DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203441-S10

SUPPLEMENT APPROVAL

Shire-NPS Pharmaceuticals, Inc.
Attention: Linda Mota
Associate Director
Global Regulatory Affairs
300 Shire Way
Lexington, MA 02421

Dear Ms. Mota:

Please refer to your Supplemental New Drug Application (sNDA) dated and received on September 15, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for GATTEX (teduglutide [rDNA origin]), reconstituted lyophilized powder for subcutaneous injection, 5 mg.

This supplemental application proposes the following modification to the approved risk evaluation and mitigation strategy (REMS) for GATTEX: Removal of the communication plan as an element of the REMS and placement of the Dear Healthcare Professional Letters issued to prescribers who are identified as untrained at 60 days from the date of their initial prescription, and again at 12 and 24 months from the date of their initial prescription from communication plan into the elements to assure safe use (ETASU). This supplement is in response to our August 15, 2016 REMS Modification Notification letter.

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.

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

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for GATTEX (teduglutide [rDNA origin]) was originally approved on December 21, 2012, and the most recent modification was approved on May 27, 2016. The REMS consists of a communication plan, elements to assure safe use and a timetable for submission of assessments of the REMS. In order to ensure the benefits of GATTEX (teduglutide [rDNA origin]) outweigh

its risks and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the following REMS Modifications: removal of the communication plan as an element of the REMS, and to maintain the ongoing distribution of the DHCP Letters to prescribers identified as untrained as an activity under the elements to assure safe use.

Your proposed modified REMS, submitted on September 15, 2016, amended 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.

The revised REMS assessment plan must include, but is not limited to, the following:

1. Date(s) the Dear Healthcare Professional letter mailing(s) were sent and number of healthcare professionals that were sent this letter.
    a. Number of mailings returned
    b. Sources of the recipient lists
2. Number of HCPs who completed the Post-training Knowledge Assessment Questions via the Shire REMS website or through mailing. It should be noted these Post-training Knowledge Assessment Questions are not a part of the REMS but will help to assess the effectiveness of the REMS training and hence are another part of the assessment plan.
    a. Demographics of prescribers (by specialty type) that completed the post-training knowledge assessment questions, to the extent possible
    b. Summary of the method used to complete the Post-training Knowledge Assessment Questions (on-line, fax/mail)
    c. Number of prescribers who completed each knowledge assessment question correctly and the number of prescribers who did not complete each post training knowledge assessment question correctly
3. Number of prescribers identified through specialty pharmacy dispensing data to have dispensed a patient prescription who did not complete the Post-training Knowledge Assessment Questions (during the reporting period and cumulative).
    a. Number of prescribers who did not complete the Post-training Knowledge Assessment Questions who were contacted by Shire, and then who completed the Post-training Knowledge Assessment Questions
4. KAB surveys of prescribers' and patients' understanding of the potential risks associated with use of GATTEX for Short Bowel Syndrome and their understanding of the recommended monitoring during treatment with GATTEX.

5. Narrative summary of adverse events of interest including the risks of acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, biliary and pancreatic disorders, reporting from spontaneous sources, published literature, regulatory agencies, clinical studies and trials (clinical serious adverse events/SAEs) and solicited sources for entry into the Shire drug safety database.
6. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

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 CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - 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

NEW SUPPLEMENT FOR NDA 203441/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 203441/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 203441/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 203441/S-000
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 Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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 package insert(s) 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 (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), 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 by email at benjamin.vali@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
REMS

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

/s/

JOYCE A KORVICK
03/21/2017