects are consistent with the findings of apparent increase in toxicity observed in non-clinical (animals) studies and in patients with administration of palifermin concurrent with (i.e., within 24 hours of) radiotherapy and/or chemotherapy.

Toxicology (See primary review by Barbara Wilcox, Ph.D.)

The toxicology of palifermin has been assessed in rats and in cynomolgus and rhesus monkeys in acute and subacute (28-day) studies using the intravenous and subcutaneous routes of administration. No chronic toxicology studies were provided in the application. Dose-related changes were demonstrated in all three species that were consistent with the expected pharmacologic effects; specifically, acanthosis of the skin and hyperplastic/hypertrophic changes of the GI mucosa and urinary bladder. In addition, the following reversible dose-dependent toxicities were observed in rats but not in primates: increase in organ size of the liver, increase in renal organ weight with mild to moderate glomerulonephritis and glomerulosclerosis associated with urinary casts, an increase in size and number thyroid follicles associated with periglandular fibrosis, and thymus gland involution. Dose-related elevations in serum amylase and lipase were observed across species but not in all studies.

Palifermin was shown to be embryotoxic in rats and rabbits, with increased fetal loss but no developmental toxicologic changes. At high doses, there was evidence of impairment of fertility in male and female rats. Given this, the agreed-upon product labeling classifies palifermin as Pregnancy Category C.

Genotoxicity studies were negative, however such studies are generally not informative for proteins.

Given the presence of KGF receptors on malignancies arising from the epithelium, studies were performed with human tumor cell lines assessing stimulation of cell line growth *in vitro and in vivo* (in athymic mouse xenografts). *In vitro* human tumor cell stimulation was assessed in 41 human cancer cells lines (of these, 3 were leukemia cell lines) through exposure to palifermin at varying concentrations (10-100,000 ng/ml) in tissue culture. The positive control was a murine keratinocyte cell line and negative controls were tissue cultures of the same human tumor lines in the absence of palifermin. At the highest concentration of palifermin studied, ^{3}H-thymidine incorporation was decreased relative to negative controls; such a finding could be due either to a decrease in proliferation or to cytotoxic effects on cells. Increased proliferation was observed in 11 of the 41 cell lines [1/3 prostate, 3/13 lung, 4/11 colon, and 3/10 mammary cancer cell lines] at lower palifermin concentrations. The magnitude of increased incorporation was modest (30-100% increased incorporation as compared to negative controls). Evidence of induction of KGF receptor mRNA was observed in the mouse positive control and in seven human cancer cell lines; five of these human cancer cell lines also showed increased ^{3}H-thymidine incorporation in the experiment above.

Assessment of *in* vivo tumor growth was performed in athymic mice implanted with one of 6 human tumor cells lines, treated with 0, 150, 500, 1500 or 4000 mcg/kg of palifermin for 3 of 7

days on multiple weekly cycles. Mortality was high in all groups, including controls. Only one human tumor cell line showed a significant, dose-dependent increase in tumor growth rate. Of interest, there was evidence of an increased growth rate at lower palifermin doses, with decreased growth rate and/or inhibition at higher doses observed in xenograft models using other human cell lines. Interpretation of the study was confounded by high mortality in all groups (including controls), lack of justification for cell line selection, lack of a positive tumor control, and lack of assessment of serum concentrations or receptor occupancy.

The Applicant has agreed to evaluate the potential for mitogenic effects of palifermin on KGF receptor-bearing malignant cells in the following post-marketing commitment:

- 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 available by June 2005. The final report will be submitted to the FDA by December 2005.

Additional post-marketing commitments to evaluate the potential of palifermin to stimulate tumor proliferation are described in the summary of safety issues.

Chemistry, Manufacturing, and Controls (see primary reviews by Kurt Stromberg, Ph.D. and Marlene Swider)

Palifermin is a highly purified and well-characterized non-glycosylated 16.3 kD protein produced by genetically modified *E. coli*. Palifermin contains the identical primary structure as endogenous KGF for the first 140 amino acids from the C-terminus, but lacks the 23 amino acids from the N-terminal, which are present in endogenous KGF. The manufacture of palifermin includes [ ] *E. coli*. Synthesis [ ] The manufacturing process is under control and has been satisfactorily validated. The lot release specifications are appropriate and will ensure lot-to-lot consistency.

Amgen, Inc. manufactures drug substance at their LakeCentre facility in Boulder, CO. A pre-approval inspection of the facility was conducted on Sept. 27 through Oct 1, 2004. Observational findings were classified as VAI and there are no pending or ongoing compliance actions at this facility that would preclude approval of this application.

Drug product manufacturing is conducted by [ ] Pre-approval inspection was waived based on prior inspections of that facility in 2002 and 2004 that were classified VAI.

Proprietary Name review

The proposed proprietary name of Kepivance was assessed by the Division of Medication Errors and Technical Support and found to be acceptable.

Labeling Review

Labeling comments from all members of the review teams and consultants were considered and agreement reached on final labeling that was acceptable to all members of the team.

Recommendation

All members of the review team recommend approval for this application. I concur with the review team and also recommend approval for this application.

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Date: December 9, 2004

To: Administrative File, **STN 125103/0**

From: Marlène G. Swider, Facility Reviewer, CDER/OC/DMPQ TFRB, HFD-328

Through: Michael D. Smedley, Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328 12/13/04
Calvin Koerner, Peer Reviewer, CDER/OC/DMPQ/TRFB, HFD-328 12/13/04

Subject: **Review Memo: Biological License Application (BLA):** New BLA

US License #
Applicant Amgen, Inc.
Product Palifermin (rHuKGF)
Indication [redacted]

Due date: December 15, 2004

Recommendation: The facilities/equipment information related to this application and corresponding amendments has been reviewed and the application, as amended, is recommended for approval. Seven review items were noted during the review process and were subsequently resolved.

Review Summary

Amgen, Inc. submitted this BLA to license Palifermin and the associated Drug Substance and Drug Product manufacturing processes. Drug Substance manufacturing is conducted by Amgen, Inc. at their LakeCentre, Boulder, Colorado facility. At this facility, raw material, components and drug substance get stored and tested. Drug Product manufacturing is conducted by [redacted] This company also is responsible for [redacted]

Drug Substance Testing is conducted by Amgen LakeCentre facility, Longmont

facility and [redacted] Drug Substance Specification Testing is conducted by Amgen Inc. Thousand Oaks, CA. This facility also stores raw material, components, and drug product; and does testing.

The BLA was submitted in an electronic Common Technical Document (evs) format. Four application amendments were submitted at the request of the Therapeutics Facilities Review Branch (TFRB). The following is a list of the requested amendments and their corresponding contents:

Amendment 05 – SOPs related to Palifermin manufacturing. (September 9, 2004)

Amendment 09 – Index for floor plans, in-process control testing. (November 2, 2004)

Amendment 11 – Lot numbering system, list of [redacted] equipment. (November 10, 2004)

Amendment 17 – Identification of container closure suppliers' names, addresses and status. (Not received yet.)

The scope of this review was limited to a TFRB functionality review for the Drug Substance's Manufacturer, Controls, Container/Closure, Facility/Equipment, [redacted] sections and the Drug Product's Pharmaceutical Development, Manufacturer, Controls, Container/Closure, Facility/Equipment, [redacted] sections and the Environmental Assessment. Also, this memo includes the review of drug product information submitted in this BLA, drug substance information acquired during inspection and Amgen's past compliance manufacturing history.

Drug Product facility [redacted] was waived for inspection.

An evaluation of the supplement for completeness and adequacy was completed on November 18, 2004. Seven review items and five inspection items were noted during this evaluation.

The firm was contacted via telephone to discuss the review items on August 25, September 8, November 15, and December 8, 2004. (See Teleconference Memos attached.) The firm adequately resolved all the review items addressed during the teleconferences by submitting the corresponding amendments received by the Agency on dates shown above. The supplement amendments were evaluated during the review of the BLA and incorporated into this memo. See the Review Narrative Section for the review items and their subsequent resolution.

An inspection of the Amgen LakeCentre facility was conducted from September 27 through October 1, 2004 by Karen Hirshfield, Emily Shacter, Jiamning Li, Mike Goga and myself. A ten observation FDA Form 483 was issued to the firm on October 1, 2004. A response letter to the 483 observations was received, reviewed, and deemed adequate by the Agency. The 5 inspection items were addressed during the Pre-License Inspection (PLI). See the Conclusion section of this memo for the individual inspectional items. The inspection item resolutions are in the EIR.

BLA STN 125103/0, Amgen LakeCentre, Boulder, CO

Products Affected

Palifermin (rHuKGF)

Review Narrative

Drug Substance

Manufacturer, 3.2.S.2
Section on Manufacturers Names, Description of Manufacturing Process and Process Controls, Control of Materials, and Controls of Critical Steps and Intermediates were provided.

Manufacturers Names, 3.2.S.1
This section included name, address, and responsibility of each manufacturer and their respective production facility involved in the manufacturing and testing of the product.

Drug Substance Manufacturer is:

- Amgen Inc. (ACO) LakeCentre Facility (LC) 5550 Airport Boulevard Boulder, CO 80301 USA (FEI # [ ]. Inspected on : 1/22-2/5/03, 6/9 – 17/04, and 8/23 – 27/04.

Drug Product Manufacturer is:

- [ ]

Drug Substance Testing is conducted by:

- Amgen Inc. (ACO) LakeCentre Facility (LC) 5550 Airport Boulevard Boulder, CO 80301 USA (FEI # [ ]
- Longmont Facility 4000 Nelson Road Longmont, CO 80503 USA (FEI [ ]
- [ ]

Drug Substance Specification Testing is conducted by:

- Amgen Inc. (ATO) One Amgen Center Drive Thousand Oaks, CA 91320-1799 USA (FEI# [ ] ACO and Longmont.

Review Comment – Information is satisfactory. FEI for each facility was obtained from FACTS. I have no further comments.

Description of Manufacturing Process and Process Controls 3.2.S.2.2 — This section included

24 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Teleconference Memorandum

Date: 8 December 2004
From: Marlene G. Swider, CDER, OC, DMPQ, TFRB, HFD-328 MGS
To: File: STN 125103/0
Subject: Teleconference to discuss information missing from original BLA to license palifermin and the associated Drug Substance and Drug Product manufacturing processes.

Meeting Date: 8 December 2004 **Time:** 3:00 p.m.
Location: 5515 Security Lane, Rm. 1051
Sponsor: Amgen, Inc.
CDER Meeting Leader: Marlene Swider, OC, DMPQ, TFRB. HFD-328
FDA Attendees: Marlene Swider, OC, DMPQ, TFRB. HFD-328
Sponsor Attendees: Rose Lopez, Regulatory Affairs Specialist

Meeting Objectives To request a follow up on previous information requested on November 15, 2004, but still not received in FDA on the suppliers' names, addresses and status.

Discussion Points:

Concern #1

The information above is still missing in the original BLA as an amendment.

Decisions/Agreements Reached:

The firm acknowledged already sending this information as amendment No. 17.

Action Items:
(None)

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: Oct. 5, 2004	**DESIRED COMPLETION DATE:** November 29 , 2004	**ODS CONSULT #:** 04-0261

TO: Earl Dye, Ph.D.
Director, Division of Review Management and Policy
HFM-585

THROUGH: Susan Giuliani
Project Manager, Division of Review Management and Policy
HFM-588

PRODUCT NAME: **Kepivance™** (Palifermin Growth Factor Injection) 6.25 mg per vial **BLA-IND #:** 125103/0	**SPONSOR:** Amgen, Inc.

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Kepivance™. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of the document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

3. DMETS recommends consulting Guiragos Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee regarding the appropriate appearance of the established name.

4. DDMAC finds the proprietary name Kepivance™ acceptable from a promotional perspective.

Carol Holquist 11/24/04

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 27, 2004

BLA-IND NUMBER: 125103/0

NAME OF DRUG: **Kepivance™**
(Palifermin Growth Factor Injection)
6.25 mg per vial

NDA SPONSOR: Amgen, Inc.

I. INTRODUCTION

This consult was written in response to a request from the Division of Review Management and Policy, for an assessment of the proprietary name "Kepivance™" regarding potential name confusion with other proprietary or established drug names. The sponsor originally submitted the proposed names [ ] and [ ] for review (ODS Consult # 04-01030). However, these names were withdrawn by the sponsor, and the name Kepivance was subsequently submitted. The container label, carton and package insert labeling were provided for review and comment. The sponsor also submitted additional information, including an independent analysis conducted by [ ] for review and comment.

PRODUCT INFORMATION

Kepivance™ is the proposed name for palifermin, a human keratinocyte growth factor, produced by recombinant DNA technology in *Escherichia* coli. It is indicated [ ] in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support. The recommended dosage of Kepivance™ is 60 micrograms/kg per day, administered as an intravenous bolus injection for three consecutive days before and three consecutive days after myelotoxic therapy, for a total of six doses. Kepivance™ should be refrigerated at 2° to 8°C (36° to 46°F), and should be protected from light. Kepivance™ will be supplied as a 6.25 mg vial of palifermin powder for injection, which will be reconstituted with 1.2 mL of sterile water for injection to yield a final concentration of 5 mg/mL.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii] for existing drug names which sound-alike or look-alike to "Kepivance™" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[iv] and the data provided by Thomson & Thomson's SAEGIS Online Service[v] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Kepivance. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have any concerns from a promotional perspective regarding the proposed name Kepivance.

2. The Expert Panel identified four proprietary names that were thought to have potential for confusion with Kepivance. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

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[i] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[iii] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 1998-2004, and the electronic online version of the FDA Orange Book.

[iv] WWW location http://www.uspto.gov.

[v] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by Prescription Studies

Product Name	**Dosage form(s), Established name**	**Usual adult Dose***	**Other****
Kepivance (Rx)	**Palifermin Injection 5 mg/ml 6.25 mg per vial**	**60 mcg/kg/day, administered as an intravenous bolus injection for 3 consecutive days before after myelotoxic therapy for a total of 6 doses.**	
K-vescent (Rx)	Potassium Chloride Tablets 20 mEq	20 to 100 mEq 1-2 times daily.	**L/A, S/A
Glucovance (Rx)	Glyburide and Metformin Tablets 1.25 mg/250 mg, 2.5 mg/500 mg, and 5 mg/500 mg	Initially take one tablet once daily; or one tablet twice daily, in the morning and evening.	**S/A
Capoten (Rx)	Captopril Tablets 12.5 mg, 25 mg, 50 mg, & 100 mg	Hypertension and Congestive Heart Failure Initially, take 25 mg two to three times daily. After 1-2 weeks, may increase to 50 mg two to three times daily. Diabetic Nephropathy 25 mg three times daily, taken 1 hour before meals.	**S/A
Diprivan (Rx)	Propofol Injectable Emulsion 10 mg/mL	Induction of Anesthesia: 2 to 2.5 mg/kg Maintenance: 100 to 200 micrograms/kg/min by continuous infusion.	**L/A, S/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search modules return a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Kepivance were discussed by the Expert Panel.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Kepivance with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 129 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Kepivance (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded

on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Kepivance a.d. #3 vials	Give 5 mg of Kepivance by IV push daily for three days.
Inpatient RX: Kepivance 5mg IVP QD x3d	

2. Results:

   One participant in the verbal study identified the proposed name as Capugen, which is phonetically similar to Capoten, a currently marketed prescription drug product. The remaining interpretations were misspelled variations of the proposed name, Kepivance. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Kepivance", the products considered to have potential for name confusion with Kepivance include: K-vescent, Glucovance, and Diprivan. Upon further review of the names gathered from EPD, POCA, and the results of the prescription studies, the name Glucovance was not reviewed further due to numerous product differences such as product strength, route of administration, dosage form, and indication of use.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Kepivance and K-vescent, Glucovance, Capoten, or Diprivan. It should be noted that one participant in the verbal study identified the proposed name as Capugen, which is phonetically similar to the currently marketed product, Capoten. The majority of the incorrect interpretations from the written and verbal studies were misspelled/phonetic variations of the proposed name, Kepivance.

1. K-vescent was identified to look and sound similar to the proposed name, Kepivance. K-vescent is a supplement used to prevent and treat low potassium blood levels caused by diuretics or poor diet. The recommended dose ranges from 20 mEq to 100 mEq administered one to two times daily. Both names contain three syllables, with the letter "K" appearing at the beginning of the names. The letter combinations "vesc" (in K-vescent) and "vance" (in Kepivance) are phonetically similar, and look somewhat similar when scripted. However, the "p" sound in Kepivance helps to distinguish the names from each other phonetically, and the down stroke of the letter "p" helps to distinguish the names from each other orthographically. In addition, there are product differences which help to distinguish K-vescent from Kepivance, such as K-vescent

route of administration (intravenous vs. oral), dosage form (injection vs. tablet), strength (6.25 mg per vial vs. 20 mEq), and dosing regimen (daily for 3 consecutive days before and after therapy vs. 1-2 times daily). In addition, because the dosing strength of Kepivance will be based on body weight in kilograms, the products do not overlap in this regard as well. DMETS believes that the lack of convincing look-alike and sound-alike similarities between the names, in addition to the numerous product differences minimizes the potential for confusion and errors occurring between K-vescent and Kepivance.

K-vescent	Kepivance
K-vescent	Kepivance

2. Diprivan was identified to have sound-alike and look-alike similarity to the proposed name, Kepivance, particularly when the names are written in lower case letters. Diprivan contains the active ingredient, propofol. It is indicated for the induction of maintenance of anesthesia for in-patient and out-patient surgeries, and to initiate and maintain sedation during diagnostic procedures and intubation. Both names have three syllables, and the letter combinations "privan" in Diprivan and "pivance" in Kepivance are orthographically and phonetically similar due to the presence of the letters "p", "i", "v", "a", and "n", in each name. Additionally, the letter combination "Di" (in Diprivan) can look somewhat similar to the combination ("Ke"), depending on how they are scripted. The beginnings of the names are distinguishable from each when spoken ("Di" vs. "Ke"). Both products share an overlapping route of administration (intravenous) and dosage form (injection). However, Diprivan is administered by intravenous infusion, whereas Kepivance will be given as bolus injection. There is potential for overlap in dosing strength between Diprivan and Kepivance. For example, a person weighing approximately 42 kg (92 pounds) would require a Kepivance dose of 2520 micrograms/kg/day, roughly 2.5 mg/kg, which is within the dosing range for Diprivan as induction of anesthesia. However, Diprivan and Kepivance differ in indication of use (anesthesia and sedation vs. oral muscovite), and will be administered by healthcare providers who are familiar with their use. Although Diprivan and Kepivance share some look-alike similarity, the differences, dosing regimen, in addition to differences in indication, and context of use, will minimize the potential for confusion and errors between Diprivan and Kepivance.

Diprivan	Kepivance
Diprivan	Kepivance

3. Capoten was identified to sound similar to the proposed name, Kepivance. Capoten contains the active ingredient, Captopril. It is indicated for the treatment of hypertension, congestive heart failure, myocardial infarction, and diabetic nephropathy. The recommended starting dose of Capoten is 25 mg administered two or three times daily, one hour before meals. Both names consist of three syllables with a phonetically similar letter combination at the beginning of each name ("Cap" vs. "Kep"). The remainder of the names is different and distinguishable from each other when spoken ("oten" vs. "ivance"). Capoten and Kepivance also differ in route of administration (oral vs. intravenous), dosage form (tablet vs. injection), strength (12.5 mg, 25 mg, 50 mg, and 100 mg vs. 5 mg/mL), and dosing regimen (two to three times daily vs. once for 3 consecutive days before and after surgery). DMETS believes that the phonetic differences

between the names, in addition to the differences in route of administration, dosage form, strength, and dosing regimen, will minimizes the potential for confusion between Capoten and Kepivance.

E. INDEPENDENT NAME ANALYSIS

The analysis conducted by [ ] discusses the following names that were not identified as potential look-alike or sound-alike products by DMETS: Combivent, Emivan, Epipen, Epogen, Invanz, Kefzol, Ketamine, Kytril, Mepivacaine, Relafen, and Vanceril. Following review of the proprietary name analysis submitted by [ ] DMETS concurs that none of the aforementioned names pose a significant safety risk, due to a lack of convincing look-alike and sound-alike similarities, in addition to product differences such as dosage form, route of administration, strength, dosing regimen, and indication of use.

III. LABELING, PACKAING AND SAFETY RELATED ISSUES

In review of the container labels, carton and insert labeling of Kepivance, DMETS has attempted to focus on safety issues relating to possible medications errors. DMETS has identified areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (single use vial)

B. CARTON LABELING

C. PACKAGE INSERT LABELING

[redacted]

IV. RECOMMENDATIONS

A. DMETS has no objections to the use of the proprietary name, Kepivance. This is considered a tentative decision, and the firm should be notified that the firm should be notified that this name with its associated labels and labeling must be re-evaluated 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of the proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in Section III of this review in order to minimize potential errors with the use of this product.

C. DMETS recommends consulting Guiragos Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee regarding the appropriate appearance of the established name.

D. DDMAC finds the proprietary name Kepivance acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242

11/24/04

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

11/24/04

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A. DMETS Prescription Study Results.

Voicemail	Inpatient	Outpatient
Capugen	Kepivance	Kekivana
Capuvent	Kepivance	Kepivana
Kefivan	Kepivance	Kepivana
Kempivan	Kepivance	Kepivana
Kepivan	Kepivance	Kepivana
Kepivan	Kepivance	Kepivana
Kepivan	Kepivance	Kepivana
Kepivance	Kepivance	Kepivana
Keppivance	Kepivance	Kepivance
Keppi-Vant	Kepivance	Kepivance
Ketavan	Kepivance	Kepivanu
Kete-van	Kepivance	Kepivoanu
	Kepivance	Kexivana
	Kepivance	Kexivana
		Kexivana
		Kexivana
		Kexivana

cc: NDA 125103/0
HFM-588: Division Files
HFM-585: Earl Dye, Ph.D., Acting Division Director, DRMP
HFM-573: Patricia Keegan, M.D., Director, DTBOP
HFM-588: Susan Giuliana, Project Manager, DRMP
HFM-576: Patricia Dinndorf, M.D.
HFD-040: Debi Tran, Regulatory Review Officer, DDMAC
HFD-430: Robert Kang, Project Manager, DDRE
HFD-420: Sammie Beam, Project Manager, DMETS
HFD-420: Lisa Hubbard, Project Manager, DMETS
HFD-420: Denise Toyer, Deputy Director, DMETS
HFD-420: Tia M. Harper-Velazquez, Safety Evaluator, DMETS

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DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Teleconference Memorandum

Date: 15 November 2004
From: Marlene G. Swider, CDER, OC, DMPQ, TFRB, HFD-328 MGS
To: File: STN 125103/0
Subject: Teleconference to discuss information missing from original BLA to license palifermin and the associated Drug Substance and Drug Product manufacturing processes.

Meeting Date: 15 November 2004 **Time:** 4:00 p.m.
Location: 5515 Security Lane, Rm. 1051
Sponsor: Amgen, Inc.
CDER Meeting Leader: Marlene Swider, OC, DMPQ, TFRB. HFD-328
FDA Attendees: Marlene Swider, OC, DMPQ, TFRB. HFD-328
Sponsor Attendees: Geza Eckecs, Associate Manager Regulatory Affairs CMC

Meeting Objectives: To request supplier's names, addresses and status.

Discussion Points:

Concern #1

The information above is missing in the original BLA.

Decisions/Agreements Reached:

The firm acknowledged the absence of this information in the BLA.

Action Items:
The firm will provide response as an amendment to the BLA.

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Teleconference Memorandum

Date: 8 September 2004
From: Marlene G. Swider, CDER, OC, DMPQ, TFRB, HFD-328 MGS
To: File: STN 125103/0
Subject: Teleconference to discuss information missing from original BLA to license palifermin and the associated Drug Substance and Drug Product manufacturing processes.

Meeting Date: 8 September 2004 **Time:** 2:00 p.m.
Location: 5515 Security Lane, Rm. 1051
Sponsor: Amgen, Inc.
CDER Meeting Leader: Marlene Swider, OC, DMPQ, TFRB. HFD-328
FDA Attendees: Marlene Swider, OC, DMPQ, TFRB. HFD-328
Sponsor Attendees: Geza Eckecs, Associate Manager Regulatory Affairs CMC

Meeting Objectives To request a list of [ ] equipment for DS and DP, a list of [ ] systems during the manufacture of palifermin, an index list for the floor diagrams, and a detailed explanation of their lot numbering system.

Discussion Points:

Concern #1

The information above is missing or incomplete in the original BLA.

Decisions/Agreements Reached:

The firm acknowledged the absence of this information in the BLA.

Action Items:
The firm will provide response as an amendment to the BLA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
5515 Security Lane
Rockville MD 20852-1448

Teleconference Memorandum

Date: 25 August, 2004
From: Marlene G. Swider, CDER, OC, DMPQ, TFRB, HFD-328 MGS
To: File: STN 125103/0
Subject: Teleconference to discuss information missing from original BLA to license palifermin and the associated Drug Substance and Drug Product manufacturing processes.

Meeting Date: 25 August, 2004 **Time:** 1:35 p.m.
Location: 5515 Security Lane, Rm. 1051
Sponsor: Amgen, Inc.
CDER Meeting Leader: Marlene Swider, OC, DMPQ, TFRB. HFD-328
FDA Attendees: Marlene Swider, OC, DMPQ, TFRB. HFD-328
Sponsor Attendees: Geza Eckecs, Associate Manager Regulatory Affairs CMC

Meeting Objectives To request a list of SOP's related with the manufacture of this new product and information on the [ ] in-process testing.

Discussion Points:

Concern #1

Information on what SOPs is being implemented/affected as a result of manufacturing the new product palifermin is missing from the BLA.

Concern #2

Information on the [ ] in-process testing is not included in the manufacturing steps summarized in the BLA.

Decisions/Agreements Reached:

The firm acknowledged the absence of this information in the BLA.

Action Items:
The firm will provide response as an amendment to the BLA.