



NDA 203441/S-012

SUPPLEMENT APPROVAL

Shire-NPS Pharmaceuticals, Inc.
Attention: Kristen McLaren
Project Manager, Global Regulatory Affairs
300 Shire Way
Lexington, MA 02421

Dear Ms. McLaren:

Please refer to your supplemental New Drug Application (sNDA), dated and received on February 28, 2018 (eCTD SN0210), and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for GATTEX (teduglutide) for injection, 5 mg.

This Prior Approval sNDA provides for the following:

1. Updated the Adverse Reactions section of the prescribing information (PI) based upon a reanalysis of safety data from the original clinical trials that evaluated GATTEX (teduglutide);
2. Converted the PI to be compliant with the Pregnancy and Lactation Labeling Rule (PLLR);
3. Removed the text "rDNA origin" from the established name/drug product title within the PI;
4. Applied the aforementioned changes, accordingly, to the medication guide (MG), instructions for use (IFU), and carton and container labeling; and
5. Modified the approved GATTEX (teduglutide) Risk Evaluation and Mitigation Strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental 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 the content of labeling [21 CFR 314.50(l)] in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the PI, MG, and IFU), with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. 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*, located at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>. The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft (MS) Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate the review of your submission, provide a highlighted or marked-up copy, which shows all changes, as well as a clean MS Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, which was submitted and received on April 20, 2018 (eCTD SN0228), as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the Guidance for Industry titled, *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*, located at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf>. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 203441/S-012.**” Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for GATTEX (teduglutide) was originally approved on December 21, 2012 (Reference ID: 3253828), and the most recent REMS modification was approved on March 21, 2017 (Reference ID: 4072641). The REMS consists of elements to assure safe use and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of modifications to the REMS document and appended materials to align with labeling changes related to this efficacy supplement's approval.

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modifications are necessary to ensure the benefits of the drug outweigh the risks:

- a. Removal of the text "rDNA origin" from the established name/drug product title in the labeling and the REMS;
- b. Requiring that healthcare providers (HCPs) request paper copies of online training materials when inquiring about how to become certified; and
- c. Replacing the phone number with a facsimile number for HCPs to report their completion of training.

Your proposed modified REMS, submitted and received on November 9, 2018 (eCTD SN0277) and appended to this letter, is approved. The modified REMS consists of elements to assure safe use and a timetable for submission of assessments of the REMS. The timetable for submission of assessments of the REMS remains the same as that approved on December 21, 2012, and there are no changes to the REMS assessment plan.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a. An evaluation of how the benefit-risk profile will or will not change with the new indication.
- b. A determination of the implications of a change in the benefit-risk profile for the current REMS.
- c. *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d. *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

- e. *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f. *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 203441 REMS ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 203441 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 203441/S-XXX CHANGES BEING EFFECTED IN 30 DAYS PROPOSED MINOR REMS MODIFICATION

or

**NEW SUPPLEMENT FOR NDA 203441/S-XXX
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION**

or

**NEW SUPPLEMENT FOR NDA 203441/S-XXX
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES
SUBMITTED IN SUPPLEMENT YYY**

or

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 203441/S-XXX
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA 203441

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in MS Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but MS Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in SPL format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated eLIST.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the PI to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry titled, *Providing Regulatory Submissions in Electronic and Non-Electronic Format — Promotional Labeling and Advertising Materials for Human Prescription Drugs*, located at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>.

You must submit final promotional materials and the PI, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>.

Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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

If you have any questions, contact Benjamin Vali, Regulatory Project Manager, at (301) 796-4261 or benjamin.vali@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, M.D., M.M.Sc.
Associate Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling:

PI

MG

IFU

Carton and Container Labeling

REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JESSICA J LEE
12/18/2018