CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

22-505

Trade Name: Egrifta, 1 mg/vial.

Generic Name: tesamorelin for injection

Sponsor: Kendle International, Inc.

Approval Date: November 10, 2010

Indications: reduction of excess abdominal fat in HIV-infected patients with lipodystrophy

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APPLICATION NUMBER:

22-505

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APPLICATION NUMBER:

22-505

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022505

NDA APPROVAL

Kendle International, Inc.
Attention: Michelle Wilson, Ph.D.
Senior Regulatory Consultant
U.S. Agent for Theratechnologies, Inc.
44 Vine Street, Suite 500
Cincinnati, OH 45202

Dear Dr. Wilson:

Please refer to your New Drug Application (NDA) dated May 29, 2009, received May 29, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Egrifta (tesamorelin for injection), 1 mg/vial.

We acknowledge receipt of your amendments dated June 17 (2), 29, and 30, July 31, September 9 and 29, October 12, 29, and 30, November 20 and 30, and December 8, 17, 22, 24, and 28, 2009, and January 20 and 28, March 23, April 1, May 3, 12, and 17, June 2, 14, and 23, July 23, August 2 and 11, September 13, October 29, and November 10, 2010.

This new drug application provides for the use of Egrifta (tesamorelin for injection) for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert and text for the patient package insert and patient instructions for use submitted on November 10, 2010). Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate-container labels submitted on November 10, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22505**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because there is evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups. Administering this drug to a patient population that has not yet completed growth may result in adverse events associated with supraphysiologic levels of growth hormone, including excessive linear growth.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk when available data indicate the potential for a serious risk of microbial contamination possibly resulting in soft tissue infections which can occur during product reconstitution; or identify an unexpected serious risk when available data indicate the potential for a serious risk of malignancies or diabetic retinopathy related to elevated IGF-1 levels; or assess signals of serious risks of glucose intolerance/diabetes mellitus and hypersensitivity reactions suggested by clinical trial data.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1708-1 Manufacturing studies to determine a process for providing a daily dose (2 mg) of lyophilized product in a single vial. This single vial would replace the container-closure system described in the original application in which the daily dose is provided in two separate vials each containing 1.1 mg of lyophilized powder.

The timetable you submitted on November 10, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	May 2011
Study Completion:	July 2012
Final Report Submission:	September 2013

1708-2 A long-term observational safety study of at least 10 years duration comparing patients with HIV-associated lipodystrophy and excess abdominal fat treated with Egrifta compared to a similar group of patients not treated with Egrifta to assess potential safety concerns associated with long-term administration of Egrifta, including but not limited to the occurrence of glucose intolerance/diabetes mellitus, hypersensitivity reactions, malignancies, liver abnormalities, kidney abnormalities, diabetic retinopathy, and major adverse cardiovascular events.

The timetable you submitted on November 10, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	May 2011
Study Completion Date:	December 2024
Final Report Submission:	August 2025

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify the unexpected serious potential risk of diabetic retinopathy and secondarily the unexpected serious potential risk of long-term effects of Egrifta on glucose metabolism and major adverse cardiovascular events (MACE).

Therefore, based on appropriate scientific data, FDA has determined that you are required, to conduct the following:

1708-3 A prospective, randomized, placebo-controlled clinical trial to evaluate if Egrifta increases the risk of development or progression of diabetic retinopathy when administered to HIV-infected patients with lipodystrophy and concomitant

diabetes. The primary objective is to compare the percentage of subjects with a 3-step or greater progression in the Early Treatment Diabetic Retinopathy Study (ETDRS) scale after a minimum of three years of treatment with Egrifta versus placebo. The trial will also evaluate the long-term effect of Egrifta on glucose metabolism and conduct blinded adjudication for major adverse cardiovascular events (MACE).

The timetable you submitted on November 10, 2010, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	April 2011
Study Completion Date:	May 2016
Final Report Submission:	November 2016

Submit the protocols to your IND 061226, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

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, see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jennifer Johnson, Regulatory Project Manager, at (301) 796-2194.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures:
Physician Labeling
Patient Labeling
Instructions for Use
Carton and Container Labeling

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

/s/

CURTIS J ROSEBRAUGH
11/10/2010