CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 203441/S-002

Trade Name: **GATTEX**

Generic Name: **Teduglutide [rDNA origin]**

Sponsor: **NPS Pharmaceuticals, Inc.**

Approval Date: June 26, 2014

Indications: GATTEX® (teduglutide [rDNA origin]) for injection is a glucagon-like peptide-2 (GLP-2) analog indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.

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NDA 203441/S-002

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203441/S-002

SUPPLEMENT APPROVAL

NPS Pharmaceuticals, Inc.
Attention: Diane C. Fiorenza, RAC
Senior Director, Regulatory Affairs
550 Hills Drive 3rd Floor
Bedminster, New Jersey 07921

Dear Ms. Fiorenza:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 28, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Gattex (teduglutide [rDNA origin]) for subcutaneous injection, 5 mg.

We acknowledge receipt of your amendments dated October 28, 2013, November 20, 2013, January 14, 2014, February 10, 2014, February 25, 2014, March 12, 2014, May 6, 2014, May 21, 2014, May 28, 2014, June 5, 2014, June 11, 2014, June 19, 2014, and June 25, 2014.

This Prior Approval supplemental new drug application provides for the following changes to the Package Insert:

- Section 5 WARNINGS AND PRECAUTIONS- Assorted minor editorial changes
- Section 6 ADVERSE REACTIONS- Revision to incorporate results from the complete study report
- Section 8 USE IN SPECIFIC POPULATIONS- Revision of 8.5 to reflect additional patient exposures
- Section 11 DESCRIPTION- Assorted minor editorial changes
- Section 13 NONCLINICAL TOXICOLOGY - Revision to incorporate final results of 2-year mouse carcinogenicity study
- Section 14 CLINICAL STUDIES- Revisions to incorporate results from the complete study report
- Section 17 PATIENT COUNSELING INFORMATION- Minor editorial change

This supplemental new drug application also provides for proposed modifications to the approved 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 package insert, Medication Guide, text for the Instructions for Use), with the addition of any labeling changes in pending "Changes Being Effected" (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 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 includes 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft 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.

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Gattex was originally approved on December 21, 2012. The REMS consists of a

communication plan, elements to assure safe use, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of:

- revisions to the Dear Healthcare Professional and Dear Professional Society Letters to reflect the updated title of the patient and caregiver counseling guide,
- revisions to the Prescriber Education Slide Deck to reflect information from the completion of three major Gattex clinical trials, and
- revisions to the Patient and Caregiver Counseling Guide to focus on the Gattex REMS key safety messages, and to provide for improved readability, including renaming the *Patient and Caregiver Counseling Guide* to *What You Need to Know About Gattex Treatment: A Patient and Caregiver Counseling Guide*.

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.

Your proposed modified REMS, submitted on June 19, 2014, and appended to this letter, is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on December 21, 2012.

There are no changes to the REMS assessment plan described in our December 21, 2012 letter.

In addition to the assessments submitted according to the timetable included in the approved REMS, 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.

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.

Prominently identify the 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 2034412 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 2034412
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 2034412
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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:

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

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).

We request that you submit all cases of fluid overload and increased absorption of oral concomitant drugs with a serious outcome as 15-day "Alert Reports" to the FDA.

If you have any questions, call Jennifer Sarchet, Regulatory Project Manager, at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Joyce A. Korvick, MD., MPH
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
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
06/26/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203441/S-002

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GATTEX safely and effectively. See full prescribing information for GATTEX.

GATTEX (teduglutide [rDNA origin]), for injection, for subcutaneous use
Initial U.S. Approval: 2012

----------INDICATIONS AND USAGE----------
GATTEX® (teduglutide [rDNA origin]) for injection is a glucagon-like peptide-2 (GLP-2) analog indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended once daily dose of GATTEX is 0.05 mg/kg. (2.1)
- Administer by subcutaneous injection; alternate sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms. (2.1)
- For subcutaneous injection only. (2.1)
- For single-use only. Use within 3 hours after reconstitution, discard any unused portion. (2 5)
- 50% dosage reduction recommended in patients with moderate to severe renal impairment. (2.3) (8.6) (12.3)

----------DOSAGE FORMS AND STRENGTHS----------
- For injection: Each single-use glass vial containing 5 mg of teduglutide as a white, lyophilized powder for reconstitution with 0.5 mL Sterile Water for Injection provided in a prefilled syringe. (3)
- Reconstitution with the 0.5 mL Sterile Water for Injection provided in the prefilled syringe results in a 10 mg/mL solution. A maximum of 0.38 mL of reconstituted solution which contains 3.8 mg of teduglutide can then be withdrawn from the vial. (3) (16.1)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Neoplastic growth. There is a risk for acceleration of neoplastic growth. Colonoscopy of the entire colon with removal of polyps should be done before initiating treatment with GATTEX and is recommended after 1 year. Subsequent colonoscopies should be done as needed, but no less frequently than every 5 years. In case of intestinal malignancy discontinue GATTEX. The clinical decision to continue GATTEX in patients with non-gastrointestinal malignancy should be made based on risk and benefit considerations. (5.1)
- Intestinal obstruction. In patients who develop obstruction, GATTEX should be temporarily discontinued pending further clinical evaluation and management. (5.2)
- Biliary and pancreatic disease. Patients should undergo laboratory assessment (bilirubin, alkaline phosphatase, lipase, amylase) before starting GATTEX. Subsequent laboratory tests should be done every 6 months. If clinically meaningful changes are seen, further evaluation is recommended including imaging, and continued treatment with GATTEX should be reassessed. (5.3)
- Fluid overload. There is a potential for fluid overload while on GATTEX. If fluid overload occurs, especially in patients with cardiovascular disease, parenteral support should be appropriately adjusted, and GATTEX treatment reassessed. (5.4)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥ 10%) across all studies with GATTEX are abdominal pain, injection site reactions, nausea, headaches, abdominal distension, upper respiratory tract infection. In addition, vomiting and fluid overload were reported in the SBS studies (1 and 3) at rates ≥ 10%. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact NPS Pharmaceuticals at 1-855-5GATTEX (1-855-542-8839) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
GATTEX has the potential to increase absorption of concomitant oral medications. Careful monitoring and possible dose adjustment of oral medications that require titration or have a narrow therapeutic index is recommended. (5.5) (7.1)

----------USE IN SPECIFIC POPULATIONS----------
The safety and efficacy of GATTEX in pediatric patients have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GATTEX® (teduglutide [rDNA origin]) for injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support. *[see Clinical Pharmacology (12.2)]*

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended daily dose of GATTEX is 0.05 mg/kg body weight administered by subcutaneous injection once daily. Alternation of sites for subcutaneous injection is recommended, and can include the thighs, arms, and the quadrants of the abdomen. GATTEX should **not** be administered intravenously or intramuscularly. If a dose is missed, that dose should be taken as soon as possible on that day. Do not take 2 doses on the same day.

2.2 Monitoring to Assess Safety

A colonoscopy (or alternate imaging) of the entire colon with removal of polyps should be done within 6 months prior to starting treatment with GATTEX. A follow-up colonoscopy (or alternate imaging) is recommended at the end of 1 year of GATTEX. If no polyp is found, subsequent colonoscopies should be done no less frequently than every 5 years. If a polyp is found, adherence to current polyp follow-up guidelines is recommended.

Patients should undergo initial laboratory assessments (bilirubin, alkaline phosphatase, lipase and amylase) within 6 months prior to starting treatment with GATTEX. Subsequent laboratory assessments are recommended every 6 months. If clinically meaningful elevation is seen, further diagnostic workup is recommended as clinically indicated (ie, imaging of the biliary tract, liver, or pancreas). *[see Warnings and Precautions (5.1) (5.5)]*

2.3 Dosage Modifications in Renal Impairment

Reduce the dose by 50% in patients with moderate and severe renal impairment (creatinine clearance less than 50 mL/min), and end-stage renal disease. *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*

2.4 Discontinuation of Treatment

Discontinuation of treatment with GATTEX may result in fluid and electrolyte imbalance. Therefore, patients' fluid and electrolyte status should be carefully monitored.

2.5 Preparation for Administration

Reconstitute each vial of GATTEX by slowly injecting the 0.5 mL of preservative-free Sterile Water for Injection provided in the prefilled syringe. Allow the vial containing GATTEX and water to stand for approximately 30 seconds and then gently roll the vial between your palms for about 15 seconds. Do not shake the vial. Allow the mixed contents to stand for about 2 minutes. Inspect the vial for any undissolved powder. If undissolved powder is observed, gently roll the vial again until all material is dissolved. Do not shake the vial. If the product remains undissolved after the second attempt, do not use. GATTEX does not contain any preservatives and is for single-use only. Discard any unused portion. The product should be used within 3 hours after reconstitution. *[see How Supplied/Storage and Handling (16.2)]*

3 DOSAGE FORMS AND STRENGTHS

For Injection: Each single-use glass vial contains a dose of 5 mg teduglutide as a lyophilized powder that upon reconstitution with the 0.5 mL Sterile Water for Injection provided in the prefilled syringe delivers a maximum of 0 38 mL of the reconstituted sterile solution which contains 3.8 mg of teduglutide.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acceleration of Neoplastic Growth

Based on the pharmacologic activity and findings in animals, GATTEX has the potential to cause hyperplastic changes including neoplasia**.** In patients at increased risk for malignancy, the clinical decision to use GATTEX should be considered only if the benefits outweigh the risks. In patients with active gastrointestinal malignancy (GI tract, hepatobiliary, pancreatic), GATTEX therapy should be discontinued. In patients with active non-gastrointestinal malignancy, the clinical decision to continue GATTEX should be made based on risk-benefit considerations. *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*

Colorectal Polyps

Colorectal polyps were identified during the clinical trials. Colonoscopy of the entire colon with removal of polyps should be done within 6 months prior to starting treatment with GATTEX. A follow-up colonoscopy (or alternate imaging) is recommended at the end of 1 year of GATTEX. Subsequent colonoscopies should be done every 5 years or more often as needed. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of diagnosis of colorectal cancer**,** GATTEX therapy should be discontinued. *[see Adverse Reactions (6.1)]*

Small Bowel Neoplasia

Based on tumor findings in the rat and mouse carcinogenicity studies, patients should be monitored clinically for small bowel neoplasia. If a benign neoplasm is found, it should be removed. In case of small bowel cancer, GATTEX therapy should be discontinued. *[see Nonclinical Toxicology (13.1)]*

5.2 Intestinal Obstruction

Intestinal obstruction has been reported in clinical trials. In patients who develop intestinal or stomal obstruction, GATTEX should be temporarily discontinued while the patient is clinically managed. GATTEX may be restarted when the obstructive presentation resolves, if clinically indicated. *[see Adverse Reactions (6.1)]*

5.3 Biliary and Pancreatic Disease

Gallbladder and Biliary Tract Disease
Cholecystitis, cholangitis, and cholelithiasis, have been reported in clinical studies. For identification of the onset or worsening of gallbladder/biliary disease, patients should undergo laboratory assessment of bilirubin and alkaline phosphatase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed. If clinically meaningful changes are seen, further evaluation including imaging of the gallbladder and/or biliary tract is recommended; and the need for continued GATTEX treatment should be reassessed. *[see Adverse Reactions (6.1)]*

Pancreatic Disease
Pancreatitis has been reported in clinical studies. For identification of onset or worsening of pancreatic disease, patients should undergo laboratory assessment of lipase and amylase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed. If clinically meaningful changes are seen, further evaluation such as imaging of the pancreas is recommended; and the need for continued GATTEX treatment should be reassessed. *[see Adverse Reactions (6.1) and Nonclinical Toxicology (13.1)]*

5.4 Fluid Overload
Fluid overload and congestive heart failure have been observed in clinical trials, which were felt to be related to enhanced fluid absorption associated with GATTEX. If fluid overload occurs, parenteral support should be adjusted and GATTEX treatment should be reassessed, especially in patients with underlying cardiovascular disease. If significant cardiac deterioration develops while on GATTEX, the need for continued GATTEX treatment should be reassessed. *[see Adverse Reactions (6.1)]*

5.5 Increased Absorption of Concomitant Oral Medication
Altered mental status in association with GATTEX has been observed in patients on benzodiazepines in clinical trials. Patients on concomitant oral drugs (e.g., benzodiazepines, phenothiazines) requiring titration or with a narrow therapeutic index may require dose adjustment while on GATTEX. *[see Adverse Reactions (6.2)]*

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice.

Across all clinical studies, 595 subjects were exposed to at least one dose of GATTEX (249 patient-years of exposure; mean duration of exposure was 22 weeks). Of the 595 subjects, 173 subjects were treated in Phase 3 SBS studies (134/173 [77%] at the dose of 0.05 mg/kg/day and 39/173 [23%] at the dose of 0.10 mg/kg/day).

The most commonly reported (≥ 10%) adverse reactions in subjects treated with GATTEX across all clinical studies (N = 595) were: abdominal pain (31 3%); injection site reactions (21.8%); nausea (18.8%); headaches (16.3%); abdominal distension (14.8%); upper respiratory tract infection (11.9%).

The rates of adverse reactions in subjects with SBS participating in 2 randomized, placebo-controlled, 24-week, double-blind clinical studies (Study 1 and Study 3) are summarized in Table 1. Only those reactions with a rate of at least 5% in the GATTEX group, and greater than placebo group, are summarized in Table 1. The majority of these reactions were mild or moderate. Of subjects receiving GATTEX at the recommended dose of 0.05 mg/kg/day, 88.3% (n=68/77) experienced an adverse reaction, as compared to 83.1% (n=49/59) for placebo. Many of these adverse reactions have been reported in association with the underlying disease and/or parenteral nutrition.

Table 1: Adverse reactions in ≥5% of GATTEX-treated SBS subjects and more frequent than placebo: Studies 1 and 3

Adverse Reaction	Placebo (N=59) n (%)	GATTEX 0.05mg/kg/day (N=77) n (%)
Abdominal Pain	16 (27.1)	29 (37.7)
Upper Respiratory Tract Infection	8 (13.6)	20 (26.0)
Nausea	12 (20.3)	19 (24.7)
Abdominal Distension	1 (1.7)	15 (19.5)
Vomiting	6 (10.2)	9 (11.7)
Fluid Overload	4 (6.8)	9 (11.7)
Flatulence	4 (6.8)	7 (9.1)
Hypersensitivity	3 (5.1)	6 (7.8)
Appetite Disorders	2 (3.4)	5 (6.5)
Sleep Disturbances	0	4 (5.2)
Cough	0	4 (5.2)
Skin Hemorrhage	1 (1.7)	4 (5.2)
Subjects with Stoma		
Gastrointestinal Stoma Complication	3 (13.6)[a]	13 (41.9)[a]

[a]Percentage based on 53 subjects with a stoma (n = 22 placebo; n = 31 GATTEX 0.05 mg/kg/day)

In placebo-controlled Studies 1 and 3, 12% of patients in each of the placebo and GATTEX study groups experienced an injection site reaction.

Adverse Reactions of Special Interest

Malignancy. Three subjects were diagnosed with malignancy in the clinical studies, all of whom were male and had received GATTEX 0.05 mg/kg/day in Study 2. One subject had a history of abdominal radiation for Hodgkin's disease two decades prior to receiving GATTEX and prior liver lesion on CT scan, and was diagnosed with metastatic adenocarcinoma of unconfirmed origin after 11 months of exposure to GATTEX. Two subjects had extensive smoking histories, and were diagnosed with lung cancers (squamous and non-small cell) after 12 months and 3 months of GATTEX exposure, respectively.

Colorectal Polyps. In the clinical studies, 13 subjects were diagnosed with polyps of the G.I. tract after initiation of study treatment. In the SBS placebo-controlled studies, 1/59 (1.7%) of subjects on placebo and 1/109 (0.9%) of subjects on GATTEX 0.05 mg/kg/day were diagnosed with intestinal polyps (inflammatory stomal and hyperplastic sigmoidal after 3 and 5 months, respectively). The remaining 11 polyp cases occurred in the extension studies – 2 colorectal villous adenomas (onset at 6 and 7 months in GATTEX 0.10 and 0.05 mg/kg/day dose groups, respectively), 2 hyperplastic polyp (onset 6 months in GATTEX 0.10 mg/kg/day dose group and 24 months in GATTEX 0.05 mg/kg/day dose group), 3 colorectal tubular adenomas (onset between 24 and 29 months in GATTEX 0.05 mg/kg/day dose group), 1 serrated adenoma (onset at 24 months in GATTEX 0.05 mg/kg/day dose group), 1 colorectal polyp biopsy not done (onset at 24 months in GATTEX 0.05 mg/kg/day dose group), 1 rectal inflammatory polyp (onset at 10 months in the GATTEX 0.05 mg/kg/day dose group, and 1 small duodenal polyp (onset at 3 months in GATTEX 0.05 mg/kg/day dose group).

Gastrointestinal Obstruction. Overall, 12 subjects experienced one or more episodes of intestinal obstruction/stenosis: 6 in SBS placebo-controlled studies and 6 in the extension studies. The 6 subjects in the placebo-controlled trials were all on GATTEX: 3/77 (3.9%) on GATTEX 0.05 mg/kg/day and 3/32 (9.4%) on GATTEX 0.10 mg/kg/day. No cases of intestinal obstruction occurred in the placebo group. Onsets ranged from 1 day to 6 months. In the extension studies, 6 additional subjects (all on GATTEX 0.05 mg/kg/day) were diagnosed with intestinal obstruction/stenosis with onsets ranging from 6 days to 19 months. Two of the 6 subjects from the placebo-controlled trials experienced recurrence of obstruction in the extension studies. Of all 8 subjects with an episode of intestinal obstruction/stenosis in these extension studies, 2 subjects required endoscopic dilation and 1 required surgical intervention.

Gallbladder, Biliary and Pancreatic Disease. For gallbladder and biliary disease in the placebo-controlled studies, 3 subjects were diagnosed with cholecystitis, all of whom had a prior history of gallbladder disease and were in the GATTEX 0.05 mg/kg/day dose group. No cases were reported in the placebo group. One of these 3 cases had gallbladder perforation and underwent cholecystectomy the next day. The remaining 2 cases underwent elective cholecystectomy at a later date. In the extension studies, 4 subjects had an episode of acute cholecystitis; 3 subjects had new-onset cholelithiasis; and 1 subject experienced cholestasis secondary to an obstructed biliary stent. For pancreatic disease in the placebo-controlled studies, 1 subject (GATTEX 0.05 mg/kg/day dose group) had a pancreatic pseudocyst diagnosed after 4 months of GATTEX. In the extension studies, 1 subject was diagnosed with chronic pancreatitis; and 1 subject was diagnosed with acute pancreatitis.

Fluid Overload. In the placebo-controlled trials, fluid overload was reported in 4/59 (6.8%) of subjects on placebo and 9/77 (11.7%) subjects on GATTEX 0.05 mg/kg/day. Of the 9 cases in the GATTEX group, there were 2 cases of congestive heart failure (CHF), 1 of whom was reported as a serious adverse event and the other as non-serious. The serious case had onset at 6 months, and was possibly associated with previously undiagnosed hypothyroidism and/or cardiac dysfunction.

Concomitant Oral Medication. GATTEX can increase the absorption of concomitant oral medications such as benzodiazepines and psychotropic agents. In the placebo-controlled trials, an analysis of episodes of cognition and attention disturbances was performed for subjects on benzodiazepines. One of the subjects in the GATTEX 0.05 mg/kg/day group (on prazepam) experienced dramatic deterioration in mental status progressing to coma during her first week of GATTEX therapy. She was admitted to the ICU where her benzodiazepine level was >300 mcg/L. GATTEX and prazepam were discontinued, and coma resolved 5 days later.

6.2 Immunogenicity

Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of GATTEX may trigger the development of antibodies. Based on data from two trials in adults with SBS (a 6-month randomized placebo-controlled trial, followed by a 24-month open-label trial), the incidence of anti-teduglutide antibody was 3% (2/60) at Month 3, 18% (13/74) at Month 6, 25% (18/71) at Month 12, 31% (10/32) at Month 24 and 48% (14/29) at Month 30 in subjects who received subcutaneous administration of 0.05 mg/kg GATTEX once daily. The anti-teduglutide antibodies were cross-reactive to native glucagon-like peptide (GLP-2) in 5 of the 6 subjects (83%) who had anti-teduglutide antibodies. Anti-teduglutide antibodies appear to have no impact on short term (up to 2.5 years) efficacy and safety although the long-term impact is unknown.

In the same two trials, a total of 36 subjects were tested for neutralizing antibodies: 9 of these subjects had no neutralizing antibodies, and the remaining 27 subjects had no detectable neutralizing antibodies although, the presence of teduglutide at low levels in these study samples could have resulted in false negatives (no neutralizing antibody detected although present).

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying diseases. For these reasons, comparison of the incidence of antibodies to GATTEX with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of GATTEX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to GATTEX exposure.

Cardiac disorders: Cardiac Arrest, Cardiac Failure
Nervous system disorders: Cerebral Hemorrhage

7 DRUG INTERACTIONS

7.1 Potential for Increased Absorption of Oral Medications

Based upon the pharmacodynamic effect of GATTEX, there is a potential for increased absorption of concomitant oral medications, which should be considered if these drugs require titration or have a narrow therapeutic index. *[see Warnings and Precautions (5.5)]*

7.2 Concomitant Drug Therapy

Clinical interaction studies were not performed. No inhibition or induction of the cytochrome P450 enzyme system has been observed based on *in vitro* studies although the relevance of *in vitro* studies to an *in vivo* setting is unknown.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Category B

Risk Summary
Adequate and well controlled studies with GATTEX have not been conducted in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of subcutaneous teduglutide at doses up to 1000 times the recommended human dose in both rats and rabbits. Because animal reproductive studies are not always predictive of human response, GATTEX should be used during pregnancy only if clearly needed.

Data
Animal data
In animal studies, no effects on embryo-fetal development were observed in pregnant rats given subcutaneous teduglutide at doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg) or pregnant rabbits given subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg). A pre- and postnatal development study in rats showed no evidence of any adverse effect on pre- and postnatal development at subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg).

8.3 Nursing Mothers
It is not known whether GATTEX is present in human milk. Teduglutide is excreted in the milk of lactating rats, and the highest concentration measured in milk was 2.9% of the plasma concentration following a single subcutaneous injection of 25 mg/kg. Because many drugs are excreted in human milk, because of the potential for serious adverse reactions to nursing infants from GATTEX and because of the potential for tumorigenicity shown for teduglutide in mice and rats, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. *[see Nonclinical Toxicology (13.1)]*

8.4 Pediatric Use
Safety and efficacy in pediatric patients have not been established.

8.5 Geriatric Use
No dose adjustment is necessary in patients above the age of 65 years. Of the 595 subjects treated with teduglutide, 43 subjects were 65 years or older, whereas 6 subjects were 75 years of age or older. In the SBS studies, no overall differences in safety or efficacy were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. *[see Clinical Pharmacology (12.3)]*

8.6 Renal Impairment
Reduce the dose of GATTEX by 50% in patients with moderate and severe renal impairment (creatinine clearance less than 50 mL/min) and end-stage renal disease (ESRD). *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*

8.7 Hepatic Impairment
GATTEX has not been formally studied in subjects with severe hepatic impairment. No dosage adjustment is necessary for patients with mild and moderate hepatic impairment based on a study conducted in Child-Pugh grade B subjects. *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*

10 OVERDOSAGE
The maximum dose of GATTEX studied during clinical development was 80 mg/day for 8 days. In the event of overdose, the patient should be carefully monitored by the medical professional.

11 DESCRIPTION
The active ingredient in GATTEX (teduglutide [rDNA origin]) for injection is teduglutide (rDNA origin), which is a 33 amino acid glucagon-like peptide-2 (GLP-2) analog manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. The chemical composition of teduglutide is L-histidyl-L-glycyl-L-aspartyl-L-glycyl-L-seryl-L-phenylalanyl-L-seryl-L-aspartyl-L-glutamyl-L-methionyl-L-asparaginyl-L-threonyl-L-isoleucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-isoleucyl-L-asparaginyl-L-tryptophanyl-L-leucyl-L-isoleucyl-L-glutaminyl-L-threonyl-L-lysyl-L-isoleucyl-L-threonyl-L-aspartic acid. The structural formula is:

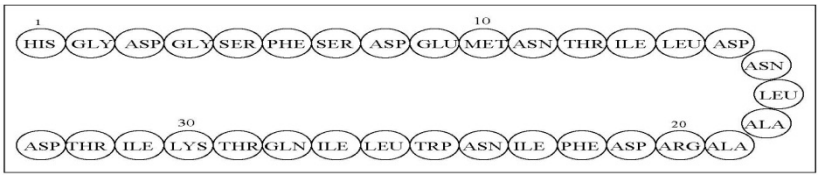

Figure 1: Structural formula of teduglutide

Teduglutide has a molecular weight of 3752 Daltons. Teduglutide drug substance is a clear, colorless to light-straw–colored liquid.

Each single-use vial of GATTEX contains 5 mg of teduglutide as a white lyophilized powder for solution for subcutaneous injection. In addition to the active pharmaceutical ingredient (teduglutide), each vial of GATTEX contains 3.88 mg L-histidine, 15 mg mannitol, 0.644 mg monobasic sodium phosphate monohydrate, 3.434 mg dibasic sodium phosphate heptahydrate as excipients. No preservatives are present.

At the time of administration the lyophilized powder is reconstituted with 0.5 mL of Sterile Water for Injection, which is provided in a prefilled syringe. A 10 mg/mL sterile solution is obtained after reconstitution. Up to 0.38 mL of the reconstituted solution which contains 3.8 mg of teduglutide can be withdrawn for subcutaneous injection upon reconstitution.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Teduglutide is an analog of naturally occurring human glucagon-like peptide-2 (GLP-2), a peptide secreted by L-cells of the distal intestine. GLP-2 is known to increase intestinal and portal blood flow, and inhibit gastric acid secretion. Teduglutide binds to the glucagon-like peptide-2 receptors located in intestinal subpopulations of enteroendocrine cells, subepithelial myofibroblasts and enteric neurons of the submucosal and myenteric plexus. Activation of these receptors results in the local release of multiple mediators including insulin-like growth factor (IGF)-1, nitric oxide and keratinocyte growth factor (KGF).

12.2 Pharmacodynamics

The ability of GATTEX to improve intestinal absorption was studied in 17 adult subjects with Short Bowel Syndrome using daily doses of 0.03, 0.10, 0.15 mg/kg (N=2-3 per dose group) in a 21-day, open-label, multi-center, dose-ranging study. All subcutaneous (abdomen) doses studied, except 0.03 mg/kg once daily, resulted in enhanced gastrointestinal fluid (wet weight) absorption of approximately 750-1000 mL/day, and increased villus height and crypt depth of the intestinal mucosa.

At a dose 5 times the maximum recommended dose, teduglutide did not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

In healthy subjects, GATTEX administered subcutaneously had an absolute bioavailability of 88% and reached maximum plasma teduglutide concentrations at 3-5 hours after administration. Following a 0.05 mg/kg subcutaneous dose in SBS subjects, the median peak teduglutide concentration (C_{max}) was 36 ng/mL and the median area under the curve ($AUC_{0\text{-}inf}$) was 0.15 μg•hr/mL. No accumulation of teduglutide was observed following repeated subcutaneous administrations.

Distribution

In healthy subjects, teduglutide has a volume of distribution (103 mL/kg) similar to blood volume.

Metabolism

The metabolic pathway of teduglutide was not investigated in humans. However, teduglutide is expected to be degraded into small peptides and amino acids via catabolic pathways, similar to the catabolism of endogenous GLP-2.

Elimination

In healthy subjects, teduglutide plasma clearance was approximately 123 mL/hr/kg which is similar to the GFR suggesting that teduglutide is primarily cleared by the kidney. Teduglutide has a mean terminal half-life ($t_{1/2}$) of approximately 2 hours in healthy subjects and 1.3 hours in SBS subjects.

Dose Linearity

The C_{max} and AUC of teduglutide was dose proportional over the dose range of 0.05 to 0.4 mg/kg GATTEX.

Hepatic Impairment

Subjects with moderate hepatic impairment had lower teduglutide C_{max} and AUC $_{(10\sim15\%)}$ compared to healthy matched control subjects after a single subcutaneous dose of 20 mg GATTEX. Teduglutide PK was not assessed in subjects with severe hepatic impairment.

Renal Impairment

In subjects with moderate to severe renal impairment or end stage renal disease (ESRD), teduglutide C_{max} and $AUC_{0\text{-}inf}$ increased with the degree of renal impairment following a single subcutaneous administration of 10 mg teduglutide. Teduglutide exposure increased by a factor of 2.1 (C_{max}) and 2.6 ($AUC_{0\text{-}inf}$) in ESRD subjects compared to healthy subjects.

Geriatric Patients

No differences were observed between healthy subjects younger than 65 years and those older than 65 years. Experience in subjects 75 years and above is limited.

Gender

No clinically relevant gender differences were observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic potential of Gattex was assessed in 2-year subcutaneous carcinogenicity studies in rats and mice. In a 2-year carcinogenicity study in Wistar Han rats at subcutaneous doses of 3, 10 and 35 mg/kg/day (about 60, 200 and 700 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct and jejunum of male rats. In a 2-year carcinogenicity study in Crl:CD1(ICR) mice at subcutaneous doses of 1, 3.5 and 12.5 mg/kg/day (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused a significant increase in papillary adenomas in the gall bladder; it also caused adenocarcinomas in the jejunum in male mice at the high dose of 12.5 mg/kg/day (about 250 times the recommended human dose).

Teduglutide was negative in the Ames test, chromosomal aberration test in Chinese hamster ovary cells, and *in vivo* mouse micronucleus assay.

Teduglutide at subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

14.1 Study 1 (Placebo-controlled) and Study 2 (Open-label extension of Study 1)

Study 1. The efficacy, safety, and tolerability of GATTEX was evaluated in a randomized, double-blind, placebo-controlled, parallel-group, multi-national, multi-center clinical trial (Study 1) in adults with SBS who were dependent on parenteral nutrition/intravenous (PN/I.V.) support for at least 12 months and required PN at least 3 times per week. For 8 weeks (or less) prior to randomization, investigators optimized the PN/I.V. volume of all subjects. Optimization was followed by a 4-week to 8-week period of fluid stabilization. Subjects then were randomized (1:1) to placebo (n=43) or GATTEX 0.05 mg/kg/day (n=43). Study treatment was administered subcutaneously once daily for 24 weeks. PN/I.V. volume adjustments (up to 30% decrease) and clinical assessments were made at 2, 4, 8, 12, 20, and 24 weeks.

The primary efficacy endpoint was based on a clinical response, defined as a subject achieving at least 20% reduction in weekly PN/I.V. volume from Baseline (immediately before randomization) to both Weeks 20 and 24.

The mean age of subjects was 50.3 years. Mean duration of PN/I.V. dependency prior to enrollment was 6.25 years (range 1-25.8 years). The most common reasons for intestinal resection leading to SBS were vascular disease (34.1%, 29/85), Crohn's Disease (21.2%, 18/85), and "other" (21.2%, 18/85). Stoma was present in 44.7% (38/85) of subjects, and the most common type was jejunostomy/ileostomy (81.6%, 31/38). The mean length of remaining small intestine was 77.3±64.4 cm (range: 5 to 343 cm). The colon was not in continuity in 43.5% (37/85) subjects. At baseline, the mean (± SD) prescribed days per week for PN/I.V. infusion was 5.73 (±1.59) days.

The percentages of treatment group responders were compared in the intent-to-treat population of this study which was defined as all randomized patients. 63% (27/43) of GATTEX-treated subjects versus 30% (13/43) of placebo-treated subjects were considered responders (p=0.002).

At Week 24, the mean reduction in weekly PN/I.V. volume was 4.4 Liters for GATTEX-treated subjects (from pre-treatment baseline of 12.9 Liters) versus 2.3 Liters for placebo-treated subjects (from pre-treatment baseline of 13.2 Liters/week) (p<0.001).

Twenty-one subjects on GATTEX (53.8%) versus 9 on placebo (23.1%) achieved at least a one-day reduction in PN/I.V. support.

The mean changes from Baseline in PN/I.V. volume by visit are shown in Figure 2.

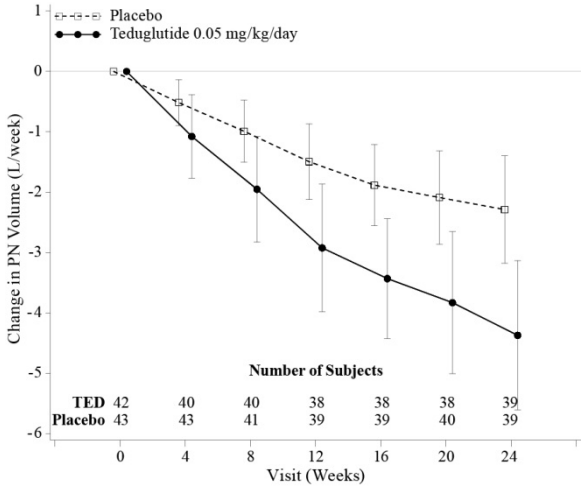

Figure 2: Change (±95% CI) in PN/I.V. volume (L/week)

Study 2. Study 2 was a 2-year open-label extension of Study 1 in which 88 subjects received GATTEX 0.05 mg/kg/day. Ninety-seven percent (76/78) of subjects who completed Study 1 elected to enroll in Study 2 (37 received GATTEX; (39 received Placebo). An additional 12 subjects entered Study 2, who had been optimized and stabilized but not randomized in Study 1 because of closed enrollment.

30 months exposure

Thirty GATTEX subjects completed a total duration of 30 months (Study 1 followed by Study 2 treatment). Of these, 28 subjects (93%) achieved a 20% or greater reduction of parenteral support. Of responders in Study 1 who had completed 2 additional years of continuous treatment with GATTEX, 96% (21/22) sustained their response to GATTEX. The mean reduction in PN/I.V. (n=30) was 7.55 L/week (a 65.6% reduction from baseline). Ten subjects were weaned off their PN/I.V. support while on GATTEX treatment for 30 months. Subjects were maintained on GATTEX even if no longer requiring PN/I.V. support. These 10 subjects had required PN/I.V. support for 1.2 to 15.5 years, and prior to GATTEX had required between 3.5 L/week and 13.4 L/week of PN/I.V. support. At the end of study, 21 (70%), 18 (60%) and 18 (60%) of the 30 completers achieved a reduction of 1, 2, or 3 days per week in PN/I.V. support, respectively.

24 month exposure

Of the 39 placebo subjects from Study 1 entering Study 2, 29 completed 24 months of treatment with GATTEX. The mean reduction in PN/I.V. was 3.11 L/week (an additional 28.3% reduction) from the start of Study 2. Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral support. At the end of study, 14 (48.3%), 7 (24 1%) and 5 (17.2%) achieved a reduction of 1, 2, or 3 days per week in PN/I.V. support, respectively. Two subjects were weaned off their PN/I.V. support while on GATTEX. Of the 12 subjects entering Study 2 directly, 6 completed 24 months of treatment with GATTEX. Similar effects were seen. One of the six subjects was weaned off their PN/I.V. support while on GATTEX.

14.2 Study 3 (Placebo-controlled) and Study 4 (Blinded uncontrolled extension of Study 3)

Study 3. Study 3 was a randomized, double-blind, placebo-controlled, three parallel-group, multinational study in adults with Short Bowel Syndrome who were dependent on parenteral nutrition/intravenous (PN/I.V.) support for at least 12 months and required PN at least 3 times per week. After a period of optimization

and stabilization similar to Study 1, subjects were randomized to receive 24 weeks of one of the following treatment regimens: GATTEX 0.05 mg/kg/day (n=35), GATTEX 0.10 mg/kg/day dose (n=33), or placebo (n=16). The treatment groups were compared using the intent-to-treat population of this study which was defined as all randomized patients who were administered at least one dose of study drug. This population contained one less patient in the 0.10 mg/kg/day dose group hence n=32 in this group for all analyses. The primary efficacy endpoint was a graded categorical score that did not achieve statistical significance for the high dose. Further evaluation of PN/I.V. volume reduction using the endpoint of response (defined as at least 20% reduction in PN/I.V. fluid from Baseline to Weeks 20 and 24) showed that 46% of subjects on GATTEX 0.05 mg/kg/day responded versus 6% on placebo. Subjects on GATTEX at both dose levels experienced a 2.5 L/week reduction in parenteral support requirements versus 0.9 L/week for placebo at 24 weeks. Two subjects in the GATTEX 0.05 mg/kg/day dose group were weaned off parenteral support by Week 24.

Study 4. Study 4 was a blinded, uncontrolled extension of Study 3, in which 65 subjects from Study 3 received GATTEX for up to an additional 28 weeks of treatment. Of responders in Study 3 who entered Study 4, 75% sustained response on GATTEX after one year of treatment. In the GATTEX 0.05 mg/kg/day dose group, a 20% or greater reduction of parenteral support was achieved in 68% (17/25) of subjects. The mean reduction of weekly PN/I.V. volume was 4.9 L/week (52% reduction from baseline) after one year of continuous GATTEX treatment. The subjects who had been completely weaned off PN/I.V. support in Study 3 remained off parenteral support through Study 4. During Study 4, an additional subject from Study 3 was weaned off parenteral support.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

GATTEX® (teduglutide [rDNA origin]) for injection is supplied in a sterile, single-use glass vial containing 5 mg of teduglutide as a white, lyophilized powder to be reconstituted with 0.5 mL Sterile Water for Injection. The product to be dispensed is either a one-vial kit or a 30-vial kit. The one-vial kit is pre-assembled and ready to be used. The 30-vial kit is to be assembled by a pharmacist with the following two cartons:

Carton of Drug Vials (NDC 68875-0101-2):

- Thirty single-use vials of drug (NDC 68875-0101-1)

Carton of Ancillary Supplies:

- Thirty disposable prefilled syringes containing diluent (0.5 mL Sterile Water for Injection USP) for reconstitution
- Thirty separate needles (22G x 1½ in) to attach to the syringes for reconstitution
- Thirty sterile disposable 1-mL syringes with needle (26G x 5/8 in)
- Sixty alcohol swabs

The pharmacist in a dispensing pharmacy will assemble a 30-vial kit by transferring the trays containing 30 vials from a **Carton of Drug Vials** into a **Carton of Ancillary Supplies**. The final patient kits should contain the items listed as follows:

30-vial kit (NDC 68875-0102-1):
- Thirty single-use vials of drug (NDC 68875-0101-1)
- Thirty disposable prefilled syringes containing 0.5 mL Sterile Water for Injection USP for reconstitution, with 30 separate needles (22G x 1½ in) to attach to the syringes
- Thirty sterile disposable 1-mL syringes with needle (26G x 5/8 in) for dosing
- Sixty alcohol swabs

One-vial kit (NDC 68875-0103-1):
- One single-use vial of drug (NDC 68875-0101-1)
- One disposable prefilled syringe containing 0.5 mL Sterile Water for Injection USP for reconstitution, with a separate needle (22G x 1½ in) to attach to the syringe
- One sterile disposable 1-mL syringe with needle (26G x 5/8 in) for dosing
- Four alcohol swabs

Reconstitution with 0 5 mL of preservative-free Sterile Water for Injection, provided in a prefilled syringe, is required prior to subcutaneous administration of the drug. Reconstituted GATTEX is a sterile, clear, colorless to light straw-colored 10 mg/mL solution, which should be free from particulates. Upon reconstitution with the 0.5 mL Sterile Water for Injection provided in the prefilled syringe, a maximum of 0.38 mL of the reconstituted solution which contains 3.8 mg of teduglutide can be withdrawn from the vial for dosing.

16.2 Storage and Handling

Prior to Dispensing: Store refrigerated at 2 C to 8 C (36 F to 46 F) for **Cartons of Drug Vials** and the **One-vial kits**. Do not freeze. Do not use beyond the expiration date on the label. Store at room temperature up to 25 C (77 F) for the **Cartons of Ancillary Supplies**.

Instruction for the Pharmacist:
Prior to Dispensing: Store at 2 C to 8 C (36 F to 46 F) for **Cartons of Drug Vials** and the **One-vial kits**. Do not freeze.
Dispensing Instructions: Dispense with a 90-day "use by" dating and specify "Store at room temperature up to 25 C (77 F). Do not freeze." Dispense Medication Guide to each patient.

Reconstituted GATTEX is a sterile, clear, colorless to light straw-colored solution, which should be free from particulates. The drug should be completely dissolved before the solution is withdrawn from the vial. Do not shake or freeze the reconstituted solution. If the product remains undissolved after the second attempt, do not use. GATTEX does not contain any preservatives and is for single-use only. Any unused portion should be discarded. The product should be used within 3 hrs after reconstitution.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use).

General Counseling Information – Prior to treatment, patients should fully understand the risks and benefits of GATTEX. Ensure that all patients receive the Medication Guide prior to initiating GATTEX therapy.

17.1 Acceleration of Neoplastic Growth

Advise patients with active gastrointestinal malignancy (GI tract, hepatobiliary, pancreatic), that GATTEX therapy should be discontinued. In patients with active non-gastrointestinal malignancy, the clinical decision to continue GATTEX should be discussed with patients and be made based on risk-benefit considerations. *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*

Colorectal polyps.

Advise patients that colonoscopy of the entire colon with removal of polyps should be done within 6 months prior to starting treatment with GATTEX. A follow-up colonoscopy (or alternate imaging) is recommended at the end of 1 year of GATTEX. Subsequent colonoscopies should be done every 5 years or more often as needed. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of diagnosis of colorectal cancer, GATTEX therapy should be discontinued. *[see Adverse Reactions (6.1)]*

Small Bowel Neoplasia.

Advise patients that they should be monitored clinically for small bowel neoplasia. If a benign neoplasm is found, it should be removed. In case of small bowel cancer, GATTEX therapy should be discontinued. *[see Nonclinical Toxicology (13.1)]*

17.2 Intestinal Obstruction

Advise patients to tell their physician if they experience any signs or symptoms suggestive of intestinal obstruction. If obstruction is present, the physician should temporarily discontinue GATTEX. *[see Warnings and Precautions (5.2)]*

17.3 Gallbladder and Bile Duct Disease

Advise patients that laboratory assessments should be done before and then every 6 months while on GATTEX to monitor gallbladder and biliary function. If clinically significant change occurs, further evaluation (i.e., imaging studies or other) may be necessary. Advise patients to report to their physician all signs and symptoms suggestive of cholecystitis, cholangitis, or cholelithiasis while on GATTEX. *[see Warnings and Precautions (5.3)]*

17.4 Pancreatic Disease

Advise patients that laboratory assessments should be done before and then every 6 months while on GATTEX. If clinically significant change occurs, further evaluation (i.e., imaging studies or other) may be necessary. Advise patients to report to their physician all signs and symptoms suggestive of pancreatic disease while on GATTEX. *[see Warnings and Precautions (5.3)]*

17.5 Cardiovascular Disease

Advise patients with cardiovascular disease to report to their physician any signs of fluid overload or cardiac decompensation while on GATTEX. *[see Warnings and Precautions (5.4)]*

17.6 Risks Resulting from Increased Absorption of Concomitant Oral Medication

Instruct patients to report to all of their physicians any concomitant oral medications that they are taking in order to assess any potential for increased absorption during GATTEX treatment of those oral medications requiring titration or with a narrow therapeutic index. *[see Warnings and Precautions (5.5)]*

17.7 Instructions

Inform patients that GATTEX should **not** be administered intravenously or intramuscularly. The drug should be used for subcutaneous injection within 3 hours after reconstitution. Advise patients that subcutaneous administration has been associated with injection site reactions, but if they experience a severe reaction including severe rash, they should contact their physician.

Advise patients that while they may experience abdominal pain and swelling of their stoma especially when starting therapy with GATTEX, if they experience symptoms of intestinal obstruction, they should contact their physician.

Instruct patients to read the Medication Guide as they are starting GATTEX therapy and to re-read it each time their prescription is renewed.

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1776 N. Centennial Drive
McPherson, KS 67460
USA

Distributed by:
NPS Pharmaceuticals, Inc.
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1-855-5GATTEX
www.GATTEX.com

MEDICATION GUIDE

GATTEX® (Ga'-tex)
(teduglutide [rDNA origin])
for injection

Read this Medication Guide carefully before you start taking GATTEX® and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical problems or treatment.

What is the most important information I should know about GATTEX?

GATTEX may cause serious side effects, including:

- **Making abnormal cells grow faster.** GATTEX can make abnormal cells that are already in your body grow faster. There is an increase risk that abnormal cells could become cancer. If you get cancer of the bowel (intestines), liver, gall bladder, or pancreas while using GATTEX, your healthcare provider should stop GATTEX.
- If you get other types of cancers, you and your healthcare provide should discuss the risks and benefits of using GATTEX.

Polyps in the colon (large intestine). Polyps are growths on the inside of the colon.
Before you start using GATTEX, your healthcare provider will:

- Have your colon checked for polyps within 6 months before starting GATTEX
- Have any polyps removed

To keep using GATTEX, your healthcare provider should:

- Have your colon checked for new polyps at the end of 1 year of using GATTEX. If no polyp is found, your healthcare provider should check you for polyps as needed and at least every 5 years.
- Have any new polyps removed

If cancer is found in a polyp, your healthcare provider should stop GATTEX.

Blockage of the bowel (intestines). A bowel blockage keeps food, fluids, and gas from moving through the bowels in the normal way. Tell your healthcare provider if you have any of these symptoms of a bowel blockage:

- trouble having a bowel movement or passing gas
- stomach area (abdomen) pain or swelling
- nausea
- vomiting
- swelling and blockage of your stoma opening, if you have a stoma

If blockage is found, your healthcare provider may temporarily stop GATTEX.

Swelling (inflammation) or blockage of your gallbladder or pancreas.
Your healthcare provider will do tests to check your gallbladder and pancreas within 6 months before starting GATTEX and at least every 6 months while you are using GATTEX.

Tell your healthcare provider right away if you get:

- stomach area (abdomen) pain and tenderness
- nausea
- vomiting

- chills
- fever
- change in your stools
- dark urine
- yellowing of your skin or the whites of eyes

These are not all the side effects of GATTEX. For more information, see **"What are the possible side effects of GATTEX?"**

What is GATTEX?

GATTEX is a prescription medicine used in adults with Short Bowel Syndrome (SBS) who need additional nutrition or fluids from intravenous (IV) feeding (parenteral support).

It is not known if GATTEX is safe or effective in children.

What should I tell my healthcare provider before using GATTEX?

Before you use GATTEX, tell your healthcare provider if you:

- have cancer or a history of cancer
- have or had polyps anywhere in your bowel (intestines) or rectum
- have heart problems
- have high blood pressure
- have problems with your gallbladder, pancreas, kidneys
- have any other medical condition
- are pregnant or planning to become pregnant. It is not known if GATTEX will harm your unborn baby. Tell your healthcare provider right away if you become pregnant while using GATTEX.
- are breastfeeding or plan to breastfeed. It is not known if GATTEX passes into your breast milk. You and your healthcare provider should decide if you will use GATTEX or breastfeed. You should not do both.

Tell your healthcare providers about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using GATTEX with certain other medicines may affect each other causing side effects. Your other healthcare providers may need to change the dose of any oral medicines you take while using GATTEX. Tell the healthcare provider who gives you GATTEX if you will be taking a new oral medicine.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use GATTEX?

- Use GATTEX exactly as your healthcare provider tells you to.
- GATTEX is given 1 time each day at the same time.
- Inject your dose of GATTEX under the skin (subcutaneous injection) in your stomach area (abdomen), upper legs (thighs), or upper arms. **Do not inject GATTEX into a vein or muscle.**
- Use a different injection site each time you use GATTEX.
- GATTEX comes as a powder for injection in a vial that is used only 1 time (single-use vial). The powder must be mixed with Sterile Water for Injection (a diluent) provided in a pre-filled syringe before you inject it.
- GATTEX must be injected within 3 hours after you mix it with the diluent.

- **If you miss a dose, take it as soon as you remember that day. Take your next dose the next day at the same time you take it every day.**
- **Do not take 2 doses on the same day.**
- **If you use more than 1 dose, call your healthcare provider right away.**
- **Read the Instructions for Use for detailed instructions for preparing and injecting a dose of GATTEX.**

What are the possible side effects of GATTEX?

GATTEX may cause serious side effects, including:

- See **"What is the most important information I should know about GATTEX?"**
- **Fluid overload. Your healthcare provider will check you for** too much fluid in your body. Too much fluid in your body may lead to heart failure, especially if you have heart problems. Tell your healthcare provider if you get swelling in your feet and ankles, you gain weight very quickly (water weight), or you have trouble breathing.

The most common side effects of GATTEX include:

- stomach area (abdomen) pain or swelling
- skin reaction where the injection was given
- nausea
- headache
- cold or flu like symptoms
- vomiting

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of GATTEX.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store GATTEX?

- Store GATTEX powder at room temperature up to 25°C (77°F).
- Do not freeze GATTEX.
- Use the GATTEX powder by the expiration date on the "Use By" sticker on the kit. Use GATTEX within 3 hours after mixing it.
- Throw away any unused GATTEX that has been mixed, even if there is medicine left in the vial.
- Do not store any GATTEX you have mixed.

Keep GATTEX and all medicines out of the reach of children.

General information about the safe and effective use of GATTEX

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use GATTEX for a condition for which it was not prescribed. Do not give GATTEX to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about GATTEX talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about GATTEX that is written for health professionals.

For more information go to www.GATTEX.com or call 1-855-542-8839.

What are the ingredients in GATTEX?

Active ingredient: teduglutide
Inactive ingredients: L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate heptahydrate.
Sterile Water for Injection is provided as a diluent.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Hospira, Inc.
1776 N. Centennial Drive
McPherson, KS 67460
U.S.A.

Distributed by:
NPS Pharmaceuticals, Inc.
550 Hills Drive
Bedminster, NJ 07921
U.S.A.
Revised: June 2014
U.S. License No.203441

Instructions for Use

GATTEX®(Ga'-tex)

(teduglutide [rDNA origin])

for injection

Read this Instructions for Use before you start using GATTEX and each time you get a refill. There may be new information. Your healthcare provider or nurse should show you how to prepare, measure your dose, and give your injection of GATTEX the right way.

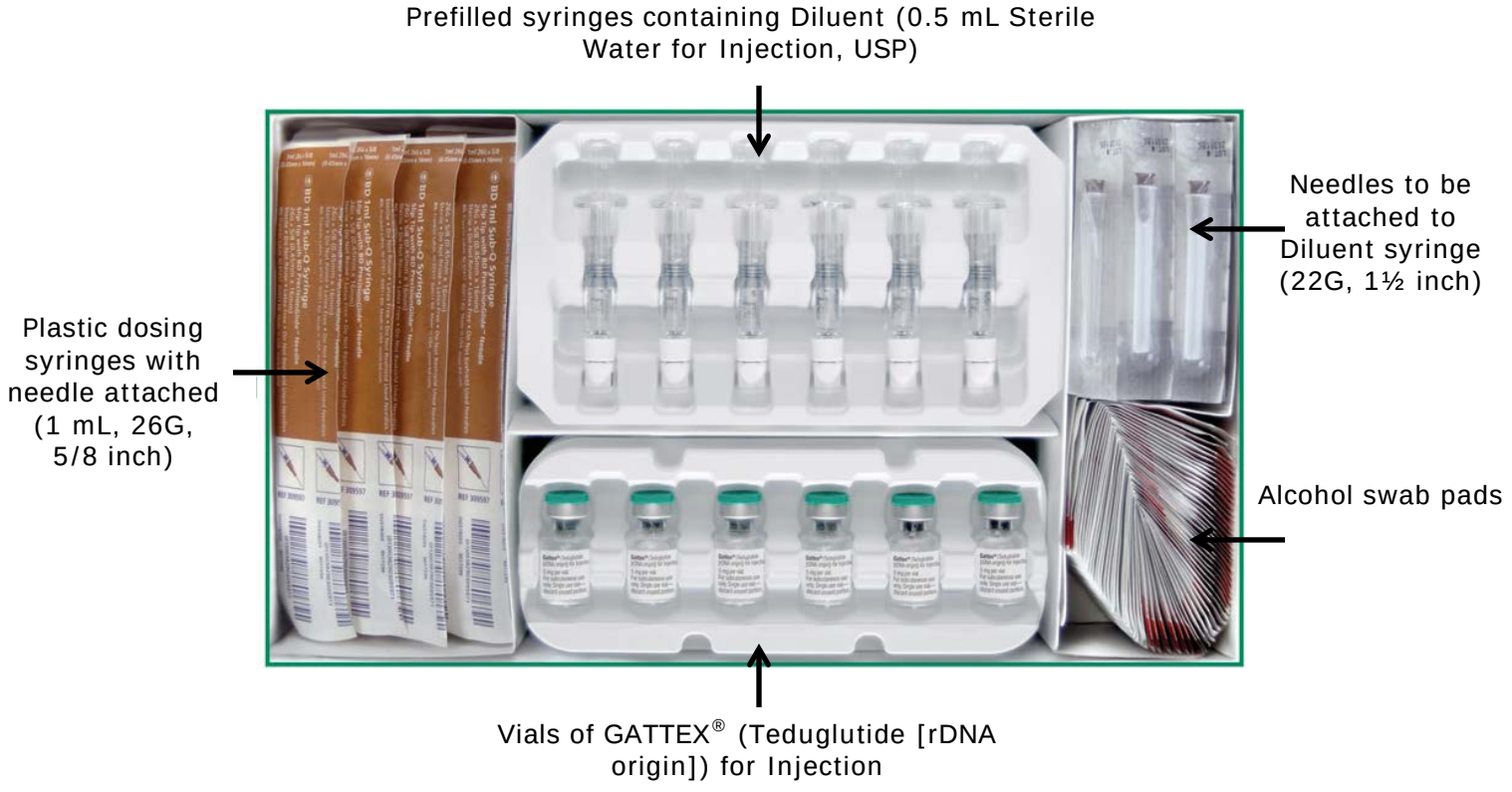
If you cannot give yourself the injection:

- ask your healthcare provider or nurse to help you, **or**
- ask someone who has been trained by a healthcare provider or nurse to give your injections

Important information:

- **Before you start,** check the "Use By" date on your GATTEX kit. Make sure that the "Use By" date has not passed. Do not use anything in the GATTEX kit after the "Use By" date on the kit.
- **Give GATTEX within 3 hours after you mix the powder with the Diluent (Sterile Water for Injection).**
- Use the syringes and needles provided in the GATTEX kit.
- Do not use a GATTEX vial more than one time, even if there is medicine left in the vial. Throw away any unused GATTEX after you give your injection.
- Safely throw away GATTEX vials after use.
- **Do not** re-use syringes or needles. See **"Step 7: Dispose of syringes and needles**" for information about how to safely throw away needles and syringes.
- To help avoid needle-stick injuries, **do not** recap needles.

GATTEX kit



Gather the supplies you will need to prepare GATTEX and to give your injection. **(See Figure A)**

Figure A

From your GATTEX kit you will need:

- 5-mg vial of GATTEX with green cap
  Your healthcare provider will tell you how many vials of GATTEX you will need for your injection.
- 2 alcohol swab pads
- Diluent syringe. Your kit has only 1 type of Diluent syringe.
  - With a white snap-off cap
    OR
  - With a gray screw top
- 22 gauge, 1½ inch needle
- Plastic dosing syringe with needle attached
- An FDA-cleared sharps disposal container. See **"Step 7: Dispose of needles and syringes."**

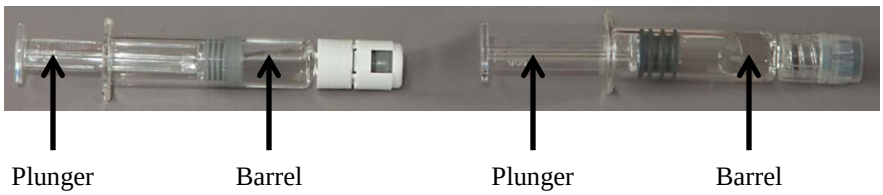
Step 1: Prepare the injection.

- Choose a well-lit, clean, flat work surface.
- Wash your hands with soap and water.

Step 2: Preparing the Diluent syringe.

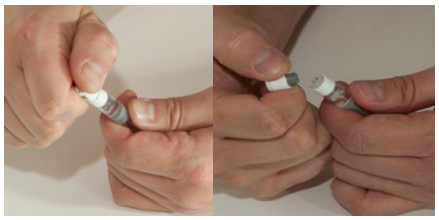
- Put the Diluent syringe and 22G 1½ inch needle in front of you on your work surface. (**See Figure B1**)

Figure B1



- Hold the Diluent syringe by the barrel.
  a. If you have the Diluent syringe with the white snap-off cap: Snap or twist off the white cap (bend the cap sideways until the cap comes off). Only the top portion of the white cap should be snapped off. The lower portion of the cap will remain in place (**See Figure B2**). Throw the cap away.

Figure B2



b. If you have the Diluent syringe with the gray screw top: Unscrew the top counter clockwise (to the left) (**See Figure B3**). Throw the top away.

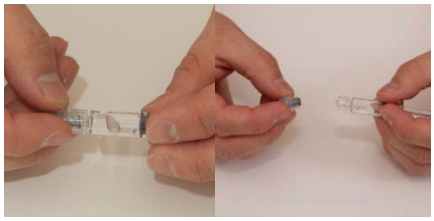


Figure B3

- Remove the 22G 1½ inch needle from the package. Use the fold in the package to peel back the plastic cover (**See Figure C**). Leave the plastic cap on the needle.

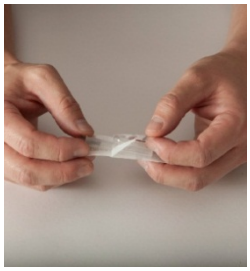


Figure C

- Push the open end of the needle onto the end of the Diluent syringe (**See Figure D**). Twist the needle clockwise (to the right) until it stops turning.

Figure D

- When the needle is tightly in place, put the Diluent syringe and needle on your work surface.

Step 3: Mix GATTEX powder with Diluent.

- Remove the green cap from the GATTEX vial. Throw away the green cap.
- Find the gray rubber seal on top of the vial (**See Figure E**).

Figure E

- Use an alcohol swab pad to clean the gray rubber seal (**See Figure F**).
- Do not touch the gray rubber seal after you clean it.

Figure F

- Pick up the Diluent syringe with the needle attached.
- Remove the plastic cap that covers the needle (**See Figure G**). Throw the cap away.

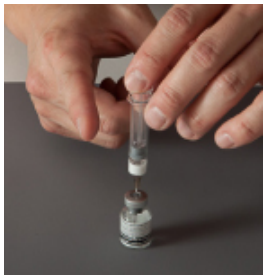
Figure G

- Hold the vial between thumb and index (pointer) finger (**See Figure H**). Be careful not to touch the gray rubber seal.
- Push the needle down through the center of the gray rubber seal.
- Slowly push down on the plunger of the Diluent syringe. Empty all the Diluent into the GATTEX vial.
- Leave the needle and Diluent syringe in place.

Figure H

- Gently tap the barrel of the Diluent syringe with a finger (**See Figure I**).
- Make sure all the Diluent has gone into the GATTEX vial.

Figure I



- Remove the Diluent syringe and needle from the GATTEX vial. Let the vial sit for about 30 seconds.
- **Do not put the needle cap back on the needle.**
- Dispose of the Diluent syringe and needle in your sharps disposal container.
- After 30 seconds, place the vial between the palms of your hands. Gently roll the vial for about 15 seconds (**See Figure J**).
- **Do not shake the vial.**
- Do not touch the gray seal. If you do, clean it again with a new alcohol pad.
- Let the vial stand on your work surface for about 2 minutes.

Figure J

Step 4: Check the mixed GATTEX.

- After 2 minutes, look at the vial of GATTEX. The liquid in the vial should be clear and colorless to pale yellow, and should not have any particles in it.
- If there is any powder in the vial that did not dissolve, gently roll the vial between your hands for 15 seconds more.
- **Do not shake the vial.**
- Check the vial again for anything that did not dissolve.
- **Do not use the vial** if there is anything in it that did not dissolve. Start from the beginning of this Instructions for Use to prepare a new vial. Use a new GATTEX vial, new Diluent syringe, and a new needle.

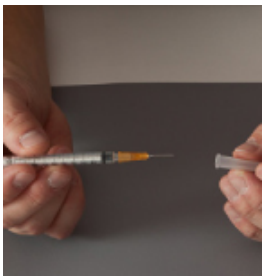
Step 5: Draw up your dose of GATTEX.

- Remove the plastic dosing syringe from the package. Use the fold in the package to peel back the plastic cover (**See Figure K**).

Figure K

- Remove the needle cap from the dosing syringe (**See Figure L**).
- Throw the needle cap away. Do not touch the needle or allow it to touch anything.

Figure L



- Carefully pull back on the plunger to the line that matches the dose prescribed by your healthcare provider.
- Use one hand to hold the vial steady. Use your other hand to insert the needle straight down into the middle of the gray rubber seal on the GATTEX vial (**See**

Figure M). You may feel some resistance as the needle passes through the rubber seal.

- Gently push down the plunger until all of the air has gone from the syringe into the vial.
- Turn the GATTEX vial and syringe upside down (**See Figure N**).

Figure M

Figure N

- Hold the GATTEX vial with one hand.
- Slowly pull back the plunger of the dosing syringe with your other hand.
- Fill the syringe until the black tip of the plunger lines up with the mark that matches your prescribed dose (**See Figure O**).
- Keep the syringe and needle in the vial.

Figure O

- You may see some bubbles inside the vial when the syringe is filled. This is normal. With the needle still in the vial, gently tap the side of the syringe with a finger to make any air bubbles rise to the top (**See Figure P**).

Figure P

- Slowly push the plunger up until all air bubbles are out of the **syringe**. Make sure the tip of the needle is in the fluid. Slowly pull back the plunger to draw up the right dose of GATTEX into the syringe.
- Remove the dosing syringe and needle from the vial (**See Figure Q**). Do not touch the needle or allow it to touch anything.

Figure Q

Step 6: Inject GATTEX.

- Choose an injection site on your stomach area (abdomen), thighs, or upper arms. Choose a different site to give the injection each day. Do not inject into areas where the skin is tender, bruised, red, or hard. **(See Figures R and S)**

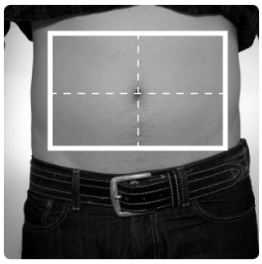


Figure R

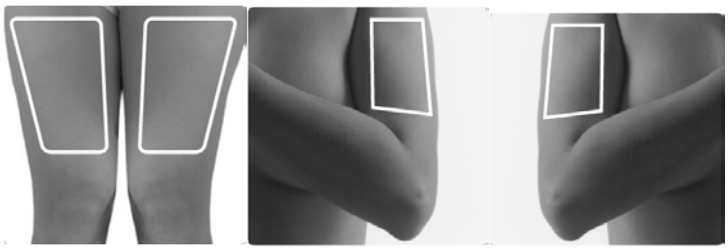


Figure S

- Clean the skin where you plan to give the injection with a new alcohol swab pad. Do not touch this area again before giving the injection.
- Use one hand to gently pinch up a fold of skin around the injection site (**See Figure T**).

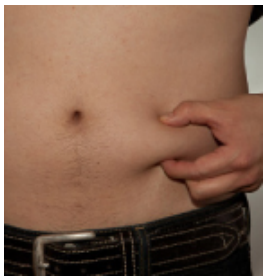
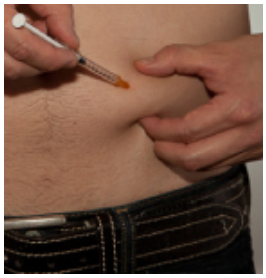


Figure T

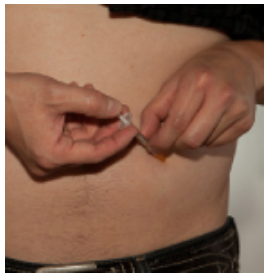
- Use your other hand to hold the syringe. Insert the full length of the needle into the skin at a 45-degree angle with a quick “dart-like” motion (**See Figure U**).

Figure U



- Let go of the skin. Hold the syringe barrel with one hand while you slowly push down the plunger until the syringe is empty (**See Figure V**).

Figure V



- When the syringe is empty, quickly pull the needle out of your skin. There may be a little bleeding at the injection site. Apply an adhesive bandage to the injection site if needed.

Step 7: Dispose of syringes and needles.

- **Do not** re-use a syringe or needle.
- To help avoid needle-stick injuries, do not recap a needle.
- Put your needles and syringes in an FDA-cleared sharps disposal container right away after use. **Do not throw away (dispose of) loose needles and syringes in your household trash.**
- If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:
  - made of heavy-duty plastic
  - can be closed with a tight-fitting, puncture-resistant lid, without sharp items being able to come out
  - upright and stable during use
  - leak-resistant, and
  - properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be local or state laws about how to throw away syringes and needles. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
- Do not dispose of your sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your sharps disposal container.
- Throw away the GATTEX vial into the container where you put the syringes and needles. If you have any questions, talk to your healthcare provider or pharmacist.

How should I store GATTEX?

- Store GATTEX powder at room temperature up to 77°F (25°C).
- Do not freeze GATTEX.
- Use the GATTEX powder by the expiration date on the “Use By” sticker on the kit. Use GATTEX within 3 hours after mixing it.
- Throw away any unused GATTEX that has been mixed, even if there is medicine left in the vial.
- Do not store any GATTEX you have mixed.

Keep GATTEX and all medicines out of the reach of children.
This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Hospira, Inc.
1776 N. Centennial Drive
McPherson, KS 67460
U.S.A.

Distributed by:
NPS Pharmaceuticals, Inc.
550 Hills Drive
Bedminster, NJ 07921
U.S.A.

Revised: June 2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203441/S-002

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(Stamp date)
From	Joyce Korvick, MD, MPH Deputy Director for Safety Division of Gastroenterology and Inborn Errors Products ODE III, CDER FDA
Subject	Division Director Summary Review
NDA #	203441 Supplement #002
Applicant Name	NPS Pharmaceuticals
Date of Submission	8/28/2013
PDUFA Goal Date	6/28/2014
Proprietary Name / Established (USAN) Name	Gattex (teduglutide [rDNA origin])
Dosage Forms / Strength	Lyophilized Powder for Injection, 5 mg
Currently approved Indication (no changes proposed)	GATTEX® (teduglutide [rDNA origin]) for injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ruyi He
Pharmacology Toxicology Review	Babatunde Akinshola
Clinical Pharmacology Review	Lin Zhou, Lanyan Fang
CDTL Review	Ruyi He
OPDP	Meeta Patel
OSE/DPV	Christian Cao
OSE/DRM	Therese Cvetkovich
OSE/DRISK	Nyedra Booker, Ana Tavakoli
Pediatric and Maternal Health Staff	Miriam Dinatale; Jeanine Best

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DPV=Division of Pharmacovigilance
DRISK=Division of Risk Management
DRM=Division of Risk Management
CDTL=Cross-Discipline Team Leader
OPDP= Office of Prescription Drug Promotion

Signatory Authority Review

1. Introduction

GATTEX® (teduglutide [rDNA origin]) was approved on 12/21/2012. It is a 33-amino acid recombinant analog of the human glucagon-like peptide-2 (GLP-2) which is a peptide secreted primarily from the lower gastrointestinal tract. Based upon the pharmacodynamic effects of GATTEX, there is a potential for increased absorption of from the GI tract, resulting in decreased parenteral support.

This supplement provides for changes to the professional label, Medication Guide and Risk Evaluation and Mitigation Strategy (REMS).

Approved indication (see above) was granted Orphan Drug designation on June 29, 2000.

2. Background

In the current submission, the applicant proposed to update the currently approved product label and REMS based on the final reports from the following studies:

- A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome (CL0600-021, Up to 2 years). Study CL0600-021 is the extension study to Study CL0600-020, which is one of the pivotal Phase 3 trials in the original NDA submission. This final report included clinical data.
- 104-Week Subcutaneous Injection Carcinogenicity Study with Teduglutide (ALX-0600) in Mice (P09-002)

The applicant proposed an to update to the Clinical Trials Experience, Adverse Reactions of Special Interest, Immunogenicity, Geriatric Use, and Clinical Studies Sections in the GATTEX® label, based on the long-term safety results from Study CL0600-021. In addition, the applicant proposed to update Carcinogenesis, Mutagenesis, Impairment of Fertility section based on the results from nonclinical Study P09-002.

The proposed REMS modification applies to the REMS document and appended materials, and REMS Supporting Document. (Submitted August 28, 2013, and amended February 10, 2014, June 11, 2014, and June 19, 2014)

3. CMC/Device

N/A

4. Nonclinical Pharmacology/Toxicology

A Mouse Carcinogenicity Study was submitted during this review period and its design is as follows:

In the 104-week subcutaneous carcinogenicity study in CD-1 mice, teduglutide was administered to male and female mice (80/sex/group) at dose levels of 0, 1, 3.5 and 12.5 mg/kg/day (1.25 ml/kg). Mice in the control group received only the vehicle (phosphate buffer with water for injection). The dose selection was based on a >25-fold AUC ratio of animal to human exposure for the high dose in a 26-week subcutaneous study with teduglutide in CD-1 mice (study No. 7302-112).

The nonclinical pharmacology review team concluded that there "were drug-related increased incidences of papillary adenomas in the gallbladder, and of adenocarcinomas in the jejunum. There were no drug-related neoplasms in females."

The reviewers recommended the inclusion of the following in the updated labeling:

"In a 2-year carcinogenicity study in Crl:CD1(ICR) mice at subcutaneous doses of 1, 3.5 and 12.5 mg/kg/day (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused a significant increase in papillary adenomas in the gall bladder; it also caused adenocarcinomas in the jejunum in male mice at the high dose of 12.5 mg/kg/day (about 250 times the recommended human dose)."

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. (See approved labeling for final wording).

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewed the data from Study CL0600-021 for the assessment of the long term immunogenicity incidence and its impact on PK, efficacy, and safety.

The reviewers summarized the findings and reached the following conclusions which served as the basis for their recommendations for the professional labeling Section 6.2:

"Based on the combined immunogenicity data from Studies -020 and -021, the immunogenicity incidence over time was 0% (0/89) at baseline, 3% (2/60) at Month 3, 18% (13/74) at Month 6, 25% (18/71) at Month 12, 31% (10/32) at Month 24, and 48% (14/29) at Month 30 in subjects who received subcutaneous administration of 0.05 mg/kg GATTEX once daily (Table 1)."

Table 1. Summary of patients tested positive for anti-teduglutide antibodies- Study

CL0600-020 & -021 combined (generated based on Table 14.3.4.1 of CSR of CL0600-020 and Table 14.3.4.19 of CSR of CL0600-021)

Cohorts	Enrolled	Duration on Treatment (months)								
		baseline	3	6	9	12	15	18	24	30
TED/TED	n = 37	0/39[a]	0/16[a]	6/34[a]	4/34	8/33	8/32	12/34	n/a	14/29
(PBO or NT)/TED	n = 50	0/50	2/44	7/40	8/39	10/38			10/32	
Combined		0/89	2/60	13/74	12/73	18/71	8/32	12/34	10/32	14/29

[a] Data from Study CL0600-020, in which 43 subjects were enrolled into the TED treatment arm.

"ADA appears to have no impact on PK and clinical efficacy and safety based on data in subjects treated with Gattex for up to 2.5 years whereas the longer term impact is unknown. In Studies -020 and -021, a total of 37 subjects were tested for neutralizing antibodies − 17 of these subjects had no neutralizing antibodies, and the remaining 20 subjects had no detectable neutralizing antibodies although the presence of teduglutide at low levels in these study samples could have resulted in false negatives (no neutralizing antibody detected although present)."

For final agreed upon labeling, refer to approved labeling.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

NPS Pharmaceuticals submitted the final study report for Study CL0600-021, "A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome" (Up to 2 years). Study CL0600-021 is the extension study to Study CL0600-020, which is one of the pivotal phase 3 trials submitted to the original NDA submission. The initial data from study -021 was placed into the original label; the final clinical data that was submitted in this application supported the changes to labeling for the safety as well as the efficacy sections of the label. This information provides for a more complete description of longer-term exposure to Gattex. However, it should be noted that since this is an opened-label study, the data are only of a descriptive nature. The updated information is present in the labeling as follows:

"**Study 2** was a 2-year open-label extension of Study 1 in which 88 subjects received GATTEX 0.05 mg/kg/day. Ninety-seven percent (76/78) of subjects who completed Study 1 elected to enroll in Study 2 (37 received GATTEX; (39 received Placebo). An additional 12 subjects entered Study 2, who had been optimized and stabilized but not randomized in Study 1 because of closed enrollment."

"30 months exposure

Thirty GATTEX subjects completed a total duration of 30 months (Study 1 followed by Study 2 treatment). Of these, 28 subjects (93%) achieved a 20% or greater reduction of parenteral support. Of responders in Study 1 who had completed 2 additional years of continuous treatment with GATTEX, 96% (21/22) sustained their response to GATTEX. The mean reduction in PN/I.V. (n=30) was 7.55 L/week (a 65.6% reduction from baseline). Ten subjects were weaned off their PN/I.V. support while on GATTEX treatment for 30 months. Subjects were maintained on GATTEX even if no longer requiring PN/I.V. support. These 10 subjects had required PN/I.V. support for 1.2 to 15.5 years, and prior to GATTEX had required between 3.5 L/week and 13.4 L/week of PN/I.V. support. At the end of study, 21 (70%), 18 (60%) and 18 (60%) of the 30 completers achieved a reduction of 1, 2, or 3 days per week in PN/I.V. support, respectively."

"24 month exposure
Of the 39 placebo subjects from Study 1 entering Study 2, 29 completed 24 months of treatment with GATTEX. The mean reduction in PN/I.V. was 3.11 L/week (an additional 28.3% reduction) from the start of Study 2. Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral support. At the end of study, 14 (48.3%), 7 (24.1%) and 5 (17.2%) achieved a reduction of 1, 2, or 3 days per week in PN/I.V. support, respectively. Two subjects were weaned off their PN/I.V. support while on GATTEX. Of the 12 subjects entering Study 2 directly, 6 completed 24 months of treatment with GATTEX. Similar effects were seen. One of the six subjects was weaned off their PN/I.V. support while on GATTEX."

8. Safety

This supplement provides for an update of the safety labeling sections of the professional labeling based upon new information provided in this submission from the final study report of Study CL0600-021, and the accompanying safety data base.

Labeling recommendations reflect the updated data reviewed by Dr. He (see updated professional labeling, Adverse Reactions [6]). No new safety signals were identified.

(b) (4)

In order to further inform this review, Division of Pharmacovigilance (DPV) reviewed the FDA Adverse Event Reporting System (FAERS) database specifically looking for cases related to: 1.) increased absorption of fluids leading to fluid overload; 2.) increased absorption of oral concomitant medication. DPV summary statements are provided below:

""Of the 16 cases (14 reported in FAERS, 2 additional cases reported by applicant) of fluid overload, the most commonly reported symptoms were weight increased, abdominal distension, and fluid retention. Patients experienced fluid overload-associated symptoms 1 to 63 days after starting teduglutide with a median time to onset of 9 days. In the 9 cases that reported an intervention, adjustment of parenteral nutrition and teduglutide dosage were consistent with labeling recommendation. One patient died while taking teduglutide; it is unknown whether the parenteral nutrition was adjusted. The patient had a complex medical history that included coronary artery disease and chronic pelvic infection related to complications of colorectal surgery, which may contribute to the fluid retention. Another two

cases also reported that the patient had a history of cardiovascular disease: coronary artery disease (n=1) and atrial fibrillation (n=1). No cases of CHF or new onset CHF, however, were reported."

"There was one case of increased absorption of oral concomitant drugs (Vicodin, zolpidem, citalopram, and cyclobenzaprine) that also reported a death outcome. The patient had a history of alcoholic liver cirrhosis that may have contributed to higher zolpidem, citalopram, cyclobenzaprine, and Vicodin drug levels because of reduced drug-metabolism."

"The role of teduglutide in the development of fluid overload or increase absorption of oral concomitant drugs cannot be excluded in the two fatal cases. Both patients in these cases, however, had very complex medical histories that may contribute to the adverse events and death."

"DPV did not identify any new safety concerns related to fluid overload or increased absorption of oral concomitant drugs with teduglutide use."

"DPV recommends the following: Request NPS to submit all reports of fluid overload and increased absorption of oral concomitant drugs with a serious outcome as 15-day alert reports to FDA."

In summary, There are no new safety information which changes what is conveyed in the Warnings and Precautions section of the professional labeling. Additional reports regarding fluid overload and increased absorption of oral concomitant drugs should continue to be monitored. As DPV suggests, in order to more closely follow the adverse events of fluid overload and increased absorption of oral concomitant drugs, a request will be made to the sponsor to report serious cases as 15-day alert reports.

Based upon the review of the safety data updated in this submission, CDTL review, and DPV review, I concur with the recommendations.

- **Risk Evaluation and Mitigation Strategy (REMS)**

The first REMS assessment included the reporting period from December 21, 2012 through October 21, 2013. The DRISK reported that at the February 10, 2014 meeting, the review team concluded:

> "We discussed the results of the assessment report review including the patient survey results and prescriber survey participation. Revision of the goal to limit education to physicians was discussed; the team acknowledged the challenges of educating patients in the context of this REMS since it includes a patient counseling tool as the source of drug-related risk information rather than the MG. For ETASU programs without a safe use element it is reasonable to consider that patient knowledge of the risks may be lower in the absence of an active role in the REMS program. The group concluded that it may be worthwhile to explore options to improve patient understanding with the applicant in the context of the ongoing review of the REMS modification submitted by

the applicant in December 2013. In addition we will request that the applicant propose a plan intended to increase the number of survey participants."

DRISK provided comments to the Sponsor on March 4, 2014, requesting that they provide a plan to address the deficiencies found in the patient survey. The Sponsor provided a response to DRISK comments on April 11, 2014 with a plan to revise low scoring questions in the patient survey and utilize their existing patient outreach infrastructure1 to reinforce key risk messages in the Medication Guide and Patient and Caregiver Counseling Guide. These activities are conducted by the Sponsor outside of the REMS.

Upon review of the approved Gattex REMS Patient and Caregiver Counseling Guide, DRISK determined that the tool was identical to the Medication Guide. Therefore, DRISK recommended modification to the tool to focus the messages to the Gattex REMS key risk messages. Formatting changes are also proposed to improve readability.

Sponsor Proposed REMS changes:

NPS Pharmaceutical's formally proposed modifications to the REMS, dated August 28, 2013 and amended February 10, 2014, (b) (4) the Applicant proposed revisions to three slides in the *Prescriber Education Slide Deck* based on findings from the completed long-term extension study and clinical safety database. Editorial revisions were also proposed to the REMS Supporting Document.

(b) (4)

The DRISK reviewer summarized subsequent negotiations as follows:

(b) (4) The Review Team agreed with the Applicant's proposed changes to the Prescriber Education Slide Deck. Furthermore, editorial updates were made to the REMS website and the Patient and Caregiver Counseling Guide was revised based on DRISK's review of the 1-Year Gattex REMS Assessment. The Applicant submitted an amended REMS modification proposal on June 11, 2014, and June 19, 2014."

The time table for assessments will remain the same.
DRISK found the proposed Gattex REMS modification as submitted on June 19, 2014 to be acceptable. (For final REMS documents see approval letter)

I concur.

9. Advisory Committee Meeting

No Advisory Committee was held for this supplement. This supplement is an update of clinical data from study -021 which was previously reviewed in part. No new safety issues were raised by our review.

10. Pediatrics

No new pediatric data was submitted in this supplement. DGIEP consulted PMHS for assistance with updating regulatory language in sections 8.1 and 8.3 to the hybrid Proposed Pregnancy and Lactation Labeling Rule format (published in May 2008). The PMHS provided updated labeling that was shared with the applicant. See final approved label for further details.

11. Other Relevant Regulatory Issues

- OPDP review agreed with proposed changes made by the review team to the final labeling.

There are no other unresolved relevant regulatory issues

12. Labeling

- **Professional Labeling:** changes were incorporated to the following sections:

Section 5 WARNINGS AND PRECAUTIONS- Assorted minor editorial changes
Section 6 ADVERSE REACTIONS- Revision of 6.1 to incorporate additional patient exposures from study drug and results from the complete study report
Section 8 USE IN SPECIFIC POPULATIONS- Revision of 8.5 to reflect additional exposures,
Section 11 DESCRIPTION- Assorted minor editorial changes,
Section 13 NONCLINICAL TOXICOLOGY - Revision of 13.1 to incorporate final results of 2-year mouse carcinogenicity study
Section 14 CLINICAL STUDIES- To incorporate results from the complete study report
Section 17 Patient Counseling Information

These changes were agreed upon by the applicant, review team and signatory.

- **Medication Guide:** No new safety issues identified, only mirror changes were made.

I concur with these changes.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action: Approval**

- **Risk Benefit Assessment:**

  Based upon the supplemental data from the longer-term exposure study (-021), the benefits described in the original review of Gattex are supported. No new safety signals were identified. (b) (4) [redacted] There are five key serious safety issues outlined in the Warnings and Precautions section of the professional labeling: acceleration of neoplastic growth, intestinal obstruction, biliary and pancreatic disease fluid overload and increased absorption of concomitant oral medication. These adverse reactions are considered tolerable and manageable given the significant unmet medical need in the orphan condition of SBS with intestinal failure. FDA will continue to monitor these adverse reaction reports.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

  Modifications submitted by the NPS Pharmaceuticals on June 19, 2014 were accepted by the FDA and the final version is attached to the approval letter.

- **Recommendation for other Postmarketing Requirements and Commitments**

  No new safety issues were identified during the review of this supplement; therefore, no additional PMR/PMCs are necessary at this time. The reader is referred to the original approval letter for current listing of PMR/PMCs.

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
06/26/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203441/S-002

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	6/10/2014
From	Ruyi He, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 203441SE-2, Amendment to SE 2 (REMS)
Applicant	NPS Pharmaceuticals, Inc
Date of Submission	8/28/2013, and 2/10/2014
PDUFA Goal Date	6/28/2014
Therapeutic Class	Glucagon-like peptide-2 (GLP-2) analog
Proprietary Name / Established (USAN) names	Teduglutide (rDNA origin)/ GATTEX®
Proposed Indication(s)	The treatment of adult patients with Short Bowel Syndrome (SBS). GATTEX is used to improve intestinal absorption of fluid and nutrients.
Proposed Dosage forms / Strength	GATTEX should be administered by subcutaneous (SC) injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms. GATTEX should **not** be administered intravenously or intramuscularly. The recommended daily dose of GATTEX is 0.05 mg/kg body weight.
Recommended:	I recommend that NDA 203441 SE-2 for Teduglutide (rDNA origin)/ GATTEX® be approved for the revised label.

1. Introduction

GATTEX (teduglutide [rDNA origin]) is a 33–amino acid recombinant analog of human Glucagon-like peptide-2 (GLP-2), a peptide secreted primarily from the lower gastrointestinal tract. NDA 203441 was approved on December 21, 2012 for GATTEX® (teduglutide [rDNA

origin]) for injection, for subcutaneous use indicated for the treatment of adults with Short Bowel Syndrome (SBS) who are dependent on parenteral support.

The initial NDA 203441 (Sequence 0001, November 30, 2011) submission which included an interim clinical study report CL0600-021 entitled, "A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome: Interim Report." The interim report was prepared to support the initial marketing application review. As agreed with the Division, and as discussed during the pre-NDA meeting (April 25, 2011), the final clinical study report would be submitted following study completion. In addition, the division agreed that filing a second carcinogenicity study to the NDA as a postmarketing commitment.

At this time, NPS Pharmaceuticals is submitting the final reports for CL0600-021 as mentioned above. In addition, the sponsor also provided a proposed revised label for GATTEX and corresponding modified REMS document.

This indication was granted Orphan Drug designation on June 29, 2000.

2. Background

Short bowel syndrome results from surgical resection or congenital defect and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet. Patients with SBS are highly prone to malnutrition, diarrhea, dehydration, and an inability to maintain weight due to the reduced intestinal capacity to absorb macronutrients, water, and electrolytes.

Major small intestinal resection resulting in SBS often requires long-term parenteral nutrition with intravenous fluids (PN/I.V.) support due to severe malabsorption of nutrients and fluids. Although PN/I.V. support is life-saving in patients with intestinal failure, it is often associated with life-threatening complications. Therefore, therapies to treat SBS and reduce PN/I.V. dependence offer the potential to improve long-term survival and decrease complications secondary to ongoing use of PN/I.V. support. A reduction in the burden of parenteral support may also result in clinically meaningful benefits such as an increase in the number of days off of PN/I.V. support per week, decreased nocturia and less interrupted sleep, reduced infusion time per day, decreased stomal output or diarrhea, and reduced costs and resources associated with managing patients dependent on PN/I.V. support.

Historically, clinical care of patients with short bowel syndrome (SBS) has mainly focused on optimizing remnant intestinal function through dietary interventions, oral rehydration solutions, anti-diarrheal and anti-secretory agents. Although surgical procedures such as bowel lengthening surgery or intestinal transplantation have been suggested as potential treatments, both options are associated with significant morbidity and mortality and are therefore considered only in selected patients.

For treating patients with SBS, the FDA approved Zorbtive [somatropin (rDNA origin) for injection, NDA 021597] in 2003. In 2004 the FDA approved NutreStore [L-glutamine for oral solution, NDA 021667] which should be administered as a cotherapy with Zorbtive together with optimal management of short bowel syndrome, such as a specialized oral diet. Hence, there continues to exist a substantial need for additional treatment options.

Proposed GATTEX Label: The GATTEX label has been revised to reflect updated patient data resulting from the completion of the Phase 3 open-label extension study (CL0600-021). Additional revisions have been made to incorporate study findings from the completed 2-year Mouse Carcinogenicity study. Minor editorial revisions have also been incorporated into this label version for consistency and accuracy.

REMS Modification: The GATTEX REMS includes an "Elements to Assure Safe Use (ETASU)" component. The ETASU includes a Prescriber Education and Training Program that incorporates the use of Prescriber Education Slides. As a result of the completion of the Phase 3 open-label extension study (CL0600-021), revisions to 3 of the Prescriber Education Slides have been made to reflect the increased numbers of patients receiving teduglutide and duration of exposure, and details of adverse events. Specifically, 2 slides (slide numbers 7 and 11) have been revised to reflect additional patient numbers experiencing gastrointestinal polyps and biliary events. One slide (slide number 9) has been revised to reflect updated information for patients experiencing gastrointestinal obstruction.

(b) (4)

this REMS modification was resubmitted as an amendment to SE2 on February 10, 2014.

According to the sponsor, this REMS modification is to ensure the benefits of Gattex outweigh the risks of fluid overload and increased absorption of concomitant oral medication described in the labeling, NPS is proposing a REMS modification affecting the Communication Plan.

3. CMC/Device

NA

4. Nonclinical Pharmacology/Toxicology

Dr. Emmanuel Akinshola is the reviewer and Dr. Sushanta Chakder is the team leader for this NDA and they concluded in the review that from a nonclinical standpoint, this NDA is recommended for approval and the carcinogenicity findings in male mice should be included in the labeling of Gattex. He has no recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps.

Based on the Dr. Emmanuel Akinshola's review, the Applicant submitted the final report of the 2-year carcinogenicity study by subcutaneous (SC) injection in CD-1 mice. The dose-selection

was based on the pharmacokinetic endpoint (AUC ratio) of animal to human exposure, and was concurred with by the Executive CAC.

In the 104-week SC carcinogenicity study in male and female CD-1 mice (80/sex/dose), teduglutide was administered at dose levels of 0, 1.0, 3.5 or 12.5 mg/kg/day for (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively). Mice in the control group received only the vehicle (phosphate buffer in water for injection). Treatment with teduglutide significantly increased the incidence of papillary adenoma in the gallbladder of male mice when compared to control mice (control, 0/66; low dose, 5/71; mid dose, 2/70; high dose, 6/70). The incidence of Adenocarcinoma of the jejunum was also increased (4/68) in male mice administered the high dose of 12.5 mg/kg/day. This is a rare tumor in CD-1 mice, and was not observed in concurrent study control or (b) (4) historical control values (0/256). No drug-related increased incidence of any neoplasms was observed in female mice.

5. Clinical Pharmacology/Biopharmaceutics

Dr. Lanyan Fang and Lin Zhou are the Clinical Pharmacology reviewers for this NDA and Dr. Yow-Ming Wang is the Team Leader. They reviewed the NDA and concluded that from a clinical pharmacology perspective, the information submitted to support this efficacy supplement is acceptable provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert. They do not have recommendation for post-marketing requirements for this submission. Please see Dr. Zhou's review dated on May 27, 2014 for detail.

6. Clinical Microbiology

NA

7. Clinical/Statistical- Efficacy

2-Year Extension Study CL0600-021
Study CL0600-021 was a 2-year open-label extension of pivotal Study CL0600-020 in which 88 subjects received Gattex 0.05 mg/kg/day. Ninety-seven percent (76/78) of subjects from Study CL0600-020 elected to enroll in Study CL0600-021. The subject population in Study CL0600-021 consisted of 3 groups: 37 subjects treated with Gattex during Study CL0600-020 ("TED/TED" group), 39 subjects treated with placebo during Study CL0600-020 ("PBO/TED" group), and an additional 12 untreated subjects ("NT/TED" group) who had been optimized and stabilized but not randomized in Study CL0600-020 because of closed enrollment.

There continued to be evidence of increased response to treatment over time in all 3 groups exposed to Gattex in Study CL0600-021 in terms of PN/I.V. volume reduction, gaining additional days off PN/I.V. support per week, and achieving weaning off of parenteral support.

Overall, 30 of 43 subjects who received Gattex in Study CL0600-020 and who continued Gattex treatment in Study CL0600-021 completed a total of 30 months of treatment with Gattex. Of these, 28 subjects (93%) achieved a 20% or greater reduction of parenteral support. Of responders in Study CL0600-020 who completed Study CL0600-021, 96% (21/22) sustained their response to Gattex after an additional 2 years of continuous treatment. The mean reduction in PN/I.V. (n = 30) was 7.55 L/week (a 65.6% reduction from baseline). Ten subjects in the TED/TED group were weaned off their PN/I.V. support while receiving Gattex treatment for 30 months. Subjects were maintained on Gattex even if no longer requiring PN/I.V. support. These 10 subjects had required PN/I.V. support for 1.2 to 15.5 years, and prior to treatment with Gattex they had required between 3.5 and 13.4 L/week of PN/I.V. support. At the end of study, 21 (70%), 18 (60%) and 18 (60%) of the 30 completers achieved a reduction of 1, 2, or 3 days per week in PN/I.V. support, respectively.

Of the 39 subjects who entered Study CL0600-021 after receiving placebo in Study CL0600-020, 29 completed 24 months of treatment with Gattex. The mean reduction in PN/I.V. volume was 3.11 L/week (an additional 28.3% reduction) from the start of Study CL0600-021. Sixteen (55.2%) of the 29 completers achieved a 20% or greater reduction of parenteral support. At the end of the study, 14 (48.3%), 7 (21.4%) and 5 (17.2%) achieved a reduction of 1, 2, or 3 days per week in PN/I.V. support, respectively. Two subjects in the PBO/TED group were weaned off their PN/I.V. support while receiving Gattex in Study CL0600-021.

Of the 12 subjects entering Study CL0600-021 directly, 6 completed 24 months of treatment with Gattex. The mean reduction in PN/I.V. volume was 4.0 L/week (39.4% reduction from baseline – the start of Study CL0600-021) and 4 of the 6 completers (66.7%) achieved a 20% or greater reduction of parenteral support. At the end of the study, 3 (50%), 2 (33%) and 2 (33%) achieved a reduction of 1, 2, or 3 days per week in PN/I.V. support, respectively. One subject in the NT/TED group was weaned off their PN/I.V. support while receiving Gattex in Study CL0600-021.

In conclusion, in extension Study CL0600-021, all groups of subjects (TED/TED, PBO/TED, and NT/TED) demonstrated a response to Gattex. The response to long-term treatment with Gattex 0.05 mg/kg/day was maintained in subjects initially treated with Gattex in Study CL0600-020 (TED/TED group), and with further mean reductions in PN/I.V. volume relative to baseline over time and fewer days of weekly PN/I.V. required, even after an extended period of treatment with Gattex, including demonstration of complete weaning of parenteral support. Of 30 subjects who completed 30 months of treatment with Gattex, 28 (93%) achieved a 20% or greater reduction in parenteral support, resulting in a PN/I.V. volume reduction of 7.55 L/week, corresponding to a mean reduction of approximately 65.6% from baseline. PN/I.V. frequency was reduced by at least 1 day per week in 21 of 30 subjects (70%) who completed 30 months of treatment. Of the 22 responders in Study CL0600-020 who completed Study CL0600-021, 21 (96%) sustained their response to Gattex after a further 2 years of continuous treatment, demonstrating the durability of the effect of Gattex. Efficacy was also observed in subjects who initiated treatment with Gattex in Study CL0600-021 (PBO/TED and NT/TED groups). Subgroup analyses showed a range of absolute and percent reductions in PN/I.V. volume across all subgroups. Overall, 13 of 88 subjects (14.8%) were completely weaned off PN/I.V. support (ie, achieved complete enteral autonomy) during Study CL0600-

021. Including the 2 subjects weaned in Study CL0600-004 and the subject weaned after 1 year of treatment in Study CL0600-005, a total of 16 subjects who received Gattex 0.05 mg/kg/day achieved complete enteral autonomy across the SBS clinical program. The responses to treatment with Gattex were accompanied by an increase in mean plasma citrulline level, indicating increased enterocyte mass.

In summary, those data from long term extension studies support efficacy conclusions from Study 004 and Study 020.

8. Safety

Overall, 65 of 88 subjects who received long-term treatment with teduglutide 0.05 mg/kg/day completed this extension study. No new unexpected safety signals were identified beyond those identified in the CL0600-021 Interim Report (June 2011) and reviewed during the original NDA review. Subjects who completed the study and experienced reductions in PN/I.V. support maintained their nutritional status as evidenced by stable or improved mean albumin, electrolyte (calcium, magnesium, and phosphate), BUN, and creatinine levels, and weight at Month 24 compared with baseline.

SBS patients are prone to GI-related events, dehydration, fever, and an inability to maintain weight. In addition, PN/I.V. is associated with complications such as sepsis, blood clots, and liver damage. In addition, the underlying etiology and/or comorbidities of SBS may have contributed to certain adverse events that were observed in the study.

- Of the 88 subjects enrolled, all received at least 1 dose of study drug. Eighty-four subjects (95.5%) experienced at least 1 TEAE during the study. Most subjects (79/88 [89.8%]) had TEAEs considered by the investigator to be unrelated to treatment with the study drug.

- Fifteen subjects (17.0%), 12 of whom were in the NT, PBO/TED group, experienced TEAEs that led to study discontinuation. One additional subject discontinued study due to weight loss that started in the previous study (CL0600-020) and was not considered treatment-emergent in Study CL0600-021.

- There were 3 deaths in the study:

    1. Subject 0155-1009 - metastatic adenocarcinoma

    2. Subject 0138-1011 - non-small cell lung cancer

    3. Subject 0219-1004 – sepsis

- One subject (0138-1002) in the TED/TED group was diagnosed with squamous cell lung carcinoma approximately 2 years after starting teduglutide. The event was still ongoing as of the last follow-up.

- As expected based on previous evidence, TEAEs were mainly of GI origin, including abdominal pain (30/88 subjects [34.1%]) and nausea (17/88 subjects [19.3%]).

- Liver disease is a co-morbidity associated with PN/I.V. treatment. Therefore it is notable that mean liver enzyme values either showed improvement or evidence that there was no further progression of liver disease, with mean decreases from baseline in alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels observed at most evaluations. In addition liver function tests were observed for subjects who experienced a 50% or greater reduction in PN/I.V. from baseline at Month 24. In this subset of subjects (n = 30), all mean liver enzymes declined by Month 1 (most after the first 2 weeks).

- Mean albumin levels were constant throughout the study, indicating conserved nutritional status of study subjects in the setting of moderate to clinically significant reductions in PN/I.V. support.

- Kidney disease is also a comorbidity of PN/I.V. treatment. Similar to what was seen with liver enzymes, there were no clinically meaningful mean changes from baseline in kidney function tests. Five subjects had elevations in serum creatinine levels reported as TEAEs, which were mild or moderate and considered unrelated to treatment by the investigator. Two cases of renal failure (one acute and one chronic) were reported that were not considered related to study drug by the investigator.

- No clinically meaningful differences in vital signs or physical examinations were observed during the study period.

- There were no relevant changes from baseline in mean weight. For the NT, PBO/TED group, mean (± SD) weight was 62.17 ± 13.11 kg at baseline and 61.65 ±14.43 kg at the last dosing visit. For the TED/TED group, mean (± SD) weight and BMI were 62.65 ± 12.10 kg and 22.33 ± 3.25 kg/m2, respectively, at baseline and 62.39 ± 13.95 kg and 22.16 ± 3.59 kg/m2, respectively, at the last dosing visit.

- One subject had an ECG abnormality that was considered clinically significant, ie, ongoing (not treatment-emergent) T-wave amplitude flattening, which was mild and judged not to be drug related by the investigator. No action was taken, and the abnormality continued. No other abnormal, clinically significant laboratory abnormalities were reported, and no ECG abnormality was reported as a TEAE or TESAE.

- A total of 50 subjects underwent 51 colonoscopies during or as follow-up for the study. Gastrointestinal polyps were reported in a total of 9 subjects within or at the end of the 24-month treatment period with teduglutide. Of the 9 subjects with evidence of polyps,

biopsy findings included reports of adenomas in 5 subjects. The polyps identified in the remaining 4 subjects were either not classified, hyperplastic, or inflammatory.

- Based on data from two trials in adults with SBS (a 6-month randomized placebo-controlled trial, followed by a 24-month open-label trial), the incidence of anti-teduglutide antibody was 3% (2/60) at Month 3, 18% (13/74) at Month 6, 25% (18/71) at Month 12, 31% (10/32) at Month 24 and 48% (14/29) at Month 30 in subjects who received subcutaneous administration of 0.05 mg/kg GATTEX once daily. The anti-teduglutide antibodies were cross-reactive to native glucagon-like peptide (GLP-2) in 5 of the 6 subjects (83%) who had anti-teduglutide antibodies. Anti-teduglutide antibodies appear to have no impact on short term (up to 2.5 years) efficacy and safety although the long-term impact is unknown.

- In the same two trials, a total of 36 subjects were tested for neutralizing antibodies: 9 of these subjects had no neutralizing antibodies, and the remaining 27 subjects had no detectable neutralizing antibodies.

- Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying diseases. For these reasons, comparison of the incidence of antibodies to GATTEX with the incidence of antibodies to other products may be misleading.

Safety and Tolerability Summary and Conclusions
In conclusion, teduglutide administered once daily by SC injection at a dose of 0.05 mg/kg body weight is safe for use in accordance with the modified label for the treatment of adult patients with SBS.

In the assessment of safety in the teduglutide development program the majority of adverse events was GI in origin. This is not unexpected considering these are the same complications often seen in study populations of SBS subjects and Crohn's disease. In addition, considering the direct intenstinotrophic actions of teduglutide, these GI adverse events most likely represent the mechanism of action and pharmacologic/treatment effect of teduglutide. The potential risk of carcinogenesis in regard to teduglutide as an intestinal growth factor needs to be considered and a closely monitoring this potential risk is needed. Nonclinical models have suggested that when pre-existing conditions and/or malignancies are present, GLP-2 analogs such as teduglutide may promote tumor growth. No new safety signal is identified with this new supplement NDA submission. These potential risks of teduglutide are considered acceptable and manageable considering the high unmet need in the orphan condition of SBS with intestinal failure.

9. Advisory Committee Meeting

NA

10. Pediatrics

This drug has not yet been studied in children.

11. Other Relevant Regulatory Issues

We consulted Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) on March 10, 2014 to revise and update the pregnancy and nursing mothers subsections of Gattex labeling.

PMHS-MHT concluded that a pregnancy category B is the appropriate classification for Gattex labeling since animal reproduction studies failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Additionally, a literature search revealed no human pregnancy data with the use of this product. The pregnancy subsection of Gattex labeling was structured in the spirit of the proposed PLLR, while complying with the current pregnancy labeling regulations (see 21 CFR 201.57(c)(9)(i). Minor editorial revisions were made to the nursing mothers subsection of Gattex labeling for consistency with language in the proposed PLLR, while complying with the current nursing mothers pregnancy labeling regulations (see 21 CFR 201.57(c)(9)(iii). I concurred with the recommendations.

PMR/PMC

FDA has determined that the sponsor is required to conduct the following as a PMR based on approval letter dated on December 21, 2012:

1978-1 A prospective, multi-center, long-term, observational, registry study, of short bowel syndrome patients treated with teduglutide in a routine clinical setting, to assess the long-term safety of teduglutide. Design the study around a testable hypothesis to rule out a clinically meaningful increase in colorectal cancer risk above an estimated background risk in a suitable comparator. Select and justify the choice of appropriate comparator population(s) and corresponding background rate(s) relative to teduglutide-exposed patients. Provide sample sizes and effect sizes that can be ruled out under various enrollment target scenarios and loss to follow-up assumptions. The study's primary outcome should be colorectal cancer, and secondary outcomes should include other malignancies, colorectal polyps, bowel obstruction, pancreatic and biliary disease, heart failure, and long-term effectiveness. Patients should be enrolled over an initial 5-year period and then followed for a period of at least 10 years from the time of enrollment. Progress updates of registry patient accrual and a demographic summary should be provided annually. Registry safety data should be provided in periodic safety reports. The study is currently on going according to the following timeline.

Final Protocol Submission: 09/13
Study Completion: 12/29
Final Report Submission: 06/31

One postmarketing commitments as following:
1978-2 Elemental impurities specifications will be expanded to include limits and testing for all metals, as recommended in USP <232>.

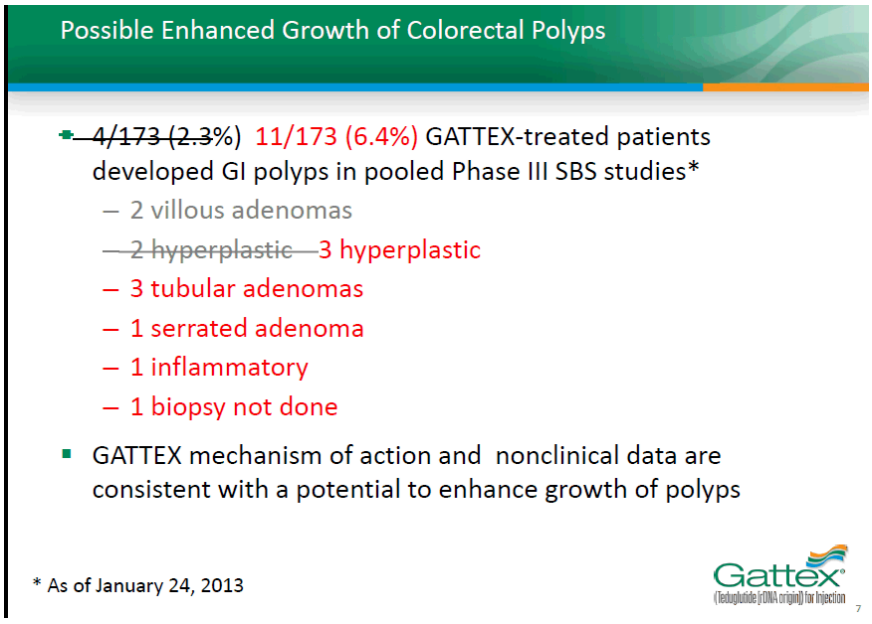
The timetable the sponsor submitted on December 18, 2012, states that the sponsor will implement these specifications by March 31, 2013; submitted as a CBE-30 supplement.

On March 27, 2013, the sponsor submitted final drug substance specifications, methods, and justification to reflect the analysis of the metals listed in USP <232>. Accordingly, this submission fulfills the Post Approval Commitment 1978-2 as outlined in the Approval letter.

Postmarket Risk Evaluation and Mitigation Strategies

The GATTEX REMS includes an "Elements to Assure Safe Use (ETASU)" component. The ETASU includes a Prescriber Education and Training Program that incorporates the use of Prescriber Education Slides. As a result of the completion of the Phase 3 open-label extension study (CL0600-021) and the completed clinical pharmacology study (TED-C10-004), revisions to 3 of the Prescriber Education Slides have been made to reflect the increased numbers of patients receiving teduglutide and duration of exposure, and details of adverse events. Specifically, 2 slides (slide numbers 7 and 11) have been revised to reflect additional patient numbers experiencing gastrointestinal polyps and biliary events. One slide (slide number 9) has been revised to reflect updated information for patients experiencing gastrointestinal obstruction (see below for details). Those changes are acceptable.

Slide #7



Slide #9

Gastrointestinal Obstruction

- 12 patients experienced one or more episodes of intestinal obstruction/stenosis*
  - 6 in SBS placebo-controlled studies
    - 3/77 (3.9%) on GATTEX, 0.05 mg/kg/day
    - 3/32 (9.4%) on GATTEX, 0.10 mg/kg/day
    - None in placebo-group
    - Onset 1 day to 6 months
  - 6 in the extension studies (all on GATTEX, 0.05 mg/kg/day)
    - Onset 6 days to ~~7 months~~ 19 months
    - Of all of these patients, ~~1 patient~~ 2 patients required endoscopic dilatation; ~~and one required surgical intervention~~ and one required surgical intervention

* As of January 24, 2013

Gattex® (Teduglutide [rDNA origin]) for Injection 9

Slide #11

Gallbladder and Biliary Tract Disease

- ~~11/173 (6.4%)~~ 13/173 (7.5%) of GATTEX-treated patients reported biliary events, including cholecystitis and gallstones/sludge in pooled Phase III SBS studies*
  - 5 patients had a history of biliary disease
  - None of these events resulted in study withdrawal

* As of January 24, 2013

Gattex® (Teduglutide [rDNA origin]) for Injection 11

REMS Modification Submission on December 6, 2013 and resubmitted on 2/10/14 as an amendment of SE2

On December 6, 2013, the sponsor submitted a new supplement: proposed REMS modification and resubmitted on February 10, 2014 as an amendment of supplement 2 that included the following proposed REMS modifications:

REMS Goal:

- (b) (4)

REMS Elements

- (b) (4)

- *Elements to Assure Safe Use (ETASU)*:
  - Revised Prescriber Education Slide Deck to update 3 slides based on the completion of a Phase 3 open-label extension study and clinical pharmacology study.
  - Added the following statement to the ETASU under healthcare prescriber training: "*Retraining will be made available to prescribers who have not written a prescription for Gattex within 12 months of completing REMS training*".
  - (b) (4)

(b) (4)

(b) (4)

The first assessment report for Gattex was submitted by the Sponsor on December 17, 2013. A review by DRISK of the 1 year REMS assessment report, covering the period December 21, 2012 to October 21, 2013, concluded that the REMS was not fully meeting all of its goals. Results from the patient survey indicated that improvements to understanding of key risk messages were needed. Patients were generally able to correctly identify the risk of potential cancerous growth, need for colon polyp removal before treatment initiation, need for regular colon exam, and symptoms of obstruction and possible gallbladder or pancreatic inflammation with Gattex. Patients however, were less able to correctly identify bowel obstruction and gall bladder/pancreatic disorders that can be associated with Gattex.

DRISK provided comments to the Sponsor on March 4, 2014, requesting that they provide a plan to address the deficiencies found in the patient survey. The Sponsor provided a response to DRISK comments on April 11, 2014 with a plan to revise low scoring questions in the patient survey and utilize their existing patient outreach infrastructure to reinforce key risk messages in the Medication Guide and Patient and Caregiver Counseling Guide. These activities are conducted by the Sponsor outside of the REMS.

Upon review of the approved Gattex REMS Patient and Caregiver Counseling Guide, DRISK determined that the tool was identical to the Medication Guide. Therefore, DRISK recommended modification to the tool to focus the messages to the Gattex REMS key risk messages. Formatting changes are also proposed to improve readability. I concurred with the recommendations. Those recommendations sent to the sponsor on June 2nd, 2014.

12. Labeling

Based on the safety results reported in this NDA supplement, labeling will be updated as following on the safety and efficacy sections.

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Fluid Overload. There is no change from original NDA assessment.

Concomitant Oral Medication. There is no change from original NDA assessment.

Study 2 under Section 14 will be updated as following per team recommendation and the sponsor agreed.

Other sections throughout the labeling are updated according to the updated information include section of Immunogenicity. I concur with labeling recommendations provided by the review team.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend that NDA 203441 SE-2 for Teduglutide (rDNA origin)/ GATTEX® be approved for the revised label.

- Recommendation for other Postmarketing Requirements and Commitments

I do not have any new recommendation for Postmarketing Requirements and Commitments

- Recommended Comments to Applicant

None.

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

/s/

RUYI HE
06/23/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203441/S-002

MEDICAL REVIEW(S)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203441 **Applicant: 0074** **Stamp Date: 8/28/13**

Drug Name: Gattex (teduglutide) **NDA/BLA Type: supplement**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			under Module 2.5 Clinical overview
9.	Has the applicant submitted the integrated summary of safety (ISS)?		x		Include in Module 2.5 Clinical overview
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		x		Include in Module 2.5 Clinical overview
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			x	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			x	Updated "A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				Dependent Short Bowel Syndrome (CL0600-021)"
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			x	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			x	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			x	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			x	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		x		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	requested by the Division during pre-submission discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		x		Will ask to provide in the 74 days letter by Stat reviewer
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?				
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?				
34.	Are all datasets to support the critical safety analyses available and complete?				
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?				
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Medical Officer	Date
Ruyi He	10/17/13
Clinical Team Leader	Date

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

/s/

RUYI HE
10/30/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203441/S-002

PHARMACOLOGY REVIEW(S)

1. DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	203441
Supporting document/s:	113
Applicant's letter date:	August 28, 2013
CDER stamp date:	August 28, 2013
Product:	Gattex® (Teduglutide)
Indication:	Short Bowel Syndrome (SBS)
Applicant:	NPS Pharmaceuticals
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	B. Emmanuel Akinshola, Ph.D.
Supervisor/Team Leader:	Sushanta K. Chakder, Ph.D.
Division Director:	Donna Griebel, M.D.
Project Manager:	Matthew C. Scherer, MBA.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203441 are owned by NPS Pharmaceuticals or are data for which NPS Pharmaceuticals has obtained a written right of reference.
Any information or data necessary for approval of NDA 203441 that NPS Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203441.

TABLE OF CONTENTS

Executive Summary

1.1 Introduction

Teduglutide is a 33 amino acid recombinant peptide analog of glucagon-like peptide-2 produced recombinantly in *E. coli*. Teduglutide differs from its natural analog (glucagon) by a single amino acid substitution of alanine for glycine at the second position of the N-terminus to provide resistance from *in vivo* degradation by dipeptidyl protease-IV (DPP-IV), thereby extending its half-life.

Teduglutide has been shown to promote the repair and normal growth of the intestine by increasing villus height and crypt depth of the intestinal epithelium, resulting in enhanced absorptive capacity of the intestine as demonstrated by greater absorption of fluids, electrolytes and nutrients, reduced fecal fluid loss, and diminished diarrhea. In addition, teduglutide accelerates intestinal adaptation, increases nutrient transporter activity, enhances barrier function in the small intestine and decreases intestinal inflammation. Teduglutide (Gattex for Injection) is approved for the treatment of adult patients with short bowel syndrome who are dependent on parenteral support. In the current prior approval supplement, the Applicant submitted the final report of the 2-year subcutaneous (SC) carcinogenicity study in CD-1 mice with proposed labeling changes.

1.2 Brief Discussion of Nonclinical Findings

The Applicant submitted the final report of the 2-year carcinogenicity study by subcutaneous (SC) injection in CD-1 mice. The dose-selection was based on the pharmacokinetic endpoint (AUC ratio) of animal to human exposure, and was concurred with by the Executive CAC.).
In the 104-week SC carcinogenicity study in male and female CD-1 mice (80/sex/dose), teduglutide was administered at dose levels of 0, 1.0, 3.5 or 12.5 mg/kg/day for (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively). Mice in the control group received only the vehicle (phosphate buffer in water for injection). Treatment with teduglutide significantly increased the incidence of papillary adenoma in the gallbladder of male mice when compared to control mice (control, 0/66; low dose, 5/71; mid dose, 2/70; high dose, 6/70). The incidence of Adenocarcinoma of the jejunum was also increased (4/68) in male mice administered the high dose of 12.5 mg/kg/day. This is a rare tumor in CD-1 mice, and was not observed in concurrent study control or (b) (4) historical control values (0/256). No drug-related increased incidence of any neoplasms was observed in female mice.

1.3 Recommendations

1.3.1 Approvability

From a nonclinical standpoint, the NDA supplement is recommended for approval. The carcinogenicity findings in male mice should be included in the labeling of Gattex.

1.3.2 Additional Non Clinical Recommendations
None

1.3.3 Labeling

Applicant's Version:

Evaluation: The format is in accordance with 21CFR 201.57(c)(14)(i) 13.1. However, the text should be modified as proposed below to reflect the findings of the mice carcinogenicity study.

Recommended version: In a 2-year carcinogenicity study in Crl:CD1(ICR) mice at subcutaneous doses of 1, 3.5 and 12.5 mg/kg/day (about 20, 70 and 250 times the recommended daily human dose of 0.05 mg/kg, respectively), teduglutide caused a significant increase in papillary adenomas in the gall bladder; it also caused adenocarcinomas in the jejunum in male mice at the high dose of 12.5 mg/kg/day (about 250 times the recommended human dose).

2 Drug Information
2.1 Drug

CAS Registry Number: 197922-42-2

Generic Name: Teduglutide

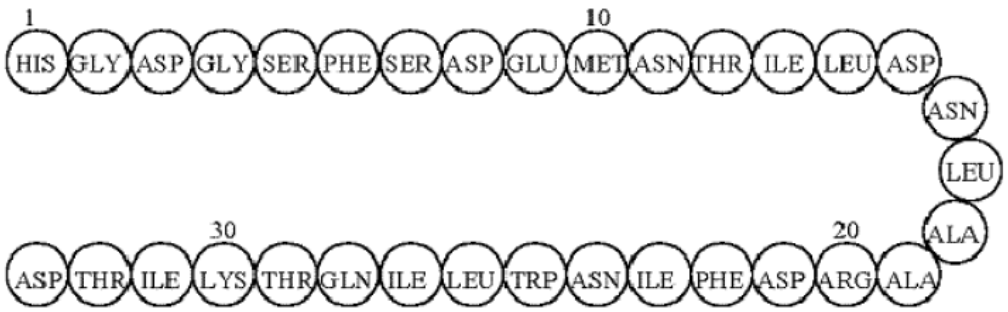
Code Name: ALX-0600

Chemical Name: L-histidyl-L-glycyl-L-aspartyl-L-glycyl-L-seryl-L-phenylalanyl-L-sery-L-aspartyl-L-glutamyl-L-methionyl-L-asparaginyl-L-threonyl-L-isoleucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-isoleucyl-L-asparaginyl-L-tryptophanyl-L-leucyl-L-isoleucyl-L-glutaminyl-L-threonyl-L-lysyl-L-isoleucyl-L-threonyl-L-aspartic acid

Molecular Formula/Molecular Weight: $C_{164}H_{252}N_{44}O_{55}S$/3752 Daltons

Structure or Biochemical Description: Teduglutide is an analog of naturally occurring human GLP-2, a peptide secreted by L cells of the distal intestine. Like GLP-2, teduglutide is 33 amino acids in length with an amino acid substitution of alanine by glycine at the second position of the N-terminus of GLP-2. The structure of teduglutide

is shown below (from page 2 of Section 2.3.S.1 of the electronic submission). Teduglutide was manufactured using a recombinant strain of *Eschericia coli*.



Pharmacologic Class: **Glucagon-like-peptide-2 (GLP-2) receptor agonist**

2.2 Relevant IND/s, NDA/s, and DMF/s

1. IND 58,213 (ALX-0600, NPS Pharamaceuticals)

2.3 Drug Formulation

Teduglutide for injection is supplied in a sterile, single-use 3-ml, USSP Type I glass vial containing 5 mg of teduglutide as a white lyophilized powder. The lyophilized powder is intended for reconstitution with 0.5 ml of sterile water for injection, USP immediately before administration by subcutaneous injection. The reconstituted product is a clear, colorless to light straw-colored solution (10 mg/ml), which also contains the following excipients: 35 mM sodium phosphate, 50 mM L-histidine, and 3 % w/v mannitol. (b) (4) The composition of the drug product is shown below (from page 1 of 2.3.P.1).

Table 2.3.P.1-1: Composition of Teduglutide for Injection

Name of Ingredients	Function	Quality Standard	Quantity per Vial
Teduglutide Drug Substance	Active Ingredient	NPS in-house standard	5 mg
L-Histidine	(b) (4)	USP	3.88 mg
Mannitol		USP	15 mg
Monobasic Sodium Phosphate, Monohydrate		USP	0.644 mg
Dibasic Sodium Phosphate, Heptahydrate		USP	3.434 mg
Water for Injection		USP	(---)[a]
(b) (4)		NF	(---)[b]

NPS = NPS Pharmaceuticals; USP = United States Pharmacopeia; NF = National Formulary

(b) (4)

2.4-2.7 Comments on Novel Excipients, Comments on Impurities/Degradants of Concern, Proposed Clinical Population and Dosing Regimen, Regulatory Background

None

3 Studies Submitted

3.1 Studies Reviewed

Study No. 8214171: Subcutaneous (SC) Carcinogenicity Study in Mice

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

None

4-7 Pharmacology, Pharmacokinetics/ADME/Toxicokinetics (TK), General Toxicology

No data were submitted.

8 Carcinogenicity

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET

Review of Carcinogenicity Study Results

P/T REVIEWER(s): B. Emmanuel Akinshola, Ph.D.
DATE: April 9, 2014
NDA: 203-441
DRUG CODE#: ALX-0600
CAS#: 197922-42-2
DIVISION: Division of Gastroenterology and Inborn Errors Products (DGIEP)
DRUG NAME: Gattex® Teduglutide

SPONSOR: NPS Pharmaceuticals, Inc.
LABORATORY: (b) (4)
CARCINOGENICITY STUDY REPORT DATE: April 22, 2013
THERAPEUTIC CATEGORY: Human Glucagon-like Peptide/Intestinal Peptide for the treatment of adult patients with SBS.

PHARMACOLOGICAL CLASSIFICATION: Glucagon-like Peptide-2 (GLP-2) analog

MUTAGENIC/GENOTOXIC: ALX-0600 was negative in the Ames test, the *in vitro* chromosomal aberration test in Chinese hamster ovary (CHO) cells and the *in vivo* mouse micronucleus assay.

MICE CARCINOGENICITY STUDY

STUDY DURATION (weeks): 104
STARTING DATE: November 2, 2009
STUDY ENDING DATE: April 22, 2012
MICE STRAIN: Crl: CD-1 mice
ROUTE: Subcutaneous (SC)
DOSING COMMENTS: Previously, the Applicant submitted (September 21, 2009) a dose selection proposal and protocol (P09-002) for a 104-week SC carcinogenicity study in CD-1 mice at dose levels of 0 (vehicle), 1.0, 3.5, and 12 mg/kg/day. The proposed high dose level was based on the pharmacokinetic (PK) endpoint or a comparison of the area under the curve (AUC) from a 26-week subcutaneous toxicology study in CD-1 mice with the human exposure. The executive CAC concurred with the Applicant's proposed doses based on a >25-fold AUC ratio of animal to human exposure for the high dose (Exec CAC meeting minutes dated November 4, 2009, Appendix-1). In the 2-year SC carcinogenicity study in CD-1 mice, doses used were 0, 1.0,

3.5 and 12.5 mg/kg/day. The high dose used in the carcinogenicity study is slightly higher (12.5 mg/kg/day) than that recommended by the Ex-CAC (12 mg/kg/day).

NUMBER OF MICE:

Study Group	Number of Animals	
	Male	Female
Control (Cl)	80	80
Low Dose	80	80
Middle Dose	80	80
High Dose	80	80

MICE DOSE LEVELS:

Study Group	Dose Level (mg/kg/day)	
	Male	Female
Control (Cl)	0	0
Low Dose	1.0	1.0
Middle Dose	3.5	3.5
High Dose	12.5	12.5

BASIS FOR DOSE SELECTION: Area under the curve (AUC) Ratio (Pharmacokinetic endpoint).
PRIOR FDA DOSE CONCURRENCE: Yes (Exec. CAC meeting minutes dated Nov. 4, 2009, Appendix-1).
MICE CARCINOGENICITY: Male and female mice: positive for papillary adenoma in the gall bladder. Male mice: positive for adenocarcinoma in the jejunum.

MICE TUMOR FINDINGS: Treatment with teduglutide (ALX-0600) at doses of ≥1 mg/kg/day resulted in papillary adenoma in the gall bladder of male mice (control, 0/66(0%); low dose, 5/71(7.0%; p=0.042 compared to control); mid dose, 2/70 (2.9%; p=0.254, compared to control) and high dose, 6/70 (8.6%; p=0.024 compared to control); p=0.0244, trend test). The incidence of gall bladder papillary adenoma in female mice was higher than control only at 3.5 mg/kg/day (0/69 (0%), 1/69 (1.4%), 3/70(4.3%; p=0.019) and 0/68(0%) in control low, mid and high dose groups, respectively). The incidences of papillary adenoma in the gall bladder of male mice at ≥1 mg/kg/day were higher than the historical control incidences (mean, 0.8%; range 0 -1.9%). In female mice treated with the 3.5 mg/kg/day dose, the incidence of gall bladder papillary adenoma was higher than the historical control incidences (mean, 0.4%; range 0-3.5%). However, there was no dose-response for the incidence of papillary adenoma in male and female mice.

Treatment with teduglutide produced adenocarcinoma of the jejunum in male mice administered the high dose of 12.5 mg/kg/day (0/68 (0%), 1/69 (1.4%), 0/73 (0%) and 4/68 (6.1%; p=0.0155, trend test) in control, low, mid and high dose groups, respectively). This is a rare tumor in CD-1

mice, and was not observed in concurrent study control or (b) (4) historical control values (0/526).

Bronchiolar-alveolar adenomas in female mice had significant increases at 3.5 and 12.5 mg/kg/day (p = 0.0209 and 0.0130, respectively) versus control. The positive trend in this case (p = 0.0155) was not statistically significant for a common tumor. Bronchiolar-alveolar carcinomas did not exhibit any significant positive trend (p = 0.0478) for common tumors. When bronchiolar-alveolar adenomas and carcinomas were combined, the positive trend was significant (p = 0.0058), along with significant increases at 3.5 and 12.5 mg/kg/day (p = 0.0103 and 0.0177, respectively). The incidence of bronchiolar-alveolar adenoma in the high dose group (13.8%) was within the historical control incidences (mean 11.1%; range 6.7-20.0%); the incidence of bronchiolar-alveolar carcinoma at the high dose (7.5%) was also within the historical control range (mean 7.0%; range 1.7 to 15.0%).

Thus, long-term (2 years) administration of teduglutide (ALX-0600) to male and female mice was associated with proliferative changes in the gall bladder (papillary adenoma) of males and females, and jejunum (adenocarcinoma) of males. The combined incidence of bronchiolar-alveolar adenomas and carcinomas in female mice were also higher than controls; however, the incidences for these tumors were within the historical control incidences.

The tumor findings in male and female mice were also analyzed by the FDA statistician, Dr. Min Min, and her analyses are summarized in the Table below (from the draft statistical review)

Tumor Types with significant findings for Dose Response Relationship or Pair-wise Comparisons (Control, low, medium and high dose groups)

				1 mg	3.5 mg	12.5 mg				
			Cont	Low	Med	High	P_Value	P_Value	P_Value	P_Value
	Organ Name	Tumor Name	N 80	N 80	N 80	N 80	Dos Resp	C vs. L	C vs. M	C vs. H
Male										
	Gallbladder	B-Papillary Adenoma	0	5	2	6	0.025	0.031	0.239	0.010
			[48]	[47]	[44]	[42]	.	.	.	.
	Jejunum	M-Adenocarcinoma	0	1	0	4	0.008	0.509	.	0.051
			[48]	[47]	[43]	[43]	.	.	.	.
	DUODENUM_JEJUM	ADENOCARCINOM	0	3	0	4	0.043	0.311	0.855	0.166
			[48]	[47]	[43]	[43]	.	.	.	.
Female										
	LUNG	BRONCHIOLA_ADENOMA	4	9	13	16	0.012	0.158	0.027	0.006
		+CARCINOMA	[39]	[46]	[49]	[48]	.	.	.	.
		B-Adenoma, Bronchiol	3	5	10	11	0.029	0.402	0.053	0.030
			[38]	[44]	[48]	[46]	.	.	.	.
	PITUITARY	ADENOMA+CARCINOMA	0	1	4	2	0.246	0.520	0.064	0.258
			[38]	[44]	[45]	[44]	.	.	.	.

In her analyses, the incidence of gall bladder adenoma in male mice was significant at the high dose with a p value of 0.01. However, a statistical significance was not achieved in the trend analysis for common tumors. The incidence of adenocarcinoma in the jejunum of male mice was significant at the high dose (p=0.051) with a positive trend (p=0.008). In male mice, the incidences of duodenal plus jejunal adenocarcinoma was statistically significant in the trend analysis for tumors.
In female mice, the incidence of bronchio-alveolar adenomas plus carcinomas was statistically significant at the high dose.

MICE STUDY COMMENTS: The dose selection for the 2-year mouse carcinogenicity study based on the pharmacokinetic endpoint (AUC ratio) appears to be appropriate and acceptable, and the doses were concurred by the Executive CAC. The mortality incidences in animals did not interfere with the interpretation of the study results. There were no test article-related differences in mean food consumption or body weights in male mice; however, test article-related increases in body weights were noted in female mice at all dose levels, and the food consumption in females was higher than that of control after Week 69. The strain selection and the conduct of the study are appropriate and acceptable.

COVERSHEET FOR CARCINOGENICITY STUDY IN MICE

1. Study No: 8214171
2. Name of Laboratory: (b) (4)
3. Strain: Crl:CD-1(ICR) Mice
4. No./sex/group: Control, 80; Low-dose, 80; Mid-dose, 80; High dose, 80
5. Dose (0, L, M, H):
   Male: 0, 1.0, 3.5, and 12.5 mg/kg/day
   Female: 0, 1.0, 3.5 and 12.5 mg/kg/day
6. Basis of dose selection stated: Yes. Based on the AUC ratio as recommended by the Executive CAC.
7. Interim sacrifice: No
8. Total duration (weeks): 104
9. No. alive at termination:

	Male		Female	
	Alive/total no. of animals	% survival	Alive/total no. of animals	% survival
Control	34/80	43	25/80	31
Low dose	37/80	46	32/80	40
Mid dose	31/80	39	22/80	28
Highdose	34/80	43	19/80	24

10. Statistical methods used: Trend and heterogenicity of survival data were evaluated using the Cox-Tarone binary regression on life tables and Gehan-Breslow nonparametric methods using the NCI Life Table Package. Animals sacrificed at the scheduled interval and animals sacrificed for other reasons were censored in the analyses. One sided tail probabilities for trend and group comparisons were evaluated at ≤5.0% significance level. One sided positive trends in common (>1%) and rare (background incidences ≥1%) tumors were evaluated at the 0.01 and 0.05 significance levels, respectively. High dose and other group comparisons in common and rare tumors were evaluated at the 0.05 significance level. Benign and malignant tumors were analyzed separately, and combined when appropriate using the criteria based on the recommendations by McConnel, et al (1986).

104-Week Subcutaneous (SC) Carcinogenicity Study in Crl:CD1®(ICR) Mice

Key study findings: Teduglutide (ALX-0600), was administered to male and female Crl:CD1(ICR) mice at 0, 1, 3.5, or 12.5 mg/kg/day, once daily by subcutaneous injection for at least 104 weeks to determine its carcinogenic potential. The dose selection was based on the pharmacokinetic endpoint (AUC ratio) and appears to be appropriate and acceptable. There was no treatment effect on survival in male or female animals. Treatment with ALX-0600 had no effect on mean body weight or mean food consumption in male mice, however, test article-related increases in mean body weights were noted in female mice at all dose levels. Food consumption in female mice was higher than that of control after Week 69.

Treatment-related microscopic changes, including hyperplasia were observed in the gall bladder (distension, epithelial hyperplasia, inflammation and fibrosis, thickening of the wall), small intestine (villus lengthening, mucosal hyperplasia in the duodenum, jejunum and ileum), large intestine (mucosal hyperplasia in the cecum, colon and rectum), mesenteric lymph node (congestion/hemorrhage, macrophage infiltrate and increased hematopoiesis in males, and congestion/hemorrhage in females), subcutaneous injection sites (inflammation), and bone marrow (increased cellularity in males) of animal treated with 1 mg/kg/day and higher doses.

The incidence of papillary adenoma in the gall bladder of male mice at low and high doses and in female mice at the mid- dose were higher than the control incidences (control, 0/66(0%); low dose, 5/71(7.0%; p=0.042 compared to control; mid dose, 2/70 (2.9%; p=0.254, compared to control) and high dose, 6/70(8.6%; p=0.024 compared to control; p=0.0244, trend test). The incidences of papillary adenoma in the gall bladder of male mice at ≥1 mg/kg/day were higher than the historical control incidences (mean, 0.8%; range 0 -1.9%). In female mice treated with the 3.5 mg/kg/day dose, the incidence of gall bladder papillary adenoma was higher than historical control incidences (mean, 0.4%; range 0-3.5%). However, there was no clear dose-response for the incidence of papillary adenoma in male and female mice.

Treatment with teduglutide produced adenocarcinoma of the jejunum in male mice administered the high dose of 12.5 mg/kg/day ((0/68 (0%), 1/69 (1.4%), 0/73 (0%) and 4/68 (6.1%); p=0.0155) in control, low, mid and high dose groups, respectively). This is a rare tumor in CD-1 mice, and was not observed in concurrent study control or (b) (4) historical control values (0/526).

In female mice, there was a significant increase in the incidence of bronchiolar-alveolar adenomas plus carcinomas (combined) at 3.5 and 12.5 mg/kg/day doses (p = 0.0058, trend analysis; p=0.029 and 0.0130, respectively, pairwise comparison). However, the incidences were within the historical control incidences for this strain of mice from the conducting laboratory.

Exposure to ALX-0600 generally increased with the increase in dose levels from 1.0 to 12.5 mg/kg/day. During Week 52 of the dosing phase, the mean AUC_{0-24} was 44.0 and 29.3 µg·hr/ml in male and female animals dosed at 12.5 mg/kg/day, respectively.

Study number: 8214171

Volume # and page #: EDR submission dated April 22, 2013

Conducting laboratory and location: (b) (4)

Date of Study initiation: November 9, 2009

GLP compliance: A statement of GLP compliance was included.

QA report: yes (X) no ()

Drug, lot #, and % purity: Teduglutide, lot # 08406011, 97.8 % purity; lot # 10704410, 98.9 % purity; lot # 10704412, 98.9 % purity.

CAC concurrence: Yes (Exec. CAC meeting dated Nov. 4, 2009, Appendix-1)

Study Type: 2-year bioassay

Specie/strain: Crl:CD1® (ICR) Mice

Number/sex/group; age at start of study: 5-6 weeks old at the start of study. Number of animals per group is provided in the Table below.

Study Group	Number of Animals	
	Male	Female
Control (C1)	80	80
Low Dose	80	80
Middle Dose	80	80
High Dose	80	80

Animal housing: Male and female mice were housed individually in stainless steel wire mesh-bottomed cages where rodent diet and water were available ad libitum. The environmental conditions targeted in animal room were: temperature range of 18 to 26 ^{o}C [for Day 1 of the predose phase through Day 559 of the dosing phase] and 20 to 26 ^{o}C [from Day 560 of the

dosing phase through the remaining study duration], a relative humidity of 30 to 70 %, a minimum of 10 air changes/hour, and a 12-hour light/12-hour dark cycle.

Formulation/vehicle: The vehicle was phosphate buffer prepared in sterile water for injection and pH-adjusted to 7.2 to 7.6 with hydrochloric acid and/or sodium hydroxide as needed and was stored refrigerated.

Drug stability/homogeneity: Teduglutide was found to be stable in the diluent buffer or vehicle at 0.8 to 20 mg/ml for up to 17 days at refrigerated conditions (4 ^{o}C); up to 1 day at room temperature, and up to 6 hours at 40 ^{o}C. Homogeneity analysis was not conducted for ALX-0600 because the formulations were solutions for the concentration range of the dose formulations.

Methods:

Doses: Male: 1.0, 3.5, and 12.5 mg/kg/day
Female: 1.0, 3.5, and 12.5 mg/kg/day

Basis of dose selection: The high dose selection was based on the pharmacokinetic endpoint (AUC ratio) and concurred by the Executive CAC.

Restriction paradigm for dietary restriction studies: None

Route of administration: Subcutaneous (SC) injection

Frequency of drug administration: Once daily

Dual controls employed: No

Interim sacrifices: None

Study Design: The study design is shown in the table below (from page 17 of the study report).

Group	No. of Animals		Dose Level	Dose Concentration
	Male	Female	(mg/kg/day)[b]	(mg/mL)[b]
Carcinogenicity Animals				
1 (Control)[a]	80	80	0	0
2 (Low)	80	80	1.0	0.8
3 (Mid)	80	80	3.5	2.8
4 (High)	80	80	12.5	10.0
Toxicokinetic Animals				
5 (Control)[a]	32	32	0	0
6 (Low)	64	64	1.0	0.8
7 (Mid)	64	64	3.5	2.8
8 (High)	64	64	12.5	10.0
Antibody Animals				
9 (Control)[a]	12	12	0	0
10 (Low)	12	12	1.0	0.8
11 (Mid)	12	12	3.5	2.8
12 (High)	12	12	12.5	10.0

a Group 1, 5, and 9 received control article/diluent only.
b Animals were dosed at the volume of 1.25 mL/kg.

Satellite group for toxicokinetics: Yes (shown in the Applicant's table above)

Deviations from original study protocol: There were minor protocol deviations which did not seem to have any impact on the results and interpretations.

Statistical methods:

Mortality: Mortality data were analyzed by the National Cancer Institute (NCI) life table package consisting of Kaplan-Meier product-limit estimation curves (Kaplan and Meier, 1958), Cox-Tarone binary regression (Cox, 1972 and Tarone, 1975) and Gehan-Breslow nonparametric tests (Thomas et al., 1977).

Tumor Data: Tumor incidences were analyzed by linear logistic regression of tumor prevalence tests (Dinse and Lagakos, 1983). Rapidly lethal and palpable tumors were analyzed in the same manner as survival, using the first palpation time (if applicable) as the tumor onset time. In cases where occult neoplastic lesions were assigned as the cause of death in the animals, an IARC-type (peto et al., 1980) was used to incorporate such information.

Observations and times:

Mortality: Twice daily.

Clinical signs: Twice daily.

Body weights: Weekly for weeks 1 to 14, once every 4 weeks thereafter, and during week 105 of the dosing phase.

Food consumption: Food consumption was measured and recorded weekly for weeks 1 through 13, once every 4 weeks thereafter, and during week 104 of the dosing phase.

Ophthalmoscopy: Not conducted.

Hematology: Blood samples for serum banking were collected from 5 animals/sex/group at the scheduled sacrifice prior to necropsy. Blood samples were stored in the freezer (-60^{0}C to -80^{0}C) until shipped for analysis.

Serum Chemistry: Blood samples for serum banking were collected from 5 animals/sex/group at the scheduled sacrifice prior to necropsy. Blood samples were stored in the freezer (-60^{0}C to -80^{0}C) until shipped for analysis.

Serology: Samples were collected from all animals (two slides/animal) at scheduled and unscheduled sacrifices and delivered to Clinical Pathology. Examination of blood smears was not warranted by the principal investigator and was not done.

Antibody Analysis: Blood samples for antibody analysis were collected via cardiac puncture during weeks 13 and 26 of the dosing phase for groups 9 through 12.

Gross pathology: Gross pathology examinations were conducted at necropsy done on carcinogenicity animals that died or were sacrificed at an unscheduled interval. Animals sacrificed at scheduled termination were necropsied at termination.

Organ Weights: The following organs were weighed and the lengths of the organs were measured (separately) for animals at scheduled sacrifice only:

Large Intestine (including cecum and colon)

Small Intestine (including duodenum, ileum and jejunum)

Histopathology: All tissues from all main study animals were examined. Tissues examined are shown in the list (from page 4597 of the study report) below.

adrenal (2)	mammary gland (females)
aorta	muscle, biceps femoris
brain	optic nerve (2)[a]
cecum	ovary (2)
cervix	pancreas
colon	pituitary gland
duodenum	prostate
epididymis (2)	rectum
esophagus	salivary gland [mandibular (2)]
eye (2)[a]	sciatic nerve
femur with bone marrow (articular surface of the distal end)	seminal vesicle
	skin/subcutis
gallbladder	spinal cord (cervical, thoracic, and lumbar)
Harderian gland[a]	spleen
heart	sternum with bone marrow
ileum	stomach
injection site(s)	testis (2)[a]
jejunum	thymus
kidney (2)	thyroid (2 lobes) with parathyroid
lesions	tongue
liver	trachea
lung with large bronchi	urinary bladder
lymph node (mandibular)	uterus
lymph node (mesenteric)	vagina

a Preserved in modified Davidson's fixative.

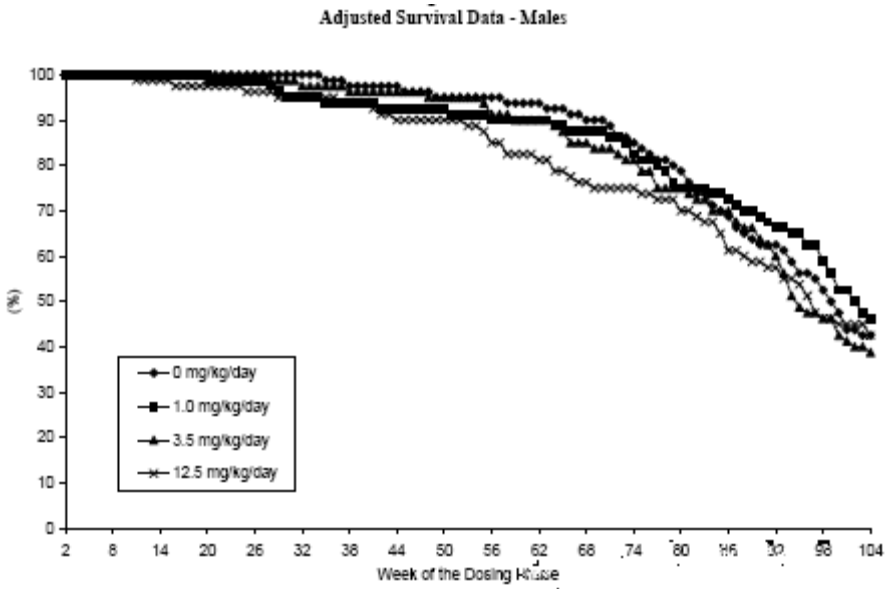
Toxicokinetics: Blood samples (as much as possible) were collected from non-fasted TK animals via cardiac puncture after carbon dioxide inhalation for determination of the plasma concentrations of ALX-0600. Samples were collected from treatment groups (4/sex/group) at 0, 0.25, 0.50, 1, 2, 3, 4, 8, and 24 during weeks 3 and 52 of the dosing phase.

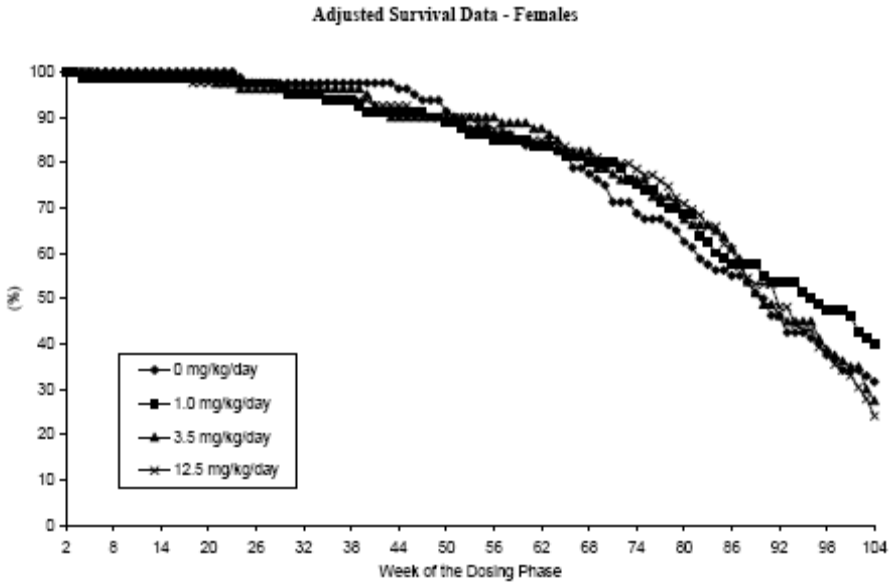
Results:

Mortality: There was no effect of ALX-0600 on survival in male or female animals. The survival rates were similar among all groups and both sexes. Summary of the survival data are presented in the table below. Kaplan-Meier survival plots for male and female mice from the study report are provided below. No statistically significant changes in survival distribution were observed in males and females.

Table: Survival rate of male and female mice

Sex	Dose (mg/kg)	Number at start	Number alive after 52 weeks	Proportion alive after 52 weeks	Number alive after 78 weeks	Proportion alive after 78 weeks	Number alive after 90 weeks	Proportion alive after 90 weeks	Number alive at termination	Proportion alive at termination
Female	0	80	71	89%	53	66%	40	50%	25	31%
	1.0	80	70	88%	56	70%	44	55%	32	40%
	3.5	80	72	90%	58	73%	39	49%	22	28%
	12.5	80	71	89%	59	74%	42	53%	19	24%
Male	0	80	76	95%	65	81%	50	63%	34	43%
	1.0	80	73	91%	63	79%	55	69%	37	46%
	3.5	80	76	95%	60	75%	51	64%	31	39%
	12.5	80	72	90%	58	73%	47	59%	34	43%





Clinical signs: No treatment-related clinical signs were noted. Males and females receiving teduglutide had higher incidences of swollen midline ventral abdomen, which may be due to intestinal growth, and related to the mechanism of action of the test article. Sores/scabs of the dorsal neck and missing or red ear were observed in more males than females, and were not clearly related to the dose.

Body weight: No test article-related differences in mean body weights were noted in male animals. The mean initial (week 1) and final (week 105) body weights of control (group 1) males were 30.7 and 45.9 g, respectively. Mean body weights in male animals dosed at 3.5 mg/kg/day (33.1 to 41.2 g) were significantly greater than controls (32.1 to 39.7 g) during weeks 2, 4, 5, 6, and 10 of dosing. Similarly, the mean body weights of male animals dosed at 12.5 mg/kg/day (33.1 to 37.2 g) were significantly greater than controls (32.1 to 36.1 g) during weeks 2, 4, and 5 of dosing. However, the differences were minimal and range from 3.0 to 4.4 %.
The mean initial (week 1) and final (week 105) body weights of control (group 1) females were 24.4 and 39.7 g, respectively.

Test article-related increases in mean body weights were noted in females at all dose levels. The mean body weights of female animals dosed at 1 mg/kg/day (28.4 to 38.2 g) were significantly higher than controls (27.3 to 36.0 g) from dosing weeks 5 to 50 (by 4.0 to 8.3 %); and the mean body weights of females dosed at 3.5 mg/kg/day (27.0 to 46.3 g) were significantly higher than that of control animals (24.4 to 39.7 g) from dosing weeks 3 to 105 (by 3.6 to 16.6 %). Finally, the mean body weights of female animals dosed at 12.5 mg/kg/day (25.9 to 44.6 g) were also significantly greater than that of control animals (24.8 to 39.2 g) from dosing weeks 2 to 102 (by 3.1 to 13.8 %). The following graphs (from page 46 and 47 of the study report) and table show the body weights of male and female mice.

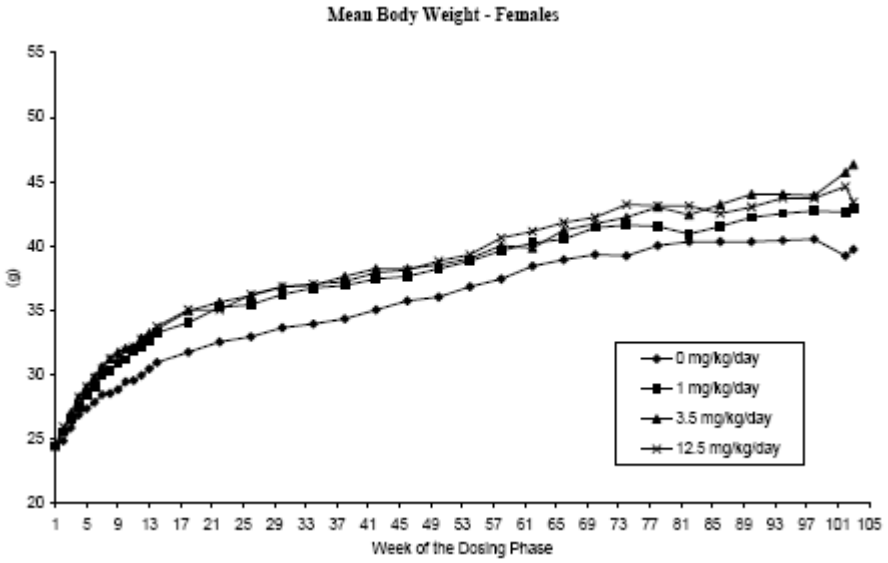


Table: Mean Body weight of male and female mice (g)

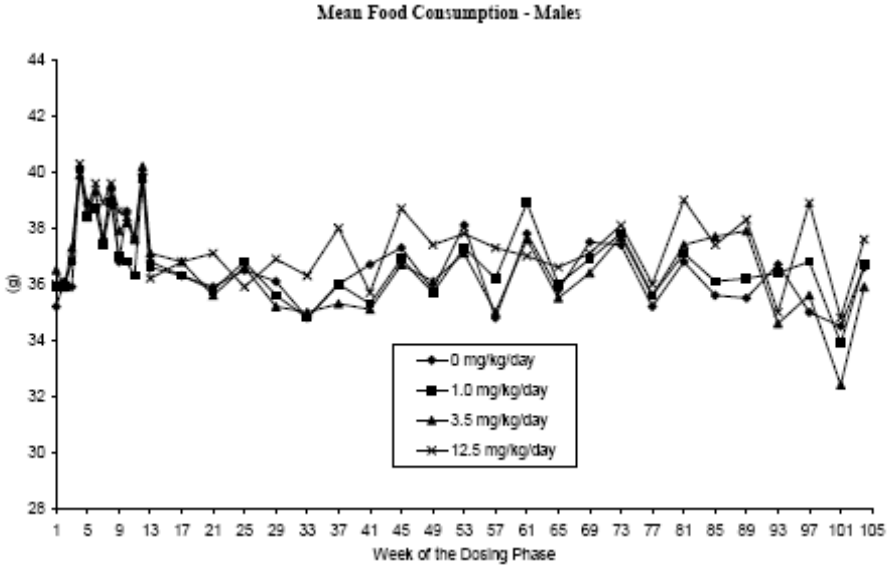
	Week	0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day	Statistics
Male	1	30.7 ± 2.47	30.6 ± 2 20	30.8 ± 2.44	30.9 ± 2.48	P
	2	32.1 ± 2 35	32.6 ± 2.40	33.1 ± 2.50*	33.1 ± 2.48*	P
	4	34.4 ± 2.46	34.8 ± 2.83	35.9 ± 2.54*	35.6 ± 2.57*	P
	5	36.1 ± 2 56	36.5 ± 2 90	37.3 ± 2.81*	37.2 ± 2.70*	P
	6	37.1 ± 2.71	37.2 ± 2.86	38.2 ± 2.96*	37.8 ± 2.85	P
	10	39.7 ± 3 54	40.2 ± 3 27	41.2 ± 3.68*	40.6 ± 3.23	P
	105	45.9 ± 5.42	46.5 ± 4.65	46.3 ± 4.69	47.1 ± 5.11	P
Female	1	24.4 ± 2 36	24.4 ± 2 22	24.4 ± 2.35	24.4 ± 2.19	P
	10	29.4 ± 3 22	31.1 ± 2.86*	32.0 ± 2.76*	31.8 ± 2.53*	P
	22	32.5 ± 3 96	35.2 ± 3.77*	35.6 ± 3.59*	35.0 ± 3.47*	P
	30	33.6 ± 4.45	36.2 ± 4 14*	36.8 ± 3.93*	36.8 ± 3.75*	P
	42	35.0 ± 5 31	37.4 ± 4.61*	38.2 ± 4.46*	37.9 ± 4.14*	P
	50	36.0 ± 5.73	38.2 ± 5.62*	38.5 ± 4.56*	38.8 ± 4.48*	P
	66	38.9 ± 6 13	40.5 ± 6.87*	41.2 ± 5.25*	41.8 ± 5.37*	P
	78	40.0 ± 6.89	41.5 ± 5.98	43.0 ± 5.96*	43.1 ± 7.06*	P
	102	39.2 ± 5.81	42.6 ± 5.19	45.7 ± 7.48*	44.6 ± 7.10*	P
	105	39.7 ± 6.25	42.9 ± 4.32	46.3 ± 7.52*	43.4 ± 9.41	P

* P < or = 0.05; P = ANOVA (and Dunnett's, if applicable)

Food consumption: The mean initial (week 1) and final (week 104) food consumptions for control (group 1) males were 35.2 to 36.6 g/animal/week, respectively. No clear test article-related differences in mean food consumption were noted in male animals. The mean food consumption in male animals from all groups was generally comparable, but significantly increased in males dosed at 12.5 mg/kg/day (36.3 to 38.9 g/animal/week) at six weekly intervals (weeks 7, 9, 33, 37, 57, and 89) in comparison to control males (34.8 to 37.6 g/animal/week) by 3.5 to 7.9 %.

The mean initial (week 1) and final (week 104) food consumptions for control (group 1) females were 29.5 to 32.6 g/animal/week, respectively. The mean food consumption was generally comparable in all female animal groups until dosing week 69 when food consumption in treated females began to exceed that noted in control females. Female mice dosed at 1, 3.5, or 12.5 mg/kg/day had increased food consumption (38.0 to 40.4 g/animal/week) when compared to female controls (32.6 to 35.7 g/animal/week) from week 69 to week 104 of the dosing period.

The following figures (from page 48 and 49 of the study report) and table from the sponsor's submission show the food intake in male and female animals.



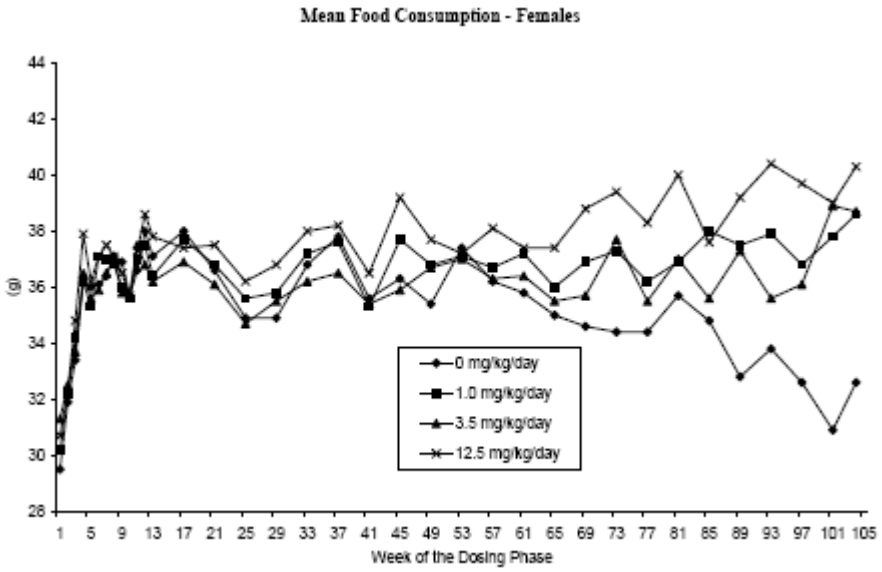


Table: Mean Food intake of male and female mice (g/animal/period)

	Week	0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day	Statistics
Male	1	35.2 ± 3 19	35.9 ± 2.77	36.5 ± 3.19*	36.0 ± 2.90	P
	7	37.6 ± 3.76	37.4 ± 3 12	37.6 ± 3.46	38.9 ± 3.50*	P
	9	36.8 ± 3.61	37.0 ± 3 10	37.9 ± 4.38	38.6 ± 3.90*	P
	37	36.0 ± 3.41	36.0 ± 3 34	35.3 ± 3.56	38.0 ± 3.94*	P
	57	34.8 ± 3.66	36.2 ± 4.00	35.0 ± 4.22	37.3 ± 3.70*	P
	89	35.5 ± 4 54	36.2 ± 4 24	37.9 ± 5.55*	38.3 ± 5.51*	P
	104	36.6 ± 5.69	36.7 ± 5 25	35.9 ± 4.22	37.6 ± 5.35	P
Female	1	29.5 ± 2.87	30.2 ± 3.46	31.3 ± 3.10*	30.7 ± 3.85	P
	4	36.2 ± 4 27	36.2 ± 4 31	32.5 ± 3.76	37.9 ± 4.13*	P
	69	34.6 ± 6.40	36.9 ± 5 31	35.7 ± 5.35	38.8 ± 7.02*	P
	73	34.4 ± 5.77	37.3 ± 5 10*	37.7 ± 5.02*	39.4 ± 6.48*	P
	81	35.7 ± 5 97	36.9 ± 9 50	37.0 ± 5.30	40.0 ± 5.62*	P
	85	34.8 ± 4.76	38.0 ± 5.76*	35.6 ± 5.81	37.6 ± 6.35	P
	89	32.8 ± 5 31	37.5 ± 6.04*	37.3 ± 6.03*	39.2 ± 6.88*	P
	93	33.8 ± 4 91	37.9 ± 7 58*	35.6 ± 5.55	40.4 ± 8.08*	P
	97	32.6 ± 3.70	36.8 ± 5.49*	36.1 ± 6.43*	39.7 ± 8.96*	P
	101	30.9 ± 5.04	37.8 ± 5 53*	38.9 ± 6.87*	39.0 ± 8.68*	P
	104	32.6 ± 4.13	38.6 ± 5.94*	38.7 ± 5.96*	40.3 ± 9.64*	P

* P < or = 0.05
P = ANOVA (and Dunnett's, if applicable)

Ophthalmoscopy: Not conducted.

Hematology: Not conducted

Serum Chemistry: Not studied.

Organ Weights: The lengths and weights of the small and large intestines were increased in all treated animals at all dose levels compared to control animals. The observed changes correlated with the microscopic findings of increased villus length and mucosal hyperplasia. The group mean values are summarized in the following tables (from page 32 of the study report) below.

Mean Intestine Length (mm) with Standard Deviation

Sex	Male				Female			
Dose Level (mg/kg/day)	0	1.0	3.5	12.5	0	1.0	3.5	12.5
Number measured	34	37	31	34	25	32	22	18
Small Intestine[a]								
Mean	471.9	569.5	591.4	598.2	487.2	591.0	648.8	636.1
SD	44.8	55.2	71.1	51.5	64.1	58.9	82.7	58.3
Large Intestine[b]								
Mean	131.7	157.4	154.9	158.4	128.4	154.3	162.3	159.1
SD	22.7	20.2	21.3	25.3	13.6	14.6	18.1	27.8

SD = Standard deviation.
a Includes duodenum, ileum, and jejunum.
b Includes cecum and colon.

Mean Intestine Weight (g) with Standard Deviation

Sex	Male				Female			
Dose Level (mg/kg/day)	0	1.0	3.5	12.5	0	1.0	3.5	12.5
Number measured	34	37	31	34	25	31	22	18
Small Intestine[a]								
Mean	2.2	4.2	5.1	5.0	2.3	4.8	5.8	5.3
SD	0.4	1.0	1.8	1.0	0.6	0.9	2.0	1.3
Large Intestine[b]								
Mean	0.7	1.1	1.2	1.2	0.7	1.1	1.2	1.2
SD	0.2	0.2	0.4	0.3	0.2	0.2	0.2	0.2

SD = Standard deviation.
a Includes duodenum, ileum, and jejunum.
b Includes cecum and colon.

Gross pathology: Treatment-related macroscopic changes were observed in the gall bladder (distended, large) and mesenteric lymph node (large, discolored) of animals dosed at ≥ 1 mg/kg/day. Several gross pathological findings noted in the intestines (duodenum, jejunum, ileum, colon, and/or cecum) including thickened, distended, large, abnormal shape, discolored, adhesion, constricted, and/or mass each occurred at a very low incidence (4 or less/group). Some of these macroscopic observations correlated with the finding of adenocarcinoma in the intestine. The incidences of the principal treatment-related macroscopic findings are shown in the table (from page 32 of the study report) below.

Incidence of Selected Test Article-Related Macroscopic Findings

Sex	Male				Female			
Dose Level (mg/kg/day)	0	1.0	3.5	12.5	0	1.0	3.5	12.5
Gall Bladder								
Distended	1	9	18	31	5	42	40	39
Large	1	2	4	3	0	4	2	3
Mesenteric Lymph Node								
Large	5	3	8	7	5	14	18	13
Discolored	1	6	11	10	1	20	15	11

Histopathology:

Non-neoplastic: Treatment-related non-neoplastic microscopic findings were observed in the gall bladder (epithelial hyperplasia, distention, inflammation, and fibrosis/thickening of the wall), small intestine (increased villi length, and hyperplasia of the mucosal epithelium), and large intestine (mucosal hyperplasia of the cecum, colon and rectum) of mice dosed at ≥ 1 mg/kg/day. A test article-related increase in congestion/hemorrhage of the mesenteric lymph nodes in mice dosed at ≥ 1 mg/kg/day is correlated to discoloration and increased size of the nodes. The

observed increase in macrophage infiltrates in the medullary sinuses and increased hematopoiesis in male mice dosed at ≥ 1 mg/kg/day is treatment-related and may also have contributed to the macroscopic observations in the mesenteric lymph node. Treatment-related increase in the incidence of inflammation at the subcutaneous injection sites was also observed in treated animals. The following tables show the incidences of non-neoplastic microscopic findings.

Selected Microscopic Observations in the Gall Bladder of Male and Female Mice

Organ		Male				Female			
		0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day	0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day
Gall Bladder	Number Examined	66	71	70	70	69	69	70	68
	Distended	2	10	22	30	3	40	40	32
	Hyperplasia, Epithelium	Min. 2 Slight 1 Mod. 1 Mar. 0	Min. 11 Slight12 Mod. 10 Mar. 1	Min. 23 Slight10 Mod. 1 Mar. 1	Min. 12 Slight14 Mod. 5 Mar. 0	Min. 0 Slight 0 Mod. 0 Mar. 0	Min. 9 Slight 6 Mod. 2 Mar. 1	Min. 10 Slight 4 Mod. 3 Mar. 0	Min. 12 Slight 1 Mod. 1 Mar. 0
	Fibrosis/ Thickening, Wall	Min. 1 Slight 0 Mod. 0	Min. 22 Slight 8 Mod. 1	Min. 14 Slight 8 Mod. 1	Min. 12 Slight 4 Mod. 1	Min. 3 Slight 0 Mod. 0	Min. 9 Slight 8 Mod. 1	Min. 10 Slight 6 Mod. 1	Min. 15 Slight 6 Mod. 0
	Inflammation	Min. 1 Slight 0 Mod. 0 Mar. 0	Min. 4 Slight 5 Mod. 0 Mar. 0	Min. 3 Slight 4 Mod. 0 Mar. 0	Min. 7 Slight 2 Mod. 1 Mar. 0	Min. 3 Slight 2 Mod. 0 Mar. 0	Min. 4 Slight 4 Mod. 0 Mar. 1	Min. 5 Slight 0 Mod. 1 Mar. 0	Min. 7 Slight 4 Mod. 0 Mar. 0

Min. Minimal
Mod. Moderate
Mar. Marked

Selected Microscopic Observations in the Small Intestine of Male and Female Mice

Organ		Male				Female			
		0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day	0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day
Duodenum	Number Examined	70	69	71	66	73	69	71	67
	Villus, Increased Length	Min. 0 SL. 0	Min. 22 SL. 8	Min. 21 SL. 11	Min. 15 SL. 8	Min. 0 SL. 0	Min. 12 SL. 2	Min. 20 SL. 10	Min. 24 SL. 4
	Hyperplasia, Mucosa	Min. 0 SL. 0 Mod. 0 Mar. 0	Min. 18 SL. 5 Mod. 0 Mar. 0	Min. 24 SL. 6 Mod.1 Mar. 0	Min. 17 SL. 8 Mod. 0 Mar. 0	Min. 11 Sl. 11 Mod. 2 Mar . 0	Min. 20 SL. 4 Mod. 2 Mar. 0	Min. 20 SL. 7 Mod. 1 Mar. 0	Min. 8 SL. 12 Mod. 4 Mar. 1
Jejunum	Number Examined	68	69	73	68	69	69	68	69
	Villus, Increased Length	Min. 0 SL. 0	Min. 21 SL. 0	Min. 22 SL. 2	Min. 11 SL. 1	Min. 0 SL. 0	Min. 11 SL. 0	Min. 15 SL. 3	Min. 7 SL. 3
	Hyperplasia, Mucosa	Min. 0 SL. 1	Min. 8 SL. 0	Min. 5 SL. 0	Min. 3 SL. 0	Min. 2 SL. 0	Min. 4 SL. 0	Min. 9 SL. 2	Min.12 SL. 1
Ileum	Number Examined	68	70	71	64	69	65	69	62
	Villus, Increased Length	Min. 0 SL. 0	Min. 14 SL. 8	Min. 14 SL. 15	Min. 6 SL. 9	Min. 0 SL. 0	Min. 8 SL. 9	Min. 12 SL. 22	Min. 16 SL. 12
	Hyperplasia, Mucosa	Min. 0 SL. 0	Min. 8 SL. 2	Min. 11 SL. 2	Min. 4 SL. 1	Min. 4 SL. 0	Min. 5 SL. 0	Min. 2 SL. 0	Min. 3 SL. 0

Min. Minimal
SL. Slight
Mod. Moderate
Mar. Marked

Selected Microscopic Observations in the Large Intestine of Male and Female Mice

Organ		Male				Female			
		0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day	0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day
Cecum	Number Examined	68	65	70	64	70	72	67	59
	Hyperplasia, Mucosa	Min. 0 Slight 0	Min. 6 Slight 3	Min. 11 Slight 2	Min. 9 Slight 4	Min. 0 Slight 0	Min. 0 Slight 1	Min. 3 Slight 1	Min. 7 Slight 4
Colon	Number examined	72	71	73	68	75	69	71	66
	Hyperplasia, Mucosa	Min. 0 Slight 0 Mod. 0	Min. 10 Slight 5 Mod. 0	Min. 12 Slight10 Mod. 1	Min. 14 Slight 7 Mod. 0	Min. 1 Slight 1 Mod. 0	Min. 5 Slight 4 Mod. 0	Min. 6 Slight 3 Mod. 0	Min. 8 Slight 1 Mod. 1
Rectum	Number Examined	71	74	74	68	75	72	74	67
	Hyperplasia, Mucosa	Min. 0 Slight 0	Min. 2 Slight 0	Min. 2 Slight 2	Min. 1 Slight 0	Min. 0 Slight 0	Min. 1 Slight 0	Min. 4 Slight 0	Min. 7 Slight 0

Min. Minimal
Mod. Moderate

Selected Microscopic Observations in the Mesenteric Lymph Node and Bone Marrow of Male and Female Mice

Organ		Male				Female			
		0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day	0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day
Mesenteric Lymph Node	Number Examined	76	80	80	79	76	80	78	79
Congestion/ Hemorrhage		10	32	42	32	7	32	26	33
Infiltrate, Macrophages		8	34	34	20	9	6	5	9
Hematopoiesis, Increased		1	16	20	15	7	9	12	14
Bone Marrow (Femur)	Number Examined	79	80	79	80	80	78	79	79
Hypercellular		7	12	15	22	22	15	15	16
Bone Marrow (Sternum)	Number Examined	80	80	80	80	80	79	79	80
Hypercellular		6	11	15	19	21	16	15	14

Selected Microscopic Observations in the Injection Sites and Lung of Male and Female Mice

Organ		Male				Female			
		0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day	0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day
Subcutaneous Site A	Number Examined	80	80	80	80	80	80	79	80
Inflammation	Minimal Slight Moderate	3 2 1	9 4 0	20 5 0	13 6 0	18 8 0	17 11 0	23 6 0	27 10 1
Subcutaneous Site B	Number Examined	80	80	80	80	80	80	79	80
Inflammation	Minimal Slight Moderate	6 1 1	8 2 0	15 1 0	14 6 0	12 8 1	24 6 0	20 5 0	28 6 1
Lung	Number Examined	80	80	80	80	80	80	79	80
Hyperplasia, Bronchiolar-Alveolar	Minimal Slight Moderate	2 1 0	6 1 0	1 2 0	1 2 0	0 0 0	0 1 0	2 0 2	1 1 0

Neoplastic: An increase in papillary adenoma of the gall bladder was observed in male animals treated with teduglutide (≥ 1 mg/kg/day). The incidence of gall bladder papillary adenoma was also higher in 3.5 mg/kg/day females. An increase in the incidence of adenocarcinoma of the jejunum was observed in male mice administered the 12.5 mg/kg/day dose. The test-article related proliferative findings of papillary adenoma, a benign neoplasm characterized by extensive proliferation of papillary projections of the epithelium with a fibrovascular stroma, extended into the lumen of the gall bladder.

Other findings include an increased incidence of lung neoplasms (bronchiolar-alveolar adenoma and carcinoma) in female mice dosed at ≥ 3.5 mg/kg/day. The incidence of bronchiolar-alveolar adenoma in the concurrent female control group was low (3.8 % in the current study versus an 11.1 % mean value with an overall range of 6.7 - 20.0 % in historical control). Similarly, the incidence of bronchiolar- alveolar carcinoma in the concurrent female control group was also low (1.3 %) compared with the mean value (7.0 %) in historical controls. The following tables show the incidences of neoplastic findings.

Table: Incidence of Neoplastic Lesions in Mice

Organ	Tumor	Male				Female			
		0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day	0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day
Duodenum	B-Adenoma	0/70 0 %	0/69 0 %	0/71 0 %	0/66 0%	0/73 0 %	0/69 0 %	1/71 (1.4 %)	1/67 1.5%
	M-Adenocarcinoma	0/70 0 %	2/69 (2.9 %)	0/71 0 %	1/66 (1.5 %)	2/73 (2.7 %)	1/69 (1.5%)	1/71 (1.4 %)	0/67 0 %
Jejunum	M-Adenocarcinoma	0/68 0 %	1/69 (1.5 %)	0/73 0 %	4/68 (5.9 %)	0/69 0 %	0/69 0 %	0/68 0 %	1/69 1.5 %
Gall Bladder	B-Papillary Adenoma	0/66 0 %	5/71 (7.0 %)	2/70 (2.9 %)	6/70 (8.6 %)	0/69 0 %	1/69 (1.4%)	3 /70 (4.3 %)	0/68 0%

Adenoma or papillary adenoma historical control incidence, mean, and range for males: 4/492; 0.8 %; 0-1.9 %
Adenoma or papillary adenoma historical control incidence, mean, and range for females: 2/511; 0.4 %; 0-3.5 %

Table: Incidence of Neoplastic Lesions in Mice

Organ	Tumor	Male				Female			
		0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day	0 mg/kg/day	1.0 mg/kg/day	3.5 mg/kg/day	12.5 mg/kg/day
Lung	B-Adenoma, Bronchiolar-Alveolar	15/80 (18.8%)	16/80 (20%)	17/80 (21.3%)	12/80 (15 %)	3/80 (3.8 %)	5/80 (6.3%)	10/79 (12.7%)	11/80 (13.8%)
	M-Carcinoma, Bronchiolar-Alveolar	13/80 (16.3%)	9/80 (11.3%)	5/80 (6.3 %)	4/80 (5.0 %)	1/80 (1.3 %)	4/80 (5.0%)	3/79 (3.8 %)	6/80 (7.5 %)
	Adenoma and/or Carcinoma, Bronchiolar-Alveolar	27/80 (33.8%)	24/80 (30 %)	22/80 (27.5%)	16/80 (20 %)	4/80 (5 %)	9/80 (11.3 %)	13/79 (16.5%)	16/80 (20 %)

Bronchiolar-Alveolar Adenoma historical control values for females: Mean 11.1 %; Range 6.7-20 %
Bronchiolar-Alveolar Carcinoma historical control values for females: Mean 7.0 %; Range 1.7-15 %

Toxicokinetics: After subcutaneous administration ALX-0600 to male and female mice, the plasma exposure to ALX-0600 generally increased with the increase in dose levels from 1.0 to 12.5 mg/kg/day. The T_{max} values ranged from 0.250 to 0.500 hour during week 3 and from 0.250 to 1.00 hour during week 52. The C_{max} and AUC_{0-24} values were generally similar between weeks 3 and 52, except for AUC_{0-24} values at the 1 mg/kg/day dose level. After reaching C_{max}, ALX-0600 concentrations readily declined, with $t_{1/2}$ values ranging from 0.299 to 0.789 hour during week 3 and from 0.739 to 1.28 hours during week 52. The increases in C_{max} for male and female mice were less than dose proportional. However, the increases in AUC_{0-24} were apparently dose proportional in male and female mice, with the exception of female mice during week 52, where the increases were less than dose proportional. The TK parameters for male and female mice are shown in the Table below (from page 5073 of the report).

Table 1
Toxicokinetic Parameters for Teduglutide (ALX-0600) in Mouse Plasma

Dose Group	Dose Level (mg/kg/day)	Sex	C_{max} (µg/mL)	DN C_{max} [(µg/mL)/(mg/kg/day)]	T_{max} (hr)	AUC_{0-t} (µg·hr/mL)	AUC_{0-24} (µg·hr/mL)	DN AUC_{0-24} [(µg·hr/mL)/(mg/kg/day)]	$t_{1/2}$ (hr)	Change in Exposure (Week 52/Week 3) C_{max}	Change in Exposure (Week 52/Week 3) AUC_{0-24}
					Week 3						
6	1.0	M	3.94	3.94	0.250	1.81	2.26	2.26	NC	NA	NA
		F	1.68	1.68	0.250	1.53	1.71	1.71	0.489	NA	NA
7	3.5	M	9.69	2.77	0.500	9.47	9.54	2.73	0.455	NA	NA
		F	3.96	1.13	0.500	5.65	5.71	1.63	0.459	NA	NA
8	12.5	M	29.4	2.35	0.500	36.0	36.1	2.89	0.299	NA	NA
		F	16.0	1.28	0.500	23.6	25.1	2.00	0.789	NA	NA
					Week 52						
6	1.0	M	2.38	2.38	0.500	2.91	3.11	3.11	0.836	0.604	1.38
		F	2.44	2.44	0.500	3.80	6.44	6.44	NC	1.45	3.77
7	3.5	M	5.70	1.63	0.500	10.6	12.4	3.55	1.28	0.589	1.30
		F	4.24	1.21	0.250	7.04	7.37	2.10	0.741	1.07	1.29
8	12.5	M	17.7	1.42	1.00	43.6	44.0	3.52	0.739	0.604	1.22
		F	12.0	0.960	0.500	28.8	29.3	2.34	0.868	0.750	1.17

Antibody determination: A total of 95 samples were screened by electrochemiluminescence (ECL) for the detection of antibodies to ALX-0600. Thirty five (35) samples screened positive, while 9 samples were indeterminate due to the replicate values spanning the cut point in the screening assay. Thirty four of the 35 positive samples were confirmed to be specific, and 2 of the 9 indeterminate samples were also confirmed to be specific. All of the 36 samples found to be specific in the confirmatory assay were assessed in a titer-based assay, and also tested in a neutralizing antibody assay. Twenty six of the 36 samples in the neutralizing antibody assay were classified as positive for neutralizing antibodies, but the maximum titer levels across dose groups were similar and there seemed to be no correlation between the dose levels and neutralizing antibodies. At least one animal of each sex dosed at 1, 3.5, or 12.5 mg/kg/day were confirmed to have detectable antibodies as well as neutralizing antibodies as shown in the incidence table below (from page 31 of the report).

Incidence of Antibodies to ALX-0600 (teduglutide)

		Week 13	Week 26
Males	1 mg/kg/day	3/4 (2/3)	3/4 (1/3)
	3.5 mg/kg/day	2/4 (1/2)	3/4 (3/3)
	12.5 mg/kg/day	1/4 (1/1)	4/4 (2/4)
Females	1 mg/kg/day	4/4 (2/4)	4/4 (3/4)
	3.5 mg/kg/day	3/4 (3/3)	3/4 (3/3)
	12.5 mg/kg/day	4/4 (4/4)	2/3 (1/2)

Note: Incidence listed indicates number of animals positive for the presence of antibodies in the confirmatory assay; parenthetical values are the number of animals positive for the presence of neutralizing antibodies out of the total number of animals that were positive for the presence of antibodies in the confirmatory assay.

Summary of individual study findings:

Adequacy of the carcinogenicity study and appropriateness of the test model: The study methodology appears to be appropriate and acceptable. The high dose selection was based on a >25-fold AUC ratio of animal to human exposure, and was concurred by the Executive CAC. The test model (Crl:CD1®(ICR) mice) selection was in concurrence with the Agency. Overall, the 2-year carcinogenicity study was conducted in a valid and acceptable manner.

Evaluation of tumor findings: Treatment with teduglutide at doses of ≥1 mg/kg/day resulted in papillary adenoma in the gall bladder of male (control, 0/66(0%); low dose, 5/71(7.0%; p=0.042 compared to control; mid dose, 2/70 (2.9%; p=0.254) and high dose, 6/70(8.6%; p=0.024 compared to control) mice; (p=0.0244, trend test). The incidence of gall bladder papillary adenoma in female mice was higher than control only at 3.5 mg/kg/day (0/69 (0%), 1/69 (1.4%), 3/70(4.3%; p=0.019) and 0/68(0%) in control low, mid and high dose groups, respectively). The incidences of papillary adenoma in the gall bladder of male mice at ≥1 mg/kg/day were higher than the historical control incidences (mean, 0.8%; range 0 -1.9%). In female mice treated with the 3.5 mg/kg/day dose, the incidence of gall bladder papillary adenoma was higher than historical control incidences (mean, 0.4%; range 0-3.5%). However, there was no clear dose-response for the incidence of papillary adenoma in male and female mice.
Treatment with teduglutide produced adenocarcinoma of the jejunum in male mice administered the high dose of 12.5 mg/kg/day (0/68 (0%), 1/69 (1.4%), 0/73 (0%) and 4/68 (6.1%; p=0.0155) in control, low, mid and high dose groups, respectively). This is a rare tumor in CD-1 mice, and was not observed in the concurrent study control or (b) (4) historical control values (0/526). Bronchiolar-alveolar adenomas in female mice had significant increases at 3.5 and 12.5 mg/kg/day (p = 0.0209 and 0.0130, respectively versus control). The positive trend in this case (p = 0.0155) was not statistically significant for a common tumor. Bronchiolar-alveolar carcinomas did not exhibit any significant positive trend (p = 0.0478) for common tumors. When bronchiolar-alveolar adenomas and carcinomas were combined, the positive trend was significant (p = 0.0058), along with significant increases at 3.5 and 12.5 mg/kg/day (p = 0.0103 and 0.0177, respectively). The incidence of bronchiolar-alveolar adenoma in the high dose group (13.8%) was within the historical control incidences (mean 11.1%; range 6.7-20.0%); the incidence of bronchiolar-alveolar carcinoma at

the high dose (7.5%) was also within the historical control range (mean 7.0%; range 1.7 to 15.0%).

Carcinogenicity summary: In a 104-week carcinogenicity study, male and female CD-1 mice were subcutaneously administered teduglutide (ALX-0600) once daily at 0, 1.0, 3.5 and 12.5 mg/kg/day to evaluate its oncogenic potential. The control group received the vehicle, phosphate buffer in sterile water. The high dose selection was based on a >25-fold AUC ratio of animal to human exposure, and was concurred by the Executive CAC. There were no treatment-related effects on survival in male or female mice. The survival rates were 43 %, 46 %, 39 %, and 43 % in males and 31 %, 40 %, 28 %, and 24 % in females at the scheduled termination of the study after 104 weeks of dosing.

Mean body weight changes observed in male animals treated with 3.5 and 12.5 mg/kg/day ALX0600 were found to be significantly higher than that of control animals at different periods of the dosing phase. The test article-related increases in mean body weights observed at all dose levels in female mice were attributed to increased food consumption. A minimal but significant increase in mean food consumption was noted in males treated with 12.5 mg/kg/day of the test article at 6 weekly intervals of the dosing phase. In female animals however, the mean food consumption increased notably in all treated groups relative to controls, for up to 9 of the last 10 weekly dosing intervals.

Large, distended gall bladder and large, discolored mesenteric lymph node were observed in animals given ≥ 1 mg/kg/day of the test article. Macroscopic findings in the intestines (duodenum, jejunum, ileum, colon and/or cecum) including thickened, distended, large, abnormal shape, discolored, adhesion, constricted, and/or mass each occurred at an incidence of 4 or less/group in treated animals. Small and large intestinal lengths were also increased at all dose levels compared with controls.

Microscopic findings include mucosal hyperplasia of the cecum, colon, and rectum. Congestion, hemorrhage, increased macrophages and infiltrates were observed in the mesenteric lymph node of males and females dosed at ≥ 1 mg/kg/day as well as increased hematopoiesis and macrophage infiltrates in males dosed at ≥ 1 mg/kg/day. Hypercellularity of the bone marrow (sternum) and increased incidence of subcutaneous inflammation at the injection sites were observed in animals dosed at ≥ 1 mg/kg/day. Hyperplasia of the bronchiolar-alveolar tissues of the lungs and mucosal hyperplasia and increased villus length of the duodenum, jejunum, and ileum were noted in animals dosed at ≥ 1 mg/kg/day. Distention, epithelial hyperplasia, inflammation, and fibrosis/thickening of the wall of the gall bladder were also noted.

Teduglutide (ALX-0600) at doses of ≥1 mg/kg/day resulted in papillary adenoma in the gall bladder of male (control, 0/66(0%); low dose, 5/71(7.0%; p=0.042 compared to control; mid dose, 2/70 (2.9%; p=0.254) and high dose, 6/70(8.6%; p=0.024 compared to control) mice; p=0.0244, trend test). The incidence of gall bladder papillary adenoma in female mice was higher than control only at 3.5 mg/kg/day (0/69 (0%), 1/69 (1.4%), 3/70(4.3%; p=0.019) and 0/68(0%) in control low, mid and high dose groups, respectively).
Treatment with teduglutide produced adenocarcinoma of the jejunum in male mice administered the high dose of 12.5 mg/kg/day (0/68 (0%), 1/69 (1.4%), 0/73 (0%) and 4/68 (6.1%; p=0.0155)

in control, low, mid and high dose groups, respectively). This is a rare tumor in CD-1 mice, and was not observed in concurrent study control or (b) (4) historical control values (0/526).

Bronchiolar-alveolar adenomas in female mice had significant increases at 3.5 and 12.5 mg/kg/day ($p = 0.0209$ and 0.0130, respectively) versus control. The positive trend in this case ($p = 0.0155$) was not statistically significant for a common tumor. Bronchiolar-alveolar carcinomas did not exhibit any significant positive trend ($p = 0.0478$) for common tumors. When bronchiolar-alveolar adenomas and carcinomas were combined, the positive trend was significant ($p = 0.0058$), along with significant increases at 3.5 and 12.5 mg/kg/day ($p = 0.0103$ and 0.0177, respectively).

After subcutaneous administration, plasma exposure to ALX-0600 generally increased with the increase in dose levels from 1.0 to 12.5 mg/kg/day, with a T_{max} value of 1 hour during week 52 of dosing. The increase in C_{max} for male and female mice were less than dose proportional, in contrast to the increase in AUC_{0-24} which was apparently dose proportional in male and female mice. The mean AUC_{0-24} was 44.0 and 29.3 μg·hr/ml in males and females dosed at 12.5 mg/kg/day, respectively, during week 52 of the dosing phase. The mean exposure levels in male and female mice at the high dose were about 178 and 119 times, respectively, the mean human exposure level (247 ng·hr/ml) at the recommended clinical dose (0.05 mg/kg) of ALX-0600.

APPENDIX/ATTACHMENTS:

Appendix 1: Applicants Analyses of Neoplastic findings in Male and Female Mice

Table 3
Results of Statistical Analyses of Neoplastic Lesions - Males

		Unadjusted Lifetime Incidence Rate			
	Group	1	2	3	4
	Dose: mg/kg/day	0	1.0	3.5	12.5
Tissue and Lesion	p-value	Trend (2-4 vs. 1)	2 vs. 1	3 vs. 1	4 vs. 1
Adrenal, Cortex, B-Adenoma, Subcapsular Cell					
	Incidental Tumor	3	8	4	5
	Fatal Tumor	0	0	0	0
	Total Number of Tumors	3/79	8/80	4/80	5/80
Group 2-4 vs. Group 1 (one-sided)		0.4424+	0.0711+	NA	0.3538+(E)
Adrenal, Cortex, M-Carcinoma, Subcapsular Cell					
	Incidental Tumor	1	1	1	2
	Fatal Tumor	0	0	0	0
	Total Number of Tumors	1/79	1/80	1/80	2/80
Group 2-4 vs. Group 1 (one-sided)		NA	NA	NA	NA
Adrenal, Cortex, B-Adenoma, Subcapsular Cell/ M-Carcinoma, Subcapsular Cell					
	Incidental Tumor	4	9	4	6
	Fatal Tumor	0	0	0	0
	Total Number of Tumors	4/79	9/80	4/80[b]	6/80[b]
Group 2-4 vs. Group 1 (one-sided)		0.4222+	0.0873+	NA	0.2236+
Liver, B-Adenoma, Hepatocellular					
	Incidental Tumor	31	14	10	13
	Fatal Tumor	1	0	0	0
	Total Number of Tumors	32/80[a]	14/80	10/80	13/80
Group 2-4 vs. Group 1 (one-sided)		NA	NA	NA	NA
Liver, M-Carcinoma, Hepatocellular					
	Incidental Tumor	4	4	4	3
	Fatal Tumor	3	1	6	4
	Total Number of Tumors	7/80	5/80	10/80	7/80
Group 2-4 vs. Group 1 (one-sided)		0.3486+	NA	0.4462+	NA
Liver, B-Adenoma, Hepatocellular/ M-Carcinoma, Hepatocellular					
	Incidental Tumor	35	18	14	16
	Fatal Tumor	4	1	6	4
	Total Number of Tumors	39/80	19/80	20/80	20/80
Group 2-4 vs. Group 1 (one-sided)		NA	NA	NA	NA

Incidental Tumor	0	5	2	6
Fatal Tumor	0	0	0	0
Total Number of Tumors	0/66	5/71	2/70	6/70
ne-sided)	0.0244+@	0.0429+(E)*	0.2548+(E)	0.0135+(E)*

Gallbladder, B-Papillary Adenoma

Group 2-4 vs. Group 1 (
* = Significant at 5% level.
+/- = Effect in the increased/decreased direction. (E) = Exact test. NA = Not Analyzed.
@ = Not a significant trend at 0.01 level for a common tumor.
a One tumor was fatal but was treated as incidental for the purpose of the statistical analysis.
b The following animals had both B-Adenoma, Subcapsular Cell and M-Carcinoma, Subcapsular Cell: A37476 (Group 3); A37528 (Group 4). For the purpose of the statistical analysis, each animal was counted once.

Table 3 (Continued)
Results of Statistical Analyses of Neoplastic Lesions - Males

				Unadjusted Lifetime Incidence Rate		
			Group	1	2	3	4
			Dose: mg/kg/day	0	1.0	3.5	12.5
Tissue and Lesion		p-value	Trend (2-4 vs. 1)	2 vs. 1	3 vs. 1	4 vs. 1
Lung, B-Adenoma, Bronchiolar-Alveolar						
			Incidental Tumor	15	16	16	12
			Fatal Tumor	0	0	1	0
			Total Number of Tumors	15/80	16/80	17/80[a]	12/80
Group 2-4 vs. Group 1 (one-sided)				0.2748-	NA	0.3147+	NA
Lung, M-Carcinoma, Bronchiolar-Alveolar							
			Incidental Tumor	5	7	2	1
			Fatal Tumor	8	2	3	3
			Total Number of Tumors	13/80	9/80	5/80	4/80
Group 2-4 vs. Group 1 (one-sided)				NA	NA	NA	NA
Lung, B-Adenoma, Bronchiolar-Alveolar/ M-Carcinoma, Bronchiolar-Alveolar							
			Incidental Tumor	19	22	18	13
			Fatal Tumor	8	2	4	3
			Total Number of Tumors	27/80[b]	24/80[b]	22/80	16/80
Group 2-4 vs. Group 1 (one-sided)				NA	NA	NA	NA
Duodenum, M-Adenocarcinoma							
Incidental Tumor	0	2	0	1			
Fatal Tumor	0	0	0	0			
			Total Number of Tumors	0/70	2/69	0/71	1/66
Group 2-4 vs. Group 1 (one-sided)				0.2945+(E)	0.3859+(E)	NA	NA
Jejunum, M-Adenocarcinoma							
Incidental Tumor	0	1	0	3			
Fatal Tumor	0	0	0	1			
			Total Number of Tumors	0/68	1/69	0/73	4/68[b]
Group 2-4 vs. Group 1 (one-sided)				0.0155+(E)*	NA	NA	0.1084+(E)
Testis, B-Interstitial Cell Tumor							
Incidental Tumor	2	5	5	4			

Fatal Tumor	0	1	0	0
Total Number of Tumors	2/80	6/79[a]	5/80	4/80
Group 2-4 vs. Group 1 (one-sided)	0.4104+	0.1318+(E)	0.1767+(E)	0.2882+(E)

Testis, M-Interstitial Cell Tumor Cell Tumor

Incidental Tumor	1	0	0	0
Fatal Tumor	0	0	0	0
Total Number of Tumors	1/80	0/79	0/80	0/80
Group 2-4 vs. Group 1 (one-sided)	NA	NA	NA	NA

+/- = Effect in the increased/decreased direction. (E) = Exact test. NA = Not Analyzed.
* = Significant at 5% level.
a One tumor was fatal but was treated as incidental for the purpose of the statistical analysis.
b The following animals had both B-Adenoma, Bronchiolar-Alveolar and M-Carcinoma, Bronchiolar-Alveolar: A37289 (Group 1); A37359 (Group 2). For the purpose of the statistical analysis, each animal was counted once.

Table 3 (Continued)
Results of Statistical Analyses of Neoplastic Lesions - Males

Unadjusted Lifetime Incidence Rate

Tissue and Lesion
Testis, B-Interstitial Cell Tumor/ M-Interstitial Cell Tumor Cell Tumor

Incidental Tumor	3	5	5	4
Fatal Tumor	0	1	0	0
Total Number of Tumors	3/80	6/79[a]	5/80	4/80
Group 2-4 vs. Group 1 (one-sided)	0.4942+	0.2445+(E)	0.3026+(E)	NA

Group	1	2	3	4
Dose: mg/kg/day	0	1.0	3.5	12.5
p-value	Trend (2-4 vs. 1)	2 vs. 1	3 vs. 1	4 vs. 1

Body, Whole/Cavity, B-Benign Hemangioma

Incidental Tumor	3	3	1	0
Fatal Tumor	0	0	0	0
Total Number of Tumors	3/80	3/80	1/80	0/80
Group 2-4 vs. Group 1 (one-sided)	NA	NA	NA	NA

Body, Whole/Cavity, M-Hemangiosarcoma

Incidental Tumor	2	3	2	1
Fatal Tumor	0	2	6	4
Total Number of Tumors	2/80	5/80	8/80	5/80
Group 2-4 vs. Group 1 (one-sided)	0.2514+	0.3417+	0.4435+	0.2858-

Body, Whole/Cavity, B-Benign Hemangioma/ M-Hemangiosarcoma

Incidental Tumor	5	6	3	1
Fatal Tumor	0	2	6	4
Total Number of Tumors	5/80	8/80	9/80	5/80
Group 2-4 vs. Group 1 (one-sided)	0.3783-	0.4269+	0.2817-	NA

Body, Whole/Cavity, M-Histiocytic Sarcoma

Incidental Tumor	3	5	0	4

Fatal Tumor	1	1	1	0
Total Number of Tumors	4/80	6/80	1/80	4/80
Group 2-4 vs. Group 1 (one-sided)	0.4617-	0.2528+	NA	NA

+/- = Effect in the increased/decreased direction. (E) = Exact test. NA = Not Analyzed.
a One tumor was fatal but was treated as incidental for the purpose of the statistical analysis.

Table 4
Results of Statistical Analyses of Neoplastic Lesions - Females

	Unadjusted Lifetime Incidence Rate			
Group	1	2	3	4
Dose: mg/kg/day	0	1.0	3.5	12.5
Tissue and Lesion p-value	Trend (2-4 vs. 1)	2 vs. 1	3 vs. 1	4 vs. 1
Pituitary, B-Adenoma				
Incidental Tumor	0	0	3	1
Fatal Tumor	0	1	0	1
Total Number of Tumors	0/80	1/79	3/78	2/80[a]
Group 2-4 vs. Group 1 (one-sided)	0.1636+	NA	0.0950+(E)	0.2479+(E)
Pituitary, M-Carcinoma				
Incidental Tumor	0	0	0	0
Fatal Tumor	0	0	1	0
Total Number of Tumors	0/80	0/79	1/78	0/80
Group 2-4 vs. Group 1 (one-sided)	NA	NA	NA	NA
Pituitary, B-Adenoma/ M-Carcinoma				
Incidental Tumor	0	0	3	1
Fatal Tumor	0	1	1	1
Total Number of Tumors	0/80	1/79	4/78	2/80
Group 2-4 vs. Group 1 (one-sided)	0.1982+	NA	0.0511+(E)	0.2479+(E)
Thyroid, B-Adenoma, Follicular Cell				
Incidental Tumor	0	0	3	2
Fatal Tumor	0	0	0	0
Total Number of Tumors	0/80	0/80	3/79	2/80
Group 2-4 vs. Group 1 (one-sided)	0.1148+(E)	NA	0.1901+(E)	0.3939+(E)
Lung, B-Adenoma, Bronchiolar-Alveolar				
Incidental Tumor	3	5	9	11
Fatal Tumor	0	0	1	0
Total Number of Tumors	3/80	5/80	10/79[a]	11/80
Group 2-4 vs. Group 1 (one-sided)	0.0155+@	0.3851+(E)	0.0209+*	0.0130+*
Lung, M-Carcinoma, Bronchiolar-Alveolar				
Incidental Tumor	1	1	3	2
Fatal Tumor	0	3	0	4
Total Number of Tumors	1/80	4/80	3/79	6/80
Group 2-4 vs. Group 1 (one-sided)	0.0478+@	0.4262+	0.3659+(E)	0.2797+
Incidental Tumor	4	6	12	12
Fatal Tumor	0	3	1	4
Total Number of Tumors	4/80	9/80	13/79[a]	16/80[b]
ıe-sided)	0.0058+#	0.2546+	0.0103+*	0.0177+*

Lung, B-Adenoma, Bronchiolar-Alveolar/ M-Carcinoma, Bronchiolar-Alveolar

Group 2-4 vs. Group 1 (
* = Significant at 5% level.
+/- = Effect in the increased/decreased direction. (E) = Exact test. NA = Not Analyzed.
= Significant trend at 0.01 level for a common tumor.
@ = Not a significant trend at 0.01 level for a common tumor.
a One tumor was fatal but was treated as incidental for the purpose of the statistical analysis.
b The following animal had both B-Adenoma, Bronchiolar-Alveolar and M-Carcinoma, Bronchiolar-Alveolar: A38170 (Group 4). For the purpose of the statistical analysis, each animal was counted once.

Table 4 (Continued)
Results of Statistical Analyses of Neoplastic Lesions - Females

Unadjusted Lifetime Incidence Rate

Tissue and Lesion	Group / Dose: mg/kg/day	1 0	2 1.0	3 3.5	4 12.5
	p-value	Trend (2-4 vs. 1)	2 vs. 1	3 vs. 1	4 vs. 1
Gallbladder, B-Papillary Adenoma					
	Incidental Tumor	0	1	3	0
	Fatal Tumor	0	0	0	0
	Total Number of Tumors	0/69	1/69	3/70	0/68
	Group 2-4 vs. Group 1 (one-sided)	0.1846-(E)	NA	0.1968+(E)	NA
Ovary, B-Cystadenoma					
	Incidental Tumor	1	4	4	2
	Fatal Tumor	0	0	0	0
	Total Number of Tumors	1/79	4/80	4/79	2/79
	Group 2-4 vs. Group 1 (one-sided)	0.4200-	0.1490+(E)	0.1880+(E)	NA
Ovary, B-Luteoma					
	Incidental Tumor	0	0	0	2
	Fatal Tumor	0	0	0	0
	Total Number of Tumors	0/79	0/80	0/79	2/79
	Group 2-4 vs. Group 1 (one-sided)	0.0728+(E)	NA	NA	0.4727+(E)
Ovary/Uterus, B-Granular Cell Tumor/ B-Granulosa/Theca Cell Tumor					
	Incidental Tumor	1	0	2	4
	Fatal Tumor	0	1	0	0
	Total Number of Tumors	1/79	1/80[a]	2/79	4/79
	Group 2-4 vs. Group 1 (one-sided)	0.0519+(E)	NA	NA	0.2094+(E)
Cervix/Uterus, B-Leiomyoma					
	Incidental Tumor	1	1	3	2
	Fatal Tumor	0	0	0	0
	Total Number of Tumors	1/80	1/79	3/79	2/79
	Group 2-4 vs. Group 1 (one-sided)	0.2365+(E)	NA	0.3800+(E)	NA
Cervix/Uterus, M-Leiomyosarcoma					
	Incidental Tumor	0	1	2	1
	Fatal Tumor	0	0	0	0
	Total Number of Tumors	0/80	1/79	2/79	1/79
	Group 2-4 vs. Group 1 (one-sided)	0.2365+(E)	NA	0.3800+(E)	NA

Cervix/Uterus, B-Leiomyoma/ M-Leiomyosarcoma

Incidental Tumor	2	2	5	3
Fatal Tumor	0	0	0	0
Total Number of Tumors	1/80	2/79	5/79	3/79
Group 2-4 vs. Group 1 (one-sided)	0.1983+	NA	0.1174+(E)	NA

+/- = Effect in the increased/decreased direction. (E) = Exact test. NA = Not Analyzed.
a One tumor was fatal but was treated as incidental for the purpose of the statistical analysis.

Table 4 (Continued)
Results of Statistical Analyses of Neoplastic Lesions - Females

Unadjusted Lifetime Incidence Rate

Tissue and Lesion				
Cervix/Uterus, B-Polyp, Endometrial Stromal				
Incidental Tumor	7	5	7	1
Fatal Tumor	0	0	0	0
Total Number of Tumors	7/80	5/79	7/79	1/79
Group 2-4 vs. Group 1 (one-sided)	NA	NA	NA	NA

Group	1	2	3	4
Dose: mg/kg/day	0	1.0	3.5	12.5
p-value	Trend (2-4 vs. 1)	2 vs. 1	3 vs. 1	4 vs. 1

Cervix/Uterus, M-Sarcoma, Endometrial Stromal				
Incidental Tumor	4	3	0	5
Fatal Tumor	0	1	3	1
Total Number of Tumors	4/80	4/79	3/79	6/79
Group 2-4 vs. Group 1 (one-sided)	0.1946+	NA	NA	0.3862+(E)
Cervix/Uterus, B-Polyp, Endometrial Stromal/ M-Sarcoma, Endometrial Stromal				
Incidental Tumor	10	8	7	6
Fatal Tumor	0	1	3	1
Total Number of Tumors	10/80[a]	9/79	10/79	7/79
Group 2-4 vs. Group 1 (one-sided)	NA	NA	NA	NA
Body, Whole/Cavity, M-Histiocytic Sarcoma				
Incidental Tumor	4	9	4	2
Fatal Tumor	8	7	7	4
Total Number of Tumors	12/80	16/80	11/79	6/80
Group 2-4 vs. Group 1 (one-sided)	0.0366-*	0.1224+	NA	NA

Body, Whole/Cav, Lymphosarcoma

Incidental Tumor	20	23	13	17
Fatal Tumor	9	10	14	15

Total Number of Tumors	29/80	33/80	27/79	32/80
Group 2-4 vs. Group 1 (one-sided)	0.3557	0.4046+	NA	0.2492-

Skin/Subcutis / Skin/Subcutis, Other, M-Fibrosarcoma (P)

Group 2-4 vs. Group 1 (one-si
* = Significant at 5% level. +/- = Effect in the increased/decreased direction. NA = Not Analyzed.
a The following animal had both B-Polyp, Endometrial Stromal and M-Sarcoma, Endometrial Stromal: A37926 (Group 1). For the purpose of the statistical analysis, each animal was counted once.

Appendix 2. Executive CAC Meeting Minutes

Executive CAC
Date of Meeting: November 3, 2009

Committee: Abby Jacobs, Ph.D., OND-IO, Acting Chair
Paul Brown, Ph.D., OND-IO, Member
Aisar Atrakchi, Ph.D., DPP, Alternate Member
Sushanta K. Chakder, Ph.D., DGP, Supervisory Pharmacologist
Tamal Chakraborti, Ph.D., DGP, Presenting Reviewer

Author of Draft: Tamal Chakraborti, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

The committee did not address the sponsor's proposed statistical evaluation for the carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND: 58,213
Drug Name: ALX-0600
Sponsor: NPS Pharmaceuticals Inc.

ALX-0600 is an analog of the naturally occurring glucagon-like peptide 2 (GLP-2), which has been shown to stimulate intestinal growth and regulate villous height in the small intestine.

ALX-0600 is currently being investigated as an agent for the treatment of short bowel syndrome (SBS) and is in Phase 3 clinical trials.

Mouse Carcinogenicity Study Protocol and Dose Selection

The sponsor submitted the rationale for dose selection and a protocol for a 104-week subcutaneous carcinogenicity study in CD-1 mice at doses of 0, 1, 3.5 and 12 mg/kg/day (1.25 mL/kg). Mice in the control group will receive the vehicle (phosphate buffer with mannitol and L-histidine). The dose selection was based on the pharmacokinetic (PK) endpoint or AUC comparison data from a 26-week subcutaneous toxicology study (7203-112) in CD-1 mice.

In the 26-week SC toxicology study in CD-1 mice, animals were treated at 2, 10 or 50 mg/kg/day (1, 5 and 25 mg/kg bid, 8 hours apart). The target organs of toxicity appeared to be the small and large intestines (epithelial and villus hypertrophy/hyperplasia), liver (hepatocellular hypertrophy), gallbladder (increased lymphohistiocytic infiltrates, increased cytoplasmic secretory product, and epithelial hypertrophy/hyperplasia accompanied by subacute inflammation, lumenal suppurative exudates, and edema), bile duct (hypertrophy/hyperplasia, subacute inflammation, and/ or increased secretory product), sternal bone marrow (myeloid hyperplasia), spleen (extramedullary hematopoiesis and lymphocytic hyperplasia), skin and injection sites (lytic necrosis of the subcutis, intralesional eosinophilic material, subacute and/or chronic inflammation, macrophage infiltrates, and fibroplasia/fibrosis; many of these observations were also seen at the injection sites of control animals, although at lower mean severity scores). All of the microscopic effects were reversible following the 8-week recovery period, with the exception of findings in the liver, spleen, and some injection sites. The NOAEL could not be determined as treatment-related adverse effects were observed at all dose levels. Based on the TK data from the 26-week toxicology study in CD-1 mice, and the interpolation of the above TK data using a two-compartmental model, the proposed doses for the carcinogenicity study are expected to provide exposures over the human exposure of 10-, 32- and 124-fold in males and 5-, 24- , and 79-fold in females and at the low-, mid-, and high-dose levels, respectively.

Executive CAC Recommendations and Conclusions: The Committee concurred with the sponsor's proposed doses of 0, 1, 3.5 and 12 mg/kg/day by subcutaneous injection, based on a >25-fold AUC ratio of animal to human exposure for the high dose.

_____

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC
cc:\
/Division File, DGP
/TChakraborti, DGP
/SChakder, DGP
/RPM/MScherer, DGP

Appendix 3. Executive CAC Meeting Minutes

Executive CAC
April 16, 2014
Committee: Abigail Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Hanan Ghantous, Ph.D., DAVP, Alternate Member
Lynnda Reid, Ph.D., DBRUP, Alternate Member
Sushanta Chakder, Ph.D., DGIEP, Supervisor
Babatunde (Emmanuel) Akinshola, Ph.D., DGIEP, Presenting Reviewer

Author of Minutes: Babatunde (Emmanuel) Akinshola, Ph.D.

The following information reflects a brief summary of the committee discussion and its recommendations.

NDA: 203441
Drug Name: Teduglutide (ALX-0600)
Sponsor: NPS Pharmaceuticals Inc.

Background

Teduglutide is an analog of the naturally occurring glucagon-like peptide 2 (GLP-2) which has been shown to stimulate intestinal growth and regulate villous height in the small intestine. Teduglutide is currently approved for the treatment of short bowel syndrome (SBS). The Applicant conducted a 104-week subcutaneous carcinogenicity study with teduglutide in mice to assess the carcinogenic potential.

Mouse Carcinogenicity Study
In the 104-week subcutaneous carcinogenicity study in CD-1 mice, teduglutide was administered to male and female mice (80/sex/group) at dose levels of 0, 1, 3.5 and 12.5 mg/kg/day (1.25 ml/kg). Mice in the control group received only the vehicle (phosphate buffer with water for injection). The dose selection was based on a >25-fold AUC ratio of animal to human exposure for the high dose in a 26-week subcutaneous study with teduglutide in CD-1 mice (study No. 7302-112) and was concurred with by the Ex-CAC.

The incidence of papillary adenomas in the gallbladder of high dose male mice was significantly increased when compared to control mice (control, 0/66; low dose, 5/71; mid dose, 2/70; high dose, 6/70). Jejunal adenocarcinoma had not been previously observed in control mice in the historical database of the conducting laboratory. However four adenocarcinomas of the jejunum were observed in high-dose male mice. In addition, the incidences of hyperplasia in the small intestine of dosed mice were notably increased. No drug-related increased incidence of any neoplasms was observed in female mice.

Executive CAC Recommendations and Conclusions:
Mouse:

- The committee concurred that the study was acceptable, noting prior exec CAC concurrence with the protocol.

- The committee concurred that there were drug-related increased incidences of papillary adenomas in the gallbladder, and of adenocarcinomas in the jejunum. There were no drug-related neoplasms in females.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\
/Division File, DGIEP
/S. Chakder, DGIEP
/B.E. Akinshola, DGIEP
/M. Scherer, DGIEP
/A. Seifried, OND IO

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

/s/

BABATUNDE E AKINSHOLA
05/22/2014

SUSHANTA K CHAKDER
05/22/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 203441 **Applicant: NPS Pharmaceuticals Inc.** **Stamp Date: August 28, 2013**

Drug Name: Gattex (Teduglutide Injection) **NDA/BLA Type: NDA Supplement**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	√		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	√		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	√		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			N/A
11	Has the applicant addressed any abuse potential issues in the submission?			N/A
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _YES_____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. NONE

B. Emmanuel Akinshola, Ph.D. October 17, 2013
Reviewing Pharmacologist Date

Sushanta K. Chakder, Ph.D. October 17, 2013
Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

BABATUNDE E AKINSHOLA
10/17/2013

SUSHANTA K CHAKDER
10/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203441/S-002

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 203-441
Drug Name:	ALX-0600
Applicant:	Sponsor: NPS Pharmaceuticals, Inc. 550 Hills Drive Bedminster, New Jersey 07921 United States of America Test Facility: (b) (4)
Documents Reviewed:	Electronic data submitted on January 14, 2014, Also include the sponsor's reports submitted.
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Min Min, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Gastroenterology and Inborn Errors Products
Reviewing Pharmacologist:	Babatunde Akinshola, Ph.D.
Project Manager:	Matthew Scherer
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission, the sponsor included reports of a mouse study. These studies were intended to further assess the carcinogenic potential of the test article, teduglutide (ALX-0600), when administered daily for at least 104 weeks via subcutaneous injection to mice. Teduglutide [ALX-0600; gly2(GLP-2)] is an analog of naturally occurring human glucagon-like peptide-2 (GLP-2), a peptide secreted by L cells primarily of the distal intestine and involved in the regeneration and repair of the intestinal epithelium.

Results of this review have been discussed with the reviewing pharmacologist Dr. Akinshola who suggested doing analysis for mouse studies.

2. Mouse Study

Male and female Crl:CD1(ICR) mice were assigned to 12 groups and doses were administered once daily via subcutaneous injection, as indicated in the following table. Animals in the control groups received the control article/diluent (phosphate buffer vehicle prepared in Sterile Water for Injection, USP, pH-adjusted to 7.2 to 7.6 with hydrochloric acid and/or sodium hydroxide as necessary) only.

	No. of Animals		Dose Level	Dose Concentration
Group	Male	Female	(mg/kg/day)[b]	(mg/mL)[b]
Carcinogenicity Animals				
1 (Control)[a]	80	80	0	0
2 (Low)	80	80	1.0	0.8
3 (Mid)	80	80	3.5	2.8
4 (High)	80	80	12.5	10.0
Toxicokinetic Animals				
5 (Control)[a]	32	32	0	0
6 (Low)	64	64	1.0	0.8
7 (Mid)	64	64	3.5	2.8
8 (High)	64	64	12.5	10.0
Antibody Animals				
9 (Control)[a]	12	12	0	0
10 (Low)	12	12	1.0	0.8
11 (Mid)	12	12	3.5	2.8
12 (High)	12	12	12.5	10.0

a Group 1, 5, and 9 received control article/diluent only.
b Animals were dosed at the volume of 1.25 mL/kg.

A necropsy was done on carcinogenicity animals that died or were sacrificed at an unscheduled interval. Terminal body weights were recorded for sacrificed carcinogenicity animals. After at least 104 weeks of dosing, all surviving animals had body weights recorded and were anesthetized with sodium pentobarbital, exsanguinated, and necropsied. The following tissues (when present) from each animal will be preserved in 10% neutralbuffered formalin unless otherwise indicated in the following.

adrenal (2)
aorta
brain
cecum
cervix
colon
duodenum
epididymis (2)
esophagus
eye (2)[a]
femur with bone marrow (articular surface of the distal end)
gallbladder
Harderian gland[a]
heart
ileum
injection site(s)
jejunum
kidney (2)
lesions
liver
lung with large bronchi
lymph node (mandibular)
lymph node (mesenteric)
mammary gland (females)
muscle, biceps femoris
optic nerve (2)[a]
ovary (2)
pancreas
pituitary gland
prostate
rectum
salivary gland [mandibular (2)]
sciatic nerve
seminal vesicle
skin/subcutis
spinal cord (cervical, thoracic, and lumbar)
spleen
sternum with bone marrow
stomach
testis (2)[a]
thymus
thyroid (2 lobes) with parathyroid
tongue
trachea
urinary bladder
uterus
vagina

a Preserved in modified Davidson's fixative.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Evaluations of trend and heterogeneity of survival data were performed using the Cox-Tarone binary regression on life tables and Gehan-Breslow nonparametric methods using the National Cancer Institute (NCI) Life Table Package. The Cox-Tarone method is more sensitive to late deaths, and the Gehan-Breslow method is more sensitive to early deaths due to the test article. As a result, they are both important tools to evaluate observable incidence data. Week 105 of the dosing phase was treated as the end of the study in the NCI package for males and females. Those animals sacrificed at the scheduled interval and animals sacrificed for other reasons (such as fractured bone) were censored in the analyses. One-sided tail probabilities for trend and group comparisons were evaluated at <5.0% significance level.

Sponsor's findings: Kaplan-Meier product limit survival curves are presented in Figure 1 (males) and Figure 2 (females). Administration of teduglutide did not cause any statistically significant change in survival in either sex. Nonsignificant increases and decreases in mortality in both sexes were indications of background noise.

Figure 1: Kaplan-Meier plot of Survival in Male Mice

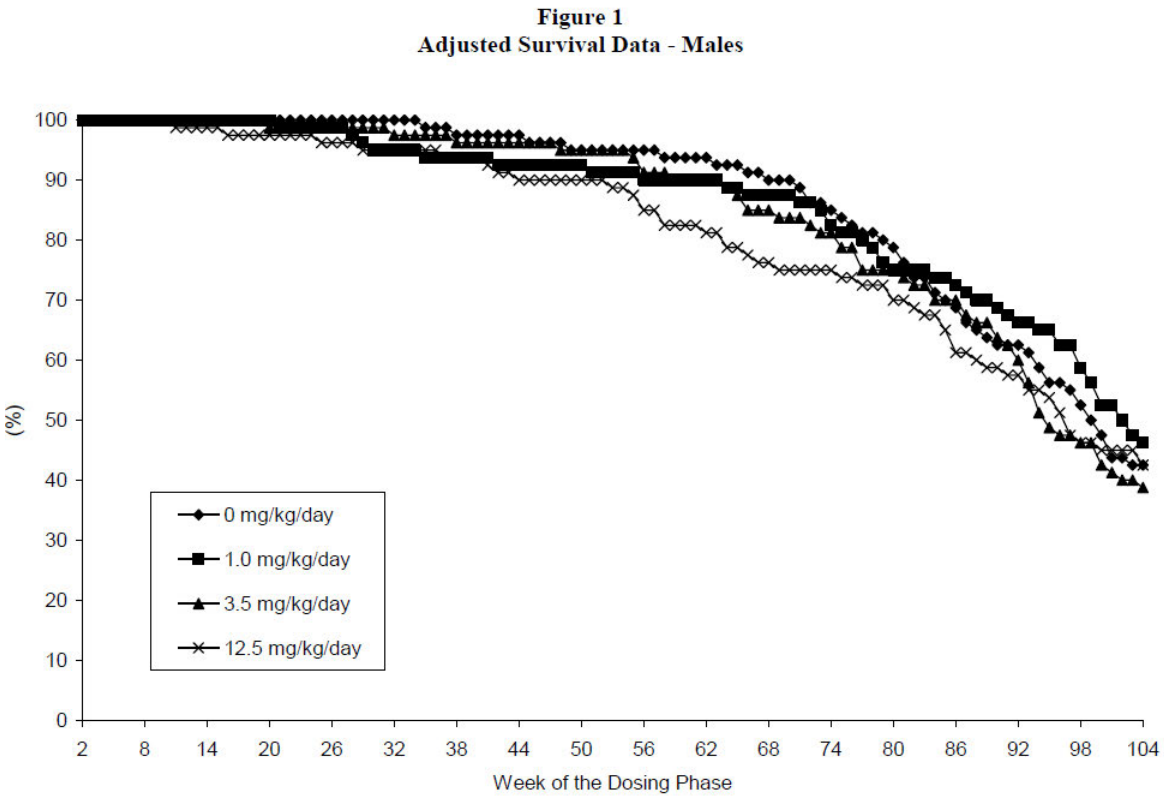
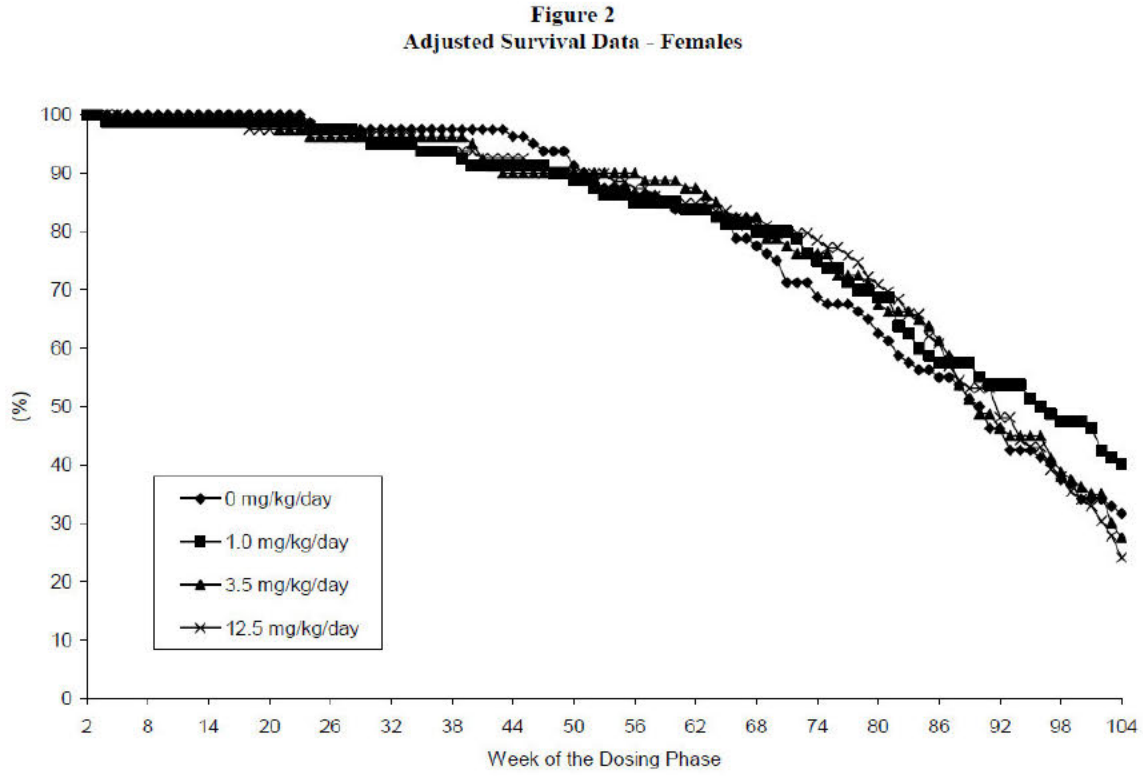


Figure 2: Kaplan-Meier plot of Survival in Female Mice



2.1.2. Tumor data analysis

Incidental tumors were analyzed by logistic regression of tumor prevalence tests. Rapidly lethal and palpable tumors were analyzed in the same manner as survival, using the first palpation time (if applicable) as the tumor onset time. In the cases where the principal investigator for anatomic pathology assigned particular occult neoplastic lesions as the cause of death in the animals, an IARC-type (Peto et al., 1980) of analysis incorporated such information. In the cases of sparse tables, the exact form of the survival-adjusted method of tumor analysis was used.

One-sided positive trends in common (background incidence rate $\geq$ 1%) and rare (background incidence $<$ 1%) tumors (if applicable), as indicated by the concurrent control, historical control from the laboratory or [redacted] (b) (4) recent database, or defined by the principal investigator for anatomic pathology, were evaluated at the 0.01 and 0.05 significance levels, respectively. High-dose and other group comparisons in common and rare tumors were evaluated at the 0.05 significance level (FDA Draft Guidance for Industry, 2001). For the purpose of statistical analysis, the original dose levels were scaled up to 10, 35, and 125 by multiplying them by 10 for Groups 2, 3, and 4, respectively. This scaling did not have any impact on statistical outcomes of the analyses.

Sponsor's findings: The positive trend in the incidence of the gall bladder papillary adenoma in males was not significant for common tumors based on [redacted] (b) (4) (0-1.85%) and [redacted] (b) (4) historical background rates in this strain of mice (1.52 to 5.0%;). The incidence rates at 1.0

and 12.5 mg/kg/day in males were statistically significant for common tumors in this case. On the other hand, administration of 3.5 mg/kg/day in the males did not result in any significant increase, making the trend actually a biphasic response. Such biphasic responses are not common carcinogenic responses in a bioassay. The positive trend in jejunum adenocarcinoma was due solely to a nonsignificant increase at 12.5 mg/kg/day in the males. Significant increases in lung bronchiolar-alveolar adenoma in females given 3.5 or 12.5 mg/kg/day without a significant positive trend for common tumors and the combined incidences of lung bronchiolar-alveolar adenoma and carcinoma with a significant positive trend and increases at the these dose levels for common tumors were probably not indicative of effects of the test article because they only occurred in one sex, increased (but not significant) survival occurred at 12.5 mg/kg/day, and they fall within background data from (b) (4), 1999-2004, (1.8 to 18.6% for adenoma and 1.8 to 8.3% for carcinoma) and (b) (4) (1.67 to 26.67% for adenoma and 0.77 to 18.37% for carcinoma;. Body, whole/cavity histiocytic sarcoma in females did not have any significant increase in any treated group and was actually associated with a significant negative trend ($p = 0.0366$), which was not considered test article-related. No other significant neoplastic effects were noted in females. The effects observed were not dose-dependent, they were considered to be consistent with expected pharmacologic effects of the test article.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform the additional analysis suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all four treatment groups (three treated groups and one control group) were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested using the Cox test (Cox, 1972). The inter-current mortality data are given in Tables 1A and 1B in the appendix for four treatment groups in males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for four treatment groups in males and females, respectively. Results for the tests for dose response relationship and homogeneity of survivals, are given in Tables 2A and 2B in the appendix for the set of one control group with three treated groups in males and females, respectively.

Reviewer's findings: The test results showed no statistically significant dose-response mortality and statistically significant difference in mortality in both females and males when compared with the control group. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships and pair-wise comparisons of each of the control group with each of the treated groups were performed using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). One critical point for Poly-k test is the choice of the appropriate value of k. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values of the tested tumor types are listed in Tables 3A and 3B in the appendix for the combined dual controls with three treated groups in males and females, respectively.

According to pharmacologist request, we have the following tumor combinations in mouse studies:

Mouse:

- Adrenal Cortex adenoma, subcapsular cell adenoma and carcinoma for male mice only.
- Adrenal Cortex subcapsular cell adenoma and carcinoma for female mice only.
- Body whole/cav hemangioma and hemangiosarcoma for female mice only.
- Cervix endometrial stromal polyp and sarcoma for female mice only.
- Duodenum adenoma and adenocarcinoma for female mice only.
- Duodenum and jejum adenocarcinoma
- Duodenum, jejum, ileum, colon and rectum adenocarcinoma
- Liver hepatocellular adenoma and carcinoma for female mice only.
- Lung bronchio-alveolar adenoma and carcinoma.
- Pituitary adenoma and carcinoma for female mice only.
- Uterus granular cell tumor and endometrial stromal polyp and sarcoma for female mice only.

Multiple testing adjustment: Adjustment for the multiple dose response relationship testing was done using the criteria developed by Lin and Rahman (1998). The criteria recommend the use of a significance level α=0.025 for rare tumors and α=0.005 for common tumors for a submission with two species, and a significance level α=0.05 for rare tumors and α=0.01 for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%. A rare tumor is defined as one in which the spontaneous tumor rate is less than 1%. The adjustment for multiple pair-wise comparisons was done using the criteria developed by Haseman (1983) that recommends the use of significance level α=0.05 for rare tumors and α=0.01 for common tumors with two species, and a significance level α=0.10 for rare tumors and α=0.025 for common tumors for a submission with only one species study in order to keep the false-positive rate at the nominal level of approximately 10%.

It should be noted that the recommended test levels by Lin and Rahman for the adjustment of multiple testing were originally based on the result of a simulation and an empirical study using the Peto method for dose response relationship analysis. However, some later simulation results by Rahman and Lin (2008) indicate that the criteria apply equally well to the analysis using the poly-3 test.

The tumor rates and the p-values of the tumor types tested for dose response relationship and pair-wise comparisons of control and treated groups are given in Table 3A and 3B in the appendix for data in males and females, respectively. As suggested by the reviewing pharmacologist Dr. Akinshola.

Reviewer's findings: Following tumor types showed p-values less than or equal to the test levels for multiplicity adjustment either tests for dose response relationship or pair-wise comparisons between control and each of individual treated groups respectively.

Tumor Types with significant findings for Dose Response Relationship or Pair-wise Comparisons (Control, low, medium and high dose groups)

	Organ Name	Tumor Name	Cont N=80	1 mg Low N=80	3.5 mg Med N=80	12.5 mg High N=80	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Male										
	Gallbladder	B-Papillary Adenoma	0	5	2	6	0.025	0.031	0.239	0.010
			[48]	[47]	[44]	[42]	.	.	.	.
	Jejunum	M-Adenocarcinoma	0	1	0	4	0.008	0.509	.	0.051
			[48]	[47]	[43]	[43]	.	.	.	.
	DUODENUM_JEJUM	ADENOCARCINOM	0	3	0	4	0.043	0.311	0.855	0.166
			[48]	[47]	[43]	[43]	.	.	.	.
Female										
	LUNG	BRONCHIOLA_ADENOMA	4	9	13	16	0.012	0.158	0.027	0.006
		+CARCINOMA	[39]	[46]	[49]	[48]	.	.	.	.
		B-Adenoma, Bronchiol	3	5	10	11	0.029	0.402	0.053	0.030
			[38]	[44]	[48]	[46]	.	.	.	.
	PITUITARY	ADENOMA+CARCINOMA	0	1	4	2	0.246	0.520	0.064	0.258
			[38]	[44]	[45]	[44]	.	.	.	.

Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the dose response relationships in the incidence of papillary adenoma in gallbladder, adenocarcinoma in jejunum and combined adenocarcinomas in jejunum and duodenum in male mice were considered to be statistically significant since the p-values were less than 0.05. Also based on the criteria of Haseman, the increased tumor incidences of papillary adenoma of gallbladder and adenocarcinoma of jejunum in high dose group and of papillary adenoma of gallbladder in low dose group in male mice were considered to be statistically significant when compared to the control group because the p-values are less than 0.10. In addition, the increased incidence the combined bronchiola adenoma and carcinoma of lung in high dose group in female mice was considered to be statistically significant when compared to the control group because the p-values are less than 0.025. Also, the increased incidence of the combined adenoma and carcinoma of pituitary in medium dose group in female mice was considered to be statistically significant when compared to the control group because the p-value is less than 0.10.

3. Summary

In this submission, the sponsor included reports of mouse studies. These studies were intended to further assess the carcinogenic potential of the test article, teduglutide (ALX-0600), when administered daily for at least 104 weeks via subcutaneous injection to mice. Teduglutide [ALX-0600; gly2(GLP-2)] is an analog of naturally occurring human glucagon-like peptide-2 (GLP-2), a peptide secreted by L cells primarily of the distal intestine and involved in the regeneration and repair of the intestinal epithelium.

Mouse Study: Male and female Crl:CD1(ICR) mice were assigned to 12 groups and doses were administered once daily via subcutaneous injection, as indicated in the following table. Animals in the control groups received the control article/diluent (phosphate buffer vehicle prepared in Sterile Water for Injection, USP, pH-adjusted to 7.2 to 7.6 with hydrochloric acid and/or sodium hydroxide as necessary) only.
The test results showed no statistically significant dose-response mortality and statistically significant difference in mortality in both females and males when compared with the control group. There were some differences between reviewer's and sponsor's survival rates and the differences may be caused by the different dates of starting the terminal killing.
Based on the criteria of adjustment for multiple testing of trends by Lin and Rahman, the dose response relationships in the incidence of papillary adenoma in gallbladder, adenocarcinoma in jejunum and combined adenocarcinomas in jejunum and duodenum in male mice were considered to be statistically significant since the p-values were less than 0.05. Also based on the criteria of Haseman, the increased tumor incidences of papillary adenoma of gallbladder and adenocarcinoma of jejunum in high dose group and of papillary adenoma of gallbladder in low dose group in male mice were considered to be statistically significant when compared to the control group because the p-values are less than 0.10. In addition, the increased incidence the combined bronchiola adenoma and carcinoma of lung in high dose group in female mice was considered to be statistically significant when compared to the control group because the p-values are less than 0.025. Also, the increased incidence of the combined adenoma and carcinoma of pituitary in medium dose group in female mice was considered to be statistically significant when compared to the control group because the p-value is less than 0.10.

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4. Appendix

Table 1A: Intercurrent Mortality Rate
Male Mice

Week	CONTROL NO.OF DEATH	PERCENT	1.0mg NO.OF DEATH	PERCENT	3.5mg NO.OF DEATH	PERCENT	12.5mg NO.OF DEATH	PERCENT
0-52	4	5.0%	7	8.8%	4	5.0%	8	10.0%
53-78	11	18.8%	10	21.3%	16	25.0%	14	27.5%
79-92	15	37.5%	10	33.8%	12	40.0%	12	42.5%
93-104	16	57.5%	16	53.8%	17	61.3%	12	57.5%
Term. Sac.	34	100.0%	37	100.0%	31	100.0%	34	100.0%

Table 1B: Intercurrent Mortality Rate
Female Mice

Week	CONTROL NO.OF DEATH	PERCENT	1.0mg NO.OF DEATH	PERCENT	3.5mg NO.OF DEATH	PERCENT	12.5mg NO.OF DEATH	PERCENT
0-52	9	11.3%	10	12.5%	8	10.0%	9	11.3%
53-78	18	33.8%	14	30.0%	14	27.5%	12	26.3%
79-92	16	53.8%	13	46.3%	21	53.8%	21	52.5%
93-104	12	68.8%	11	60.0%	15	72.5%	19	76.3%
Term. Sac.	25	100.0%	32	100.0%	22	100.0%	19	100.0%

Table 2A: Intercurrent Mortality Comparison
Male Mice

Test	P-Value (across four groups)	P-Value (Control vs low)	P-Value (Control vs medium)	P-Value (Control vs high)
Dose Response	0.6194	0.7107	0.6693	0.7479
Homogeneity	0.7311	0.6164	0.5757	0.6695

Table 2B: Intercurrent Mortality Comparison
Female Mice

Test	P-Value (across four groups)	P-Value (Control vs low)	P-Value (Control vs medium)	P-Value (Control vs high)
Dose Response	0.3784	0.3733	0.9447	0.7229
Homogeneity	0.4370	0.3122	0.9282	0.6042

Table 3A: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons
Male Mice (Control, low, medium and high dose groups)

Organ Name	Tumor Name	Cont N=80	1 mg Low N=80	3.5 mg Med N=80	12.5 mg High N=80	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL_CORTEX		(80)	(80)	(80)	(80)	.	.	.	.
	ADENOMA+CARCINOMA	6	9	5	6	0.536	0.303	0.705	0.555
		[48]	[48]	[43]	[42]	.	.	.	.
Adrenal, Cortex		(79)	(80)	(80)	(80)	.	.	.	.
	B-Adenoma	2	0	1	0	0.855	1.000	0.868	1.000
		[48]	[47]	[43]	[42]	.	.	.	.
	B-Adenoma, Subcapsular Cell	3	8	4	5	0.404	0.107	0.471	0.310
		[48]	[48]	[43]	[42]	.	.	.	.
	M-Carcinoma, Subcapsular C	1	1	1	2	0.224	0.756	0.739	0.460
		[48]	[47]	[43]	[42]	.	.	.	.
Adrenal, Medull		(79)	(79)	(80)	(79)	.	.	.	.
	B-Pheochromocytoma	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[47]	[43]	[42]	.	.	.	.
Body, Whole/Cav		(80)	(80)	(80)	(80)	.	.	.	.
	B-Hemangioma	3	3	1	0	0.978	0.668	0.934	1.000
		[48]	[47]	[43]	[42]	.	.	.	.
	M-Fibrous Histiosarcoma	1	0	1	0	0.723	1.000	0.739	1.000
		[48]	[47]	[43]	[42]	.	.	.	.
	M-Hemangiosarcoma	2	5	8	5	0.234	0.234	0.053	0.198
		[48]	[48]	[47]	[43]	.	.	.	.
	M-Histiocytic Sarcoma	4	6	1	4	0.506	0.372	0.966	0.581
		[49]	[48]	[43]	[43]	.	.	.	.
	M-Lymphosarcoma	11	7	8	9	0.411	0.912	0.821	0.714
		[50]	[50]	[45]	[45]	.	.	.	.
Brain		(80)	(80)	(80)	(80)	.	.	.	.
	B-Ependymoma	0	1	0	0	0.733	0.509	.	.
		[48]	[47]	[43]	[42]	.	.	.	.
	M-Meningeal Sarcoma	0	0	0	1	0.238	.	.	0.482
		[48]	[47]	[43]	[43]	.	.	.	.
Duodenum		(70)	(69)	(71)	(66)	.	.	.	.
	M-Adenocarcinoma	0	2	0	1	0.403	0.256	.	0.478
		[48]	[47]	[43]	[42]	.	.	.	.
Epididymis		(80)	(80)	(80)	(80)	.	.	.	.
	B-Interstitial Cell Tumor	0	1	0	0	0.733	0.509	.	.
		[48]	[47]	[43]	[42]	.	.	.	.
	B-Schwannoma	0	0	1	0	0.472	.	0.491	.
		[48]	[47]	[43]	[42]	.	.	.	.

Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Control, low, medium and high dose groups)

Organ Name	Tumor Name	Cont N=80	1 mg Low N=80	3.5 mg Med N=80	12.5 mg High N=80	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Gallbladder		(66)	(71)	(70)	(70)	.	.	.	.
	B-Papillary Adenoma	0	5	2	6	0.025	0.031	0.239	0.010
		[48]	[47]	[44]	[42]	.	.	.	.
Gl, Harderian		(80)	(80)	(80)	(80)	.	.	.	.
	B-Adenoma	10	6	8	7	0.508	0.911	0.754	0.781
		[50]	[48]	[46]	[42]	.	.	.	.
Jejunum		(68)	(69)	(73)	(68)	.	.	.	.
	M-Adenocarcinoma	0	1	0	4	0.008	0.509	.	0.051
		[48]	[47]	[43]	[43]	.	.	.	.
DUODENUM_JEJUM		(65)	(64)	(69)	(64)	.	.	.	.
	ADENOCARCINOM	0	3	0	4	0.043	0.311	0.855	0.166
		[48]	[47]	[43]	[43]	.	.	.	.
Kidney		(80)	(80)	(80)	(80)	.	.	.	.
	B-Adenoma, Tubule Cell	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[47]	[43]	[42]	.	.	.	.
	B-Lipoma	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[47]	[43]	[42]	.	.	.	.
	M-Carcinoma, Tubule Cell	0	1	0	0	0.733	0.509	.	.
		[48]	[47]	[43]	[42]	.	.	.	.
LUNG		(80)	(80)	(80)	(80)	.	.	.	.
	CARCINOMA+ADENOMA	27	24	22	16	0.950	0.693	0.770	0.960
		[54]	[50]	[48]	[46]	.	.	.	.
Liver		(80)	(80)	(80)	(80)	.	.	.	.
	B-Adenoma, Hepatocellular	32	14	10	13	0.971	1.000	1.000	0.999
		[53]	[48]	[45]	[43]	.	.	.	.
	B-Ito Cell Tumor	0	0	0	1	0.233	.	.	0.478
		[48]	[47]	[43]	[42]	.	.	.	.
	M-Carcinoma, Hepatocellular	7	5	10	7	0.361	0.827	0.287	0.571
		[49]	[48]	[45]	[45]	.	.	.	.
	M-Cholangiocarcinoma	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[47]	[43]	[42]	.	.	.	.
Lung		(80)	(80)	(80)	(80)	.	.	.	.
	B-Adenoma, Bronchiolar-Alveo	15	16	17	12	0.678	0.479	0.356	0.699
		[51]	[49]	[47]	[44]	.	.	.	.
	M-Carcinoma, Bronchiolar-Alv	13	9	5	4	0.978	0.872	0.984	0.992
		[51]	[49]	[44]	[44]	.	.	.	.

Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Control, low, medium and high dose groups)

Organ Name	Tumor Name	Cont N=80	1 mg Low N=80	3.5 mg Med N=80	12.5 mg High N=80	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Nasal Turbinate		(80)	(80)	(79)	(80)	.	.	.	.
	M-Carcinoma	0	0	1	0	0.475	.	0.496	.
		[48]	[47]	[44]	[42]	.	.	.	.
Pancreas		(80)	(80)	(80)	(80)	.	.	.	.
	B-Adenoma, Islet Cell	1	1	0	0	0.930	0.756	1.000	1.000
		[48]	[47]	[43]	[42]	.	.	.	.
Pituitary		(80)	(80)	(80)	(78)	.	.	.	.
	B-Adenoma	0	1	0	0	0.733	0.509	.	.
		[48]	[47]	[43]	[42]	.	.	.	.
Prostate		(79)	(79)	(80)	(80)	.	.	.	.
	M-Carcinoma	2	0	0	0	1.000	1.000	1.000	1.000
		[48]	[47]	[43]	[42]	.	.	.	.
Seminal Vesicle		(80)	(80)	(80)	(80)	.	.	.	.
	M-Leiomyosarcoma	0	0	0	1	0.233	.	.	0.478
		[48]	[47]	[43]	[42]	.	.	.	.
Skin/SubQ, Othe		(80)	(80)	(79)	(80)	.	.	.	.
	M-Fibrosarcoma	0	0	1	0	0.475	.	0.491	.
		[48]	[47]	[44]	[42]	.	.	.	.
Skin/Subcutis		(80)	(80)	(79)	(79)	.	.	.	.
	M-Fibrosarcoma	2	0	1	0	0.858	1.000	0.868	1.000
		[48]	[47]	[44]	[42]	.	.	.	.
Spinal Cord		(80)	(80)	(80)	(80)	.	.	.	.
	B-Astrocytoma	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[47]	[43]	[42]	.	.	.	.
Stomach, Gl		(76)	(76)	(78)	(72)	.	.	.	.
	B-Adenoma	0	1	0	0	0.735	0.509	.	.
		[48]	[48]	[43]	[42]	.	.	.	.
Subcutan Site B		(80)	(80)	(80)	(80)	.	.	.	.
	B-Mast Cell Tumor	0	0	0	1	0.233	.	.	0.478
		[48]	[47]	[43]	[42]	.	.	.	.
Testis		(80)	(79)	(80)	(80)	.	.	.	.
	B-Interstitial Cell Tumor	2	6	5	4	0.381	0.153	0.205	0.306
		[48]	[48]	[43]	[42]	.	.	.	.
	B-Sertoli Cell Tumor	0	0	0	1	0.233	.	.	0.478
		[48]	[47]	[43]	[42]	.	.	.	.
	M-Interstitial Cell Tumor	1	0	0	0	1.000	1.000	1.000	1.000
		[48]	[47]	[43]	[42]	.	.	.	.

Table 3A Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Male Mice (Control, low, medium and high dose groups)

Organ Name	Tumor Name	Cont N=80	1 mg Low N=80	3.5 mg Med N=80	12.5 mg High N=80	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Thymus		(62)	(69)	(71)	(74)	.	.	.	.
	M-Leiomyosarcoma	0	0	0	1	0.233	.	.	0.478
		[48]	[47]	[43]	[42]	.	.	.	.
Thyroid		(80)	(80)	(80)	(80)	.	.	.	.
	B-Adenoma, Follicular Cell	0	1	0	1	0.288	0.509	.	0.478
		[48]	[47]	[43]	[42]	.	.	.	.

Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Mice (Control, low, medium and high dose groups)

Organ Name	Tumor Name	Cont N=80	1 mg Low N=80	3.5 mg Med N=80	12.5 mg High N=80	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
ADRENAL_CORTEX		(80)	(80)	(80)	(80)	.	.	.	.
	CARCINOMA+ADENOMA	3	1	2	1	0.780	0.948	0.825	0.941
		[38]	[44]	[44]	[43]	.	.	.	.
Adrenal, Cortex		(80)	(80)	(79)	(79)	.	.	.	.
	B-Adenoma, Subcapsular Cell	2	0	0	1	0.588	1.000	1.000	0.879
		[38]	[44]	[44]	[43]	.	.	.	.
	M-Carcinoma, Subcapsular C	1	1	2	0	0.808	0.772	0.515	1.000
		[38]	[44]	[44]	[43]	.	.	.	.
Adrenal, Medull		(80)	(80)	(79)	(78)	.	.	.	.
	B-Pheochromocytoma	0	0	0	1	0.254	.	.	0.505
		[38]	[44]	[44]	[43]	.	.	.	.
Body, Whole/Cav		(80)	(80)	(80)	(80)	.	.	.	.
	B-Fibrous Histiocytoma	0	0	0	1	0.254	.	.	0.505
		[38]	[44]	[44]	[43]	.	.	.	.
	B-Hemangioma	2	3	3	3	0.426	0.538	0.538	0.528
		[38]	[44]	[47]	[44]	.	.	.	.
	M-Fibrous Histiosarcoma	0	1	1	0	0.648	0.520	0.510	.
		[38]	[44]	[44]	[43]	.	.	.	.
	M-Hemangiosarcoma	5	2	4	3	0.658	0.953	0.776	0.872
		[39]	[44]	[45]	[44]	.	.	.	.
	M-Histiocytic Sarcoma	12	16	11	6	0.986	0.353	0.681	0.959
		[42]	[48]	[47]	[44]	.	.	.	.
	M-Leukemia, Granulocytic	0	0	1	0	0.518	.	0.510	.
		[38]	[44]	[45]	[43]	.	.	.	.
	M-Lymphosarcoma	29	33	27	32	0.437	0.397	0.769	0.392
		[46]	[51]	[52]	[50]	.	.	.	.
Bone, Femur		(80)	(79)	(79)	(79)	.	.	.	.
	B-Osteoma	0	0	0	1	0.254	.	.	0.505
		[38]	[44]	[44]	[43]	.	.	.	.
Brain		(80)	(80)	(79)	(80)	.	.	.	.
	M-Malignant Astrocytoma	0	1	0	0	0.777	0.524	.	.
		[38]	[45]	[44]	[43]	.	.	.	.
CERVIX		(80)	(80)	(80)	(80)	.	.	.	.
	ENDOMETRIAL_STROMAL_POLYP+SAR	4	6	4	2	0.901	0.420	0.674	0.898
		[39]	[46]	[47]	[43]	.	.	.	.
Cervix		(80)	(79)	(79)	(79)	.	.	.	.
	B-Leiomyoma	0	1	0	1	0.330	0.520	.	0.505
		[38]	[44]	[44]	[43]	.	.	.	.

Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Mice (Control, low, medium and high dose groups)

Organ Name	Tumor Name	Cont N=80	1 mg Low N=80	3.5 mg Med N=80	12.5 mg High N=80	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
	B-Polyp, Endometrial Stromal	3	2	1	0	0.982	0.830	0.944	1.000
		[39]	[44]	[45]	[43]	.	.	.	.
	M-Sarcoma, Endometrial Strom	1	4	3	2	0.576	0.220	0.339	0.515
		[38]	[46]	[46]	[43]	.	.	.	.
DUODENUM		(80)	(80)	(80)	(80)	.	.	.	.
	ADENOMA+ADENOCARCINOMA	2	1	2	1	0.671	0.893	0.714	0.886
		[38]	[44]	[45]	[43]	.	.	.	.
Duodenum		(73)	(69)	(71)	(67)	.	.	.	.
	B-Adenoma	0	0	1	1	0.198	.	0.515	0.510
		[38]	[44]	[45]	[43]	.	.	.	.
	M-Adenocarcinoma	2	1	1	0	0.935	0.893	0.886	1.000
		[38]	[44]	[44]	[43]	.	.	.	.
Gallbladder		(69)	(69)	(70)	(68)	.	.	.	.
	B-Leiomyoma	1	0	0	0	1.000	1.000	1.000	1.000
		[38]	[44]	[44]	[43]	.	.	.	.
	B-Papillary Adenoma	0	1	3	0	0.715	0.520	0.129	.
		[38]	[44]	[45]	[43]	.	.	.	.
Gl, Harderian		(80)	(80)	(79)	(80)	.	.	.	.
	B-Adenoma	6	1	5	5	0.342	0.995	0.760	0.738
		[39]	[44]	[45]	[43]	.	.	.	.
Gl, Zymbal's		(80)	(80)	(80)	(80)	.	.	.	.
	M-Carcinoma	0	0	0	1	0.254	.	.	0.510
		[38]	[44]	[44]	[43]	.	.	.	.
Jejunum		(69)	(69)	(68)	(69)	.	.	.	.
	M-Adenocarcinoma	0	0	0	1	0.254	.	.	0.510
		[38]	[44]	[44]	[43]	.	.	.	.
DUODENUM_JEJUM		(56)	(50)	(54)	(50)	.	.	.	.
	ADENOCARCINOM	2	1	2	2	0.423	0.526	0.587	0.380
		[38]	[44]	[45]	[43]	.	.	.	.
Kidney		(80)	(80)	(79)	(80)	.	.	.	.
	B-Schwannoma	0	1	0	0	0.775	0.520	.	.
		[38]	[44]	[44]	[43]	.	.	.	.
LIVER		(80)	(80)	(80)	(80)	.	.	.	.
	HEPATOCELLULAR_ADENOMA+CARCIN	1	0	2	0	0.703	1.000	0.515	1.000
		[38]	[44]	[44]	[43]	.	.	.	.

Table 3B Continued: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Mice (Control, low, medium and high dose groups)

Organ Name	Tumor Name	Cont N=80	1 mg Low N=80	3.5 mg Med N=80	12.5 mg High N=80	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
LUNG		(80)	(80)	(80)	(80)	.	.	.	.
	BRONCHIOLA_ADENOMA+CARCINOMA	4	9	13	16	0.012	0.158	0.027	0.006
		[39]	[46]	[49]	[48]	.	.	.	.
Liver		(80)	(80)	(79)	(80)	.	.	.	.
	B-Adenoma, Hepatocellular	1	0	1	0	0.766	1.000	0.762	1.000
		[38]	[44]	[44]	[43]	.	.	.	.
	M-Carcinoma, Hepatocellular	0	0	1	0	0.515	.	0.510	.
		[38]	[44]	[44]	[43]	.	.	.	.
Lung		(80)	(80)	(79)	(80)	.	.	.	.
	B-Adenoma, Bronchiolar-Alveo	3	5	10	11	0.029	0.402	0.053	0.030
		[38]	[44]	[48]	[46]	.	.	.	.
Lung	M-Carcinoma, Bronchiolar-Alv	1	4	3	6	0.069	0.206	0.316	0.062
		[38]	[45]	[45]	[45]	.	.	.	.
Mammary, Female		(63)	(63)	(64)	(61)	.	.	.	.
	M-Carcinoma	4	0	0	1	0.794	1.000	1.000	0.972
		[39]	[44]	[44]	[43]	.	.	.	.
Ovary		(79)	(80)	(79)	(79)	.	.	.	.
	B-Cystadenoma	1	4	4	2	0.609	0.207	0.200	0.515
		[38]	[44]	[45]	[43]	.	.	.	.
	B-Granulosa/Theca Cell Tumor	1	0	1	3	0.067	1.000	0.762	0.316
		[38]	[44]	[44]	[43]	.	.	.	.
	B-Luteoma	0	0	0	2	0.064	.	.	0.253
		[38]	[44]	[44]	[43]	.	.	.	.
PITUITARY		(80)	(80)	(80)	(80)	.	.	.	.
	ADENOMA+CARCINOMA	0	1	4	2	0.246	0.520	0.064	0.258
		[38]	[44]	[45]	[44]	.	.	.	.
Pancreas		(78)	(80)	(78)	(80)	.	.	.	.
	B-Adenoma, Islet Cell	0	0	1	0	0.518	.	0.510	.
		[38]	[44]	[45]	[43]	.	.	.	.
	M-Carcinoma, Duct	0	0	1	0	0.515	.	0.510	.
		[38]	[44]	[44]	[43]	.	.	.	.
Pituitary		(80)	(79)	(78)	(80)	.	.	.	.
	B-Adenoma	0	1	3	2	0.202	0.520	0.129	0.258
		[38]	[44]	[44]	[44]	.	.	.	.
	M-Carcinoma	0	0	1	0	0.518	.	0.510	.
		[38]	[44]	[45]	[43]	.	.	.	.

Table 3B: Tumor Rates and P-Values for Dose Response Relationship and Pair-wise Comparisons Female Mice (Control, low, medium and high dose groups)

Organ Name	Tumor Name	Cont N=80	1 mg Low N=80	3.5 mg Med N=80	12.5 mg High N=80	P_Value Dos Resp	P_Value C vs. L	P_Value C vs. M	P_Value C vs. H
Skin/SubQ, Othe		(79)	(80)	(80)	(80)	.	.	.	.
	B-Papilloma, Squamous Cell	1	0	0	0	1.000	1.000	1.000	1.000
		[38]	[44]	[44]	[43]	.	.	.	.
	M-Fibrosarcoma	0	1	0	1	0.330	0.520	.	0.510
		[38]	[44]	[44]	[43]	.	.	.	.
Skin/Subcutis		(79)	(78)	(78)	(79)	.	.	.	.
	M-Fibrosarcoma	0	0	0	1	0.254	.	.	0.510
		[38]	[44]	[44]	[43]	.	.	.	.
Stomach, Nongl		(77)	(79)	(78)	(77)	.	.	.	.
	M-Carcinoma, Squamous Cell	1	0	0	0	1.000	1.000	1.000	1.000
		[38]	[44]	[44]	[43]	.	.	.	.
Thyroid		(80)	(80)	(79)	(80)	.	.	.	.
	B-Adenoma, Follicular Cell	0	0	3	2	0.115	.	0.129	0.258
		[38]	[44]	[45]	[43]	.	.	.	.
UTERUS		(80)	(80)	(79)	(80)	.	.	.	.
	ENDOMATRIAL_ADENOMA+CARCINOMA	7	4	7	6	0.501	0.926	0.643	0.748
		[39]	[46]	[45]	[44]	.	.	.	.
	B-Adenoma	1	0	0	0	1.000	1.000	1.000	1.000
		[38]	[44]	[44]	[43]	.	.	.	.
	B-Granular Cell Tumor	0	1	1	1	0.316	0.520	0.510	0.510
		[38]	[44]	[44]	[43]	.	.	.	.
	B-Leiomyoma	1	0	3	1	0.425	1.000	0.324	0.758
		[38]	[44]	[44]	[43]	.	.	.	.
	B-Polyp, Endometrial Stromal	4	3	6	1	0.921	0.820	0.409	0.973
		[38]	[45]	[45]	[43]	.	.	.	.
	B-Vasc Neopl- See Body Whole	0	0	1	1	0.198	.	0.515	0.510
		[38]	[44]	[45]	[43]	.	.	.	.
	M-Adenocarcinoma	0	0	0	1	0.254	.	.	0.510
		[38]	[44]	[44]	[43]	.	.	.	.
	M-Leiomyosarcoma	0	1	2	1	0.339	0.520	0.258	0.505
		[38]	[44]	[45]	[43]	.	.	.	.
	M-Sarcoma, Endometrial Strom	3	0	0	4	0.071	1.000	1.000	0.511
		[39]	[44]	[44]	[43]	.	.	.	.
WHOLE/CAV_BODY		(80)	(80)	(80)	(80)	.	.	.	.
	HEMANGIOMA+HEMANGISARCOMA	7	5	7	6	0.590	0.856	0.671	0.760
		[39]	[44]	[48]	[45]	.	.	.	

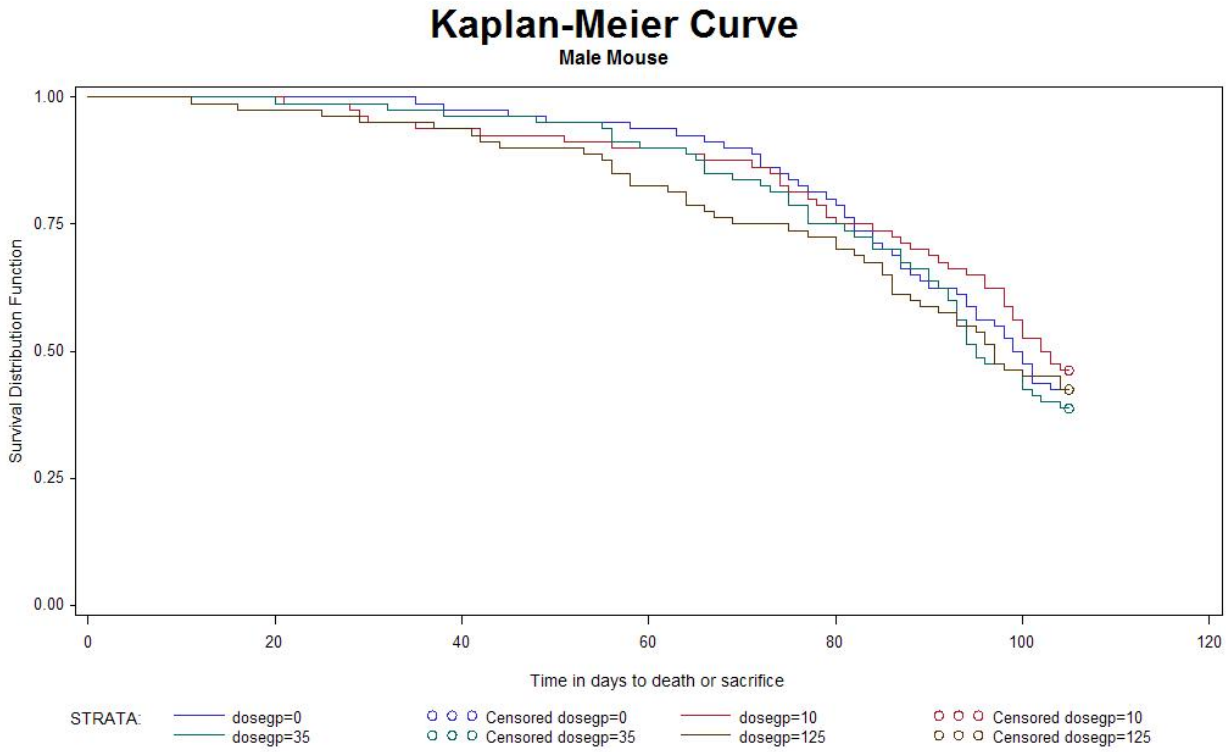
Numbers with parentheses are number of the animals with organs examined and also usable

Numbers with brackets are survival-adjusted group size

Numbers are the tumor bearing animals

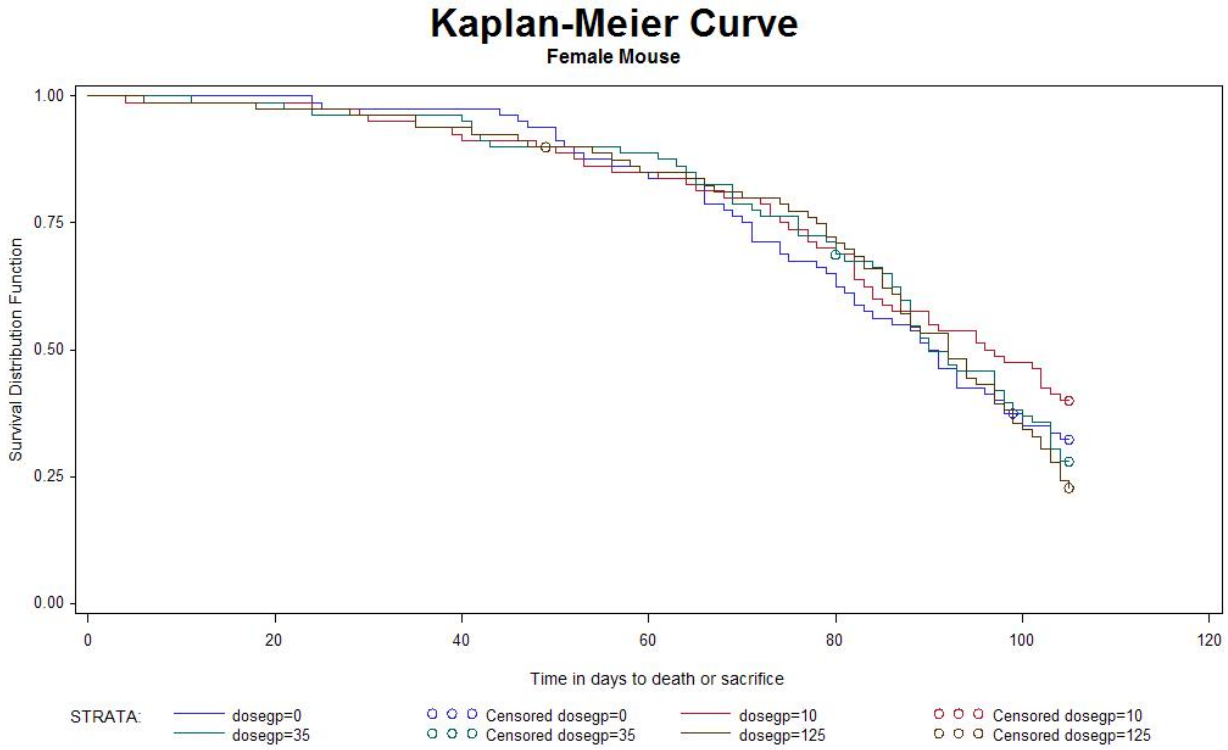
Figure 1A: Kaplan-Meier Survival Functions for Male Mice

Male Mice (Control, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Mice
Female Mice (Control, low, medium and high dose groups)



X-Axis: Weeks, Y-Axis: Survival rates

5. References:

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/s/

MIN MIN
04/17/2014

KARL K LIN
04/18/2014
Concur with review

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 203441 S002	Applicant: NPS Pharmaceuticals, Inc.	Stamp Date: 28AUG2013
Drug Name: GATTEX® (teduglutide) 0.05 mg/kg/day powder for subcutaneous injection	NDA Type: 505(b)(1) NDA Efficacy Supplement SE8 Standard	Indication: The treatment of adult patients with Short Bowel Syndrome (SBS)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter for RTF	Yes	No	NA	Comments
1	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			This electronic submission was eCTD compliant and satisfactory.
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			X	The complete clinical study report (CSR) for Study CL-0600-021 submitted was adequate and ICH E3 compliant. There was no formal ISS or ISE report submitted because no new clinical trials were conducted.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups (if applicable).			X	No subgroup analyses for gender, race and age were presented because no new clinical trials were conducted.
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).		X		Analysis datasets provided for Study CL-0600-021 were satisfactory but were in legacy format and hence not compliant with any established data standards. An appropriate data definition file in Define.PDF format was included for the analysis datasets. The clinical datasets and corresponding data definition file were not submitted for Study CL-0600-021

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____YES____

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.			X	There were no studies identified as pivotal studies in this submission. The only clinical study submitted was a completed open-label extension study (CL-0600-021) which was previously ongoing at the time of the original NDA submission.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			Analysis methods (descriptive statistics) were specified in the submitted protocol and Statistical Analysis Plan (SAP) for the open-label extension study (CL-0600-021).
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	There were no interim analyses planned or conducted.
Appropriate references for novel statistical methodology (if present) are included.			X	Only descriptive statistical analyses were conducted, and hence no references were presented.
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			Updated safety datasets were submitted for the open-label extension study (CL-0600-021). Updated ISE and ISS datasets were also submitted.
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	Investigations of the effects of dropouts are not applicable for this open-label extension study (CL-0600-021). All descriptive analyses were based on observed-case data.

Reviewer's comment

The clinical information submitted is for an open-label extension study (CL-0600-021), whose interim results were reviewed during the original NDA review cycle. There are no pivotal studies in this submission for efficacy review, but only for labeling updates. The submitted study results present descriptive statistics only as no inferential statistical analyses were planned for this study. This application is designated as 'No Action Indicated' (NAI) for a formal statistical review at this time. However, this statistical reviewer will assist the clinical team as needed.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Review Issues

Please submit the clinical datasets and corresponding data definition file for Study CL-0600-021.

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/s/

BEHRANG VALI
10/17/2013

FREDA COONER
10/17/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203441/S-002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW AMENDMENT

NDA	203441 (SDN 113)
Original Submission Dates	Stamp (8/28/2013)
PDUFA Due Date	6/28/2014
Brand Name	Gattex
Generic Name	Teduglutide
Primary Reviewer	Lin Zhou, Ph.D
Secondary Reviewer	Yow-Ming Wang, Ph.D.
OCP Division	DCP III
OND Division	DGIEP
Sponsor	NPS Pharmaceuticals
Relevant IND(s)	58,213
Submission Type	Efficacy Supplement
Formulation; Strength(s)	Lyophilized powder; 5 mg/vial to be reconstituted with 0.5 mL s injection
Proposed indication	Treatment of Short Bowel Syndrome (SBS)
Proposed Dosage and Administration	0.05 mg/kg subcutaneous (SC) injection once daily, altering sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms.

This review amendment is to document the rationale for numbers reported in the Section 6.2 Immunogenicity of the labeling of Gattex® approved on 06/26/2014.

Table 1. Number of subjects who tested positive for anti-teduglutide antibodies at completion of the extension trial (Study CL0600-021)

	Enrolled	Duration on Treatment (months)								
Cohorts	N = 87	0	3	6	9	12	15	18	24	30
TED/TED	n = 37		0/16	6/34	4/34	8/33	8/32	12/34	n/a	14/29
(PBO or NT)/TED	n = 50	0/50	2/44	7/40	8/39	10/38	n/a	n/a	10/32	n/a
Sum			2/60	13/74		18/71			10/32	14/29

TED: teduglutide treated; PBO: placebo; NT: not treated.

Table 2. Subjects who are considered true negative for neutralizing antibodies (Nab) [Definition of true negative: All samples were tested negative for Nab and had drug concentration less than 1.5 ng/mL.]

Number	Study	Subject
1	CL0600-021	0138-1003
2		0138-1005
3		0138-1007
4		0155-1004
5		0155-1007
6		0203-1002
7		0204-1002
8		0212-1003
9		0219-1004

Table 3. Subjects who are considered inconclusive for neutralizing antibodies [Definition of inconclusive: All samples were tested negative for Nab and at least one of the samples had drug concentration either unknown or greater than 1.5 ng/mL.]

Number	Study	Subject
1	CL0600-020	0132-1001
2		0211-1001
3	CL0600-021	0106-1003
4		0109-1004
5		0111-1002
6		0135-1001
7		0135-1007
8		0138-1002
9		0138-1004
10		0138-1009
11		0144-1005
12		0144-1006
13		0147-1001
14		0147-1003
15		0155-1001
16		0155-1002
17		0201-1003
18		0203-1003
19		0207-1003
20		0210-1002
21		0210-1004
22		0214-1001
23		0214-1003
24		0218-1001
25		0219-1002
26		0219-1007
27		0219-1010

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/s/

LIN ZHOU
08/01/2014

YOW-MING C WANG
08/01/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	203441 (SDN 113)
Original Submission Dates	Stamp (8/28/2013)
PDUFA Due Date	6/28/2014
Brand Name	Gattex
Generic Name	Teduglutide
Primary Reviewer	Lanyan Fang, Ph.D.; Lin Zhou, Ph.D
Secondary Reviewer	Yow-Ming Wang, Ph.D.
OCP Division	DCP III
OND Division	DGIEP
Sponsor	NPS Pharmaceuticals
Relevant IND(s)	58,213
Submission Type	Efficacy Supplement
Formulation; Strength(s)	Lyophilized powder; 5 mg/vial to be reconstituted with 0.5 water for injection
Proposed indication	Treatment of Short Bowel Syndrome (SBS)
Proposed Dosage and Administration	0.05 mg/kg subcutaneous (SC) injection once daily, altering sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms.

1 EXECUTIVE SUMMARY

GATTEX® (teduglutide [rDNA origin]) was approved on 12/21/2012. It is a 33-amino acid recombinant analog of the human glucagon-like peptide-2 (GLP-2) which is a peptide secreted primarily from the lower gastrointestinal tract.

The current submission is an efficacy supplement. The applicant intends to update the currently approved product label and REMS based on the final reports from the following studies:

- A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome (CL0600-021, Up to 2 years). Study CL0600-021 is the extension study to Study CL0600-020, which is one of the pivotal Phase 3 trials in the original NDA submission.
- 104-Week Subcutaneous Injection Carcinogenicity Study with Teduglutide (ALX-0600) in Mice (P09-002)

The applicant proposed to update Sections *Clinical Trials Experience, Adverse Reactions of Special Interest, Immunogenicity, Geriatric Use, and Clinical Studies* in the GATTEX® label, based on the long-term safety results from Study CL0600-021. In addition, the applicant proposed to update Section *Carcinogenesis, Mutagenesis, Impairment of Fertility* based on the results from nonclinical Study P09-002.

This clinical pharmacology reviews the data from Study CL0600-021 for the assessment of the long term immunogenicity incidence and its impact on PK, efficacy, and safety.

1.1 Recommendation

From a clinical pharmacology perspective, the information submitted to support this efficacy supplement is acceptable provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

1.2 Post-Marketing Requirements

There are no post-marketing requirements for this submission.

1.3 Post-Marketing Commitments

There are no post-marketing commitments for this submission.

1.4 Summary of Clinical Pharmacology Findings

Based on the combined immunogenicity data from Studies -020 and -021, the immunogenicity incidence over time was 0% (0/89) at baseline, 3% (2/60) at Month 3, 18% (13/74) at Month 6, 25% (18/71) at Month 12, 31% (10/32) at Month 24, and 48% (14/29) at Month 30 in subjects who received subcutaneous administration of 0.05 mg/kg GATTEX once daily (Table 1).

ADA appears to have no impact on PK and clinical efficacy and safety based on data in subjects treated with Gattex for up to 2.5 years whereas the longer term impact is unknown.

In Studies -020 and -021, a total of 37 subjects were tested for neutralizing antibodies − 17 of these subjects had no neutralizing antibodies, and the remaining 20 subjects had no detectable neutralizing antibodies although the presence of teduglutide at low levels in these study samples could have resulted in false negatives (no neutralizing antibody detected although present).

This summary also serves as the clinical pharmacology labeling recommendation for Section 6.2 Immunogenicity.

2. Review of Study CL0600-021

Study Design

Study CL0600-021 is an extension study to Study CL0600-020 which is a 24-week Phase 3 efficacy and safety trial included in the original NDA submission. The objective of Study CL0600-021 was to investigate long-term safety and efficacy of teduglutide in adult patients with SBS, who need parenteral support (PN/I.V.) to supplement nutrition.

In Study CL0600-21 the duration of treatment was for a period of up to 2 years per subject or, if shorter, until registration and availability of teduglutide on the market in the countries of study

participation. Subjects who received continued treatment of teduglutide in Study CL0600-020 and Study CL0600-021 can have treatment duration of up to 2.5 years (30 months).

A total of 88 subjects received daily 0.05 mg/kg teduglutide (TED) treatment in Study CL0600-021, where these subjects were classified into three different groups based on their treatment history in Study CL0600-020:

- NT/TED group: 12 subjects were screened but not randomized (i.e., not treated, NT) in Study CL0600-020,
- PBO/TED group: 39 subjects were treated with placebo (PBO) in Study CL0600-020
- TED/TED group: 37 subjects treated with teduglutide in Studies CL0600-020

Sixty-five of the 88 subjects (73.9%) completed the entire 24 months of the study. Twenty-three (26.1%) of the 88 subjects who were enrolled discontinued treatment. The reasons for discontinuation included subject decision (4/88 [4.5%]), investigator decision (2/88 [2.3%]), death (1/88 [1.1%]), and adverse events (AEs), both treatment-emergent (TEAEs) and non-TEAE (16/88 [18.2%]).

Evaluations

Efficacy: Data on the PN/I.V. volume (actual volume, L/week) were collected at baseline, 2 weeks, 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 months (or Early Termination).

The key efficacy parameters evaluated were:

- Percent and absolute change in weekly PN/I.V. volume by visit
- Binary response status by visit, where response at a given visit was defined as the achievement of at least a 20% reduction from baseline in weekly PN/I.V. volume, with additional binary response status variables based on 50% reduction, 75% reduction, and 100% reduction from baseline in weekly PN/I.V. volume, based on subject diary data
- Duration of response
- Subjects weaned off PN/I.V. and time of weaning
- Change in days of weekly PN/I.V.
- Categorical reduction in days of weekly PN/I.V.
- Binary response by visit based on prescribed weekly PN/I.V. volume

The exploratory efficacy parameters evaluated were:

- Percent and absolute change in prescribed weekly PN/I.V. volume
- Reduction from baseline of at least 20% in prescribed weekly PN/I.V. volume
- Fluid composite balance
- Change from baseline in plasma citrulline

Quality of Life: Subjects' quality of life (QoL) was evaluated by using a subject-reported outcome SBS specific QoL scale at baseline, Month 3, 6, 12, 18, and 24 (or Early Termination).

Safety: Adverse events, 12-lead electrocardiogram, vital signs, laboratory safety data, and changes in urine output and body weight were evaluated. Colonoscopy was performed at the end of the study.

Pharmacokinetics: Plasma teduglutide levels were measured at 0 h (within 60 minutes prior to dose) and at 2.5 and 5 hours (±30 minutes) post-dose at Month 18 and 24 or early termination.

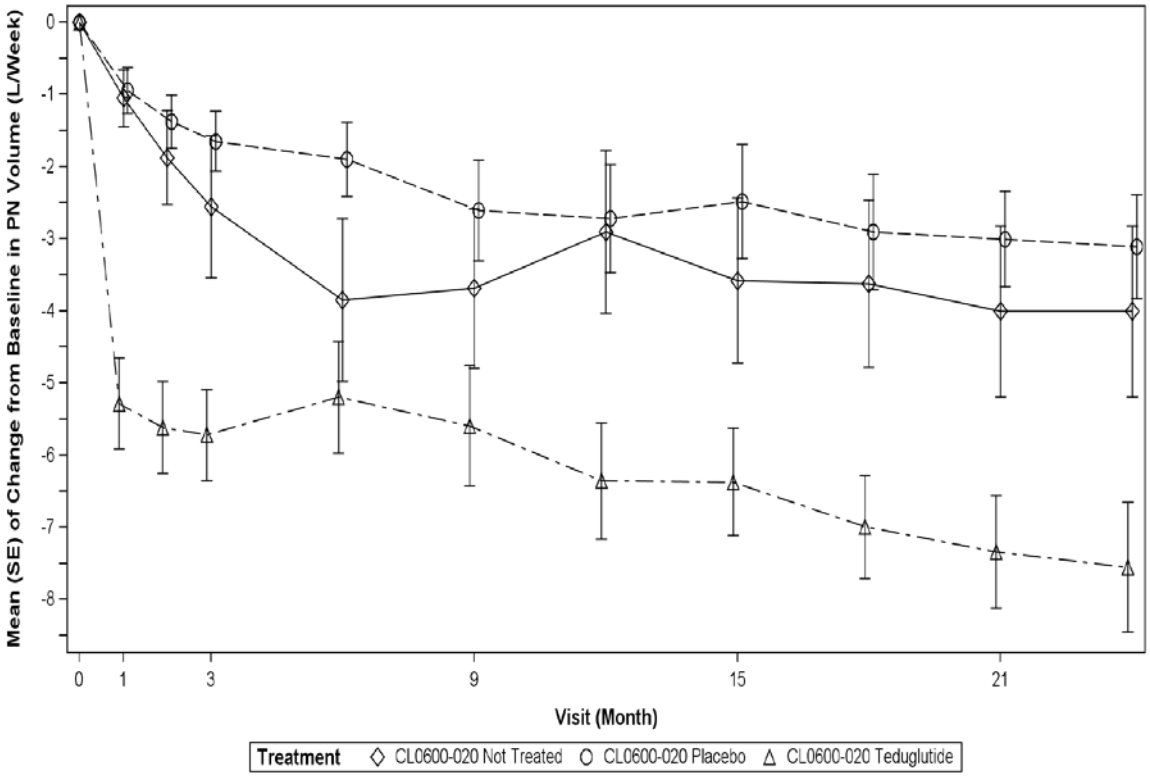
Immunogenicity: Blood samples for antibodies to teduglutide and/or ECP were drawn at baseline, Month 3, 6, 9, 12, 18 and 24 or early termination.

Results

Efficacy:

The efficacy of teduglutide increased over time in all groups exposed to teduglutide in terms of PN/I.V. volume reduction (Figure 1). The greatest reductions were in subjects who received continuous teduglutide treatment for 30 months. Please refer to the clinical review for more details on the efficacy results.

Figure 1. Mean (± SE) of Change from Baseline in Weekly PN/I.V. Volume by Visit – ITT Population (Source: Figure 11-1 of CSR of study CL0600-021)



ITT = intent-to-treat; SE = standard error

Note: All observations reported for subjects treated with teduglutide in Study CL0600-020 are relative to the baseline prior to exposure to teduglutide at the beginning of Study CL0600-020. All observations reported for untreated subjects or subjects treated with placebo in Study CL0600-020 are relative to the last visit before exposure to teduglutide in Study CL0600-021, which was considered their baseline.

Safety:

Overall, 65 of 88 subjects who received long-term treatment with teduglutide 0.05 mg/kg/day completed this extension study. No new unexpected safety signals were identified beyond those identified in the CL0600-021 Interim Report (June 2011) submitted in the original NDA review cycle or the full prescribing information for Gattex® (teduglutide) dated 21 December 2012. Please refer to the clinical review for more details on the safety results.

Immunogenicity

Immunogenicity incidence – anti-drug antibody (ADA)

As stated in the clinical pharmacology review of the original NDA for teduglutide, the immunogenicity incidence increased with the duration of treatment. In Study CL0600-020, the incidence of anti-teduglutide IgG antibody was 0% (0/39) at baseline, 0% (0/16) at Week 12 and 18% (6/34) at Week 24 in subjects who received SC administration of 0.05 mg/kg teduglutide once a day.

Upon completion of the current open label extension study (CL0600-021), subjects received teduglutide 0.05 mg/kg/day for 24-30 months. Based on the combined immunogenicity data from Studies -020 and -021, the immunogenicity incidence over time was 0% (0/89) at baseline, 3% (2/60) at Month 3, 18% (13/74) at Month 6, 25% (18/71) at Month 12, 31% (10/32) at Month 24, and 48% (14/29) at Month 30 in subjects who received subcutaneous administration of 0.05 mg/kg GATTEX once daily (Table 1).

Table 1. Summary of patients tested positive for anti-teduglutide antibodies- Study CL0600-020 & -021 combined (generated based on Table 14.3.4.1 of CSR of CL0600-020 and Table 14.3.4.19 of CSR of CL0600-021)

Cohorts	Enrolled	Duration on Treatment (months)								
		baseline	3	6	9	12	15	18	24	30
TED/TED	n = 37	0/39[a]	0/16[a]	6/34[a]	4/34	8/33	8/32	12/34	n/a	14/29
(PBO or NT)/TED	n = 50	0/50	2/44	7/40	8/39	10/38			10/32	
Combined		0/89	2/60	13/74	12/73	18/71	8/32	12/34	10/32	14/29

[a] Data from Study CL0600-020, in which 43 subjects were enrolled into the TED treatment arm.

Of note, the immunogenicity samples were analyzed with a validated meso-scale discovery electrochemiluminescent (MSD ECL) assay which has a drug tolerance level (up to 376 ng/mL) significantly higher than the observed median C_{max} (36 ng/mL) at the clinical dose of 0.05 mg/kg; therefore the assay does not have a drug interference issue.

Immunogenicity incidence – neutralizing antibody

No subjects were detected to have neutralizing antibodies during Study CL0600-021. However, this finding should be interpreted with caution as circulating drug concentration could interfere with the assay for neutralizing antibodies. The assay has a drug tolerance level of 1.5 ng/mL, which is lower than the observed mean Cmax at the clinical dose of 0.05 mg/kg.

The 08/28/13 submission did not included detailed information regarding subjects who were tested for neutralizing antibody in Study 021, therefore the following requests were sent to the sponsor:

- Updated USPI label changes – April 28, 2014(Reference ID: 3496465)
- Request for Information - May 12, 2014(Email communication)

Based on sponsor's response (Serial #0089, 0091, and 0093), in Studies -020 and -021, a total of 37 subjects were tested for neutralizing antibodies. Seventeen of these subjects were concluded to have no neutralizing antibodies (due to teduglutide concentrations < 1.5 ng/mL), and the remaining 20 subjects had no detectable neutralizing antibodies while the present teduglutide concentrations (> 1.5 ng/mL) could result in false negative.

Immunogenicity Impact on PK

Data from the open label extension study showed that ADA appeared to have no impact on the PK (Table 1) as teduglutide concentrations in ADA+ subjects were similar to those in ADA- subjects. The post-dose teduglutide concentration values were used in the comparisons between ADA+ and ADA- subjects to assess ADA impact on PK, because teduglutide has a mean terminal half-life ($t_{1/2}$) of approximately 1.3 hours in SBS subjects and does not accumulate following repeated subcutaneous administrations. Teduglutide concentration data collected at Month 18 and Month 24 were combined by timepoint (i.e., 2.5 and 5.0 hours post-dose) and summarized by ADA status in Table 2.

Table 2 Teduglutide Concentrations at 2.5 and 5.0 Hours Post-dose in ADA+ and ADA- Subjects (generated based on PK dataset "cvpkabpn" submitted on 11/20/2013)

Time points	Statistics	ADA+ Subjects	ADA- Subjects
2.5 hours post-dose	N	8	9
	Mean (SD) (ng/mL)	36.2 (18.8)	33.8 (18.6)
	Median (ng/mL)	27.9	30.1
	Min, Max (ng/mL)	15.2, 61.8	14.5, 66.4
5.0 hours post-dose	N	7	8
	Mean (SD) (ng/mL)	26.3 (15.5)	22.0 (15.5)
	Median (ng/mL)	25.3	17.8
	Min, Max (ng/mL)	10.7, 56.6	3.04, 48.2

Immunogenicity Impact on Efficacy

ADA appeared to have no impact on teduglutide efficacy in subjects who received GATTEX treatment for up to 2.5 years, as determined by a comparison of absolute and percent change in weekly PN/I.V. volume in ADA+ subjects vs. ADA- subjects.

As shown in Table 3, subjects in TED/TED group had greater weekly PN/I.V. volume reduction compared to subjects in the NT/TED and PBO/TED groups. Therefore, the assessment of ADA impact on weekly PN/I.V. volume reduction was conducted in separate groups (i.e., TED/TED and combined NT/TED and PBO/TED groups). At Month 24, in combined NT/TED and PBO/TED groups, the mean weekly PN/I.V. volume reduction was 3.17 L (30.83%) and 3.4 L (30.66%) for ADA+ and ADA- subjects, respectively. At Month 24, in TED/TED group, the mean weekly PN/I.V. volume reduction was 7.04 L (65.18%) and 7.31 L (65.55%) for ADA+ and ADA- subjects, respectively. Altogether, the mean weekly PN/I.V. volume reduction was

similar for ADA+ and ADA- subjects in TED/TED and the combined NT/TED and PBO/TED groups.

Table 3 Absolute and Percent Change in Weekly PN Volume at Month 24 - By ADA Status (Generated based on Table 14.2.1.12 of CSR of study CL0600-021)

Weekly PN Volume (L/week)		ADA+ Subjects		ADA- Subjects	
		NT/TED & PBO/TED	TED/TED	NT/TED & PBO/TED	TED/TED
	N	16	15	12	12
Actual value	Baseline Mean	10.34	11.5	9.31	11.54
	Month 24 Mean (SD)	7.17 (5.74)	4.46 (3.69)	5.90 (3.79)	4.23 (4.77)
	Median	4.36	5.60	6.49	3.29
	Min, Max	1.4, 19.5	0.0, 10.0	0.0, 12.1	0.0, 15.5
Change from Baseline	Mean (SD)	-3.17 (2.86)	-7.04 (4.43)	-3.4 (5.16)	-7.31 (5.23)
	Median	-2.9	-6.97	-1.79	-8.34
	Min, Max	-8.8, 0.7	-16.6, -1.4	-16.3, 2.7	-13.4, 4.3
Percent Change from Baseline	Mean (SD)	-30.83 (25.49)	-65.18 (29.54)	-30.66 (47.68)	-65.55 (41.48)
	Median	-30.24	-62.41	-26.08	-77.01
	Min, Max	-70.0, 16.1	-100, -17.0	-100, 57.6	-100, 38.6

Immunogenicity Impact on Safety

ADA appeared to have no impact on clinical safety based on data in subjects treated with Gattex for up to 2.5 years whereas the longer term impact is unknown.

In study CL0600-020, none of the 6 subjects who tested positive for ADA had evidence of hypersensitivity adverse event (AE) or immune related clinical symptoms. In the open-label extension study (CL0600-021), injection site and/or hypersensitivity reactions occurred in 7 subjects. Among these 7 subjects, 3 subjects tested negative for ADA while 4 subjects tested positive for ADA.

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/s/

LIN ZHOU
05/27/2014

LANYAN FANG
05/27/2014

YOW-MING C WANG
05/27/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
sNDA/BLA Number	**203441 (SDN113)**	**Brand Name**	**Gattex**
OCP Division (I, II, III, IV, V)	**DCP III**	**Generic Name**	**teduglutide**
Medical Division	**DGIEP**	**Drug Class**	**Recombinant human glucagan-like peptide-2 (GLP-2)**
OCP Reviewer	**Lanyan Fang, Ph.D.**	**Indication(s)**	**Short Bowel Syndrome**
OCP Team Leader	**Yow-Ming Wang, Ph.D.**	**Dosage Form**	**Lyophilized powder**
Pharmacometrics Reviewer Secondary Reviewer	**N/A**	**Dosing Regimen**	**subcutaneous (SC) injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms. The recommended daily dose of GATTEX is 0.05mg/kg BW.**
Date of Submission	**8/28/13**	**Route of Administration**	**S.C.**
Estimated Due Date of OCP Review		**Sponsor**	**NPS**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**6/28/14**	**Dosing Strength**	**Single-use 3 mL vial contains a dose of 5 mg GATTEX that upon reconstitution with the 0.5 mL sterile water for injection (sWFI) provided in the prefilled syringe delivers a maximum of 0.38 mL of the reconstituted solution.**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
Age:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
Immunogenicity:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		
Phase 3 clinical trial:	**X**	**1**		
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		**CL0600-021 in SBS was added in popPK data**
Immunogenicity	**X**	**1**		**Long term CL0600-021 (020 extension)**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
PK and PD comparability:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**3**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted PK and PD comparability data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the			X	

	CFR requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			No pre-submission meeting was held
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Orphan designation
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Orphan designation
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	No labeling changes related to PK and E-R
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	Labeling change for long-term safety data
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes_____

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

This submission is fileable from a clinical pharmacology's perspective. Please convey the below information request to the sponsor:

Provide analysis dataset to facilitate independent analysis of the immunogenicity impact on PK and efficacy of teduglutide. The dataset should contain at least each individual's teduglutide concentrations, anti-drug antibody (ADA) status, percent and absolute change in weekly PN/I.V. volume, and binary response status (response defined as the achievement of at least a 20% reduction from baseline in weekly PN/I.V. volume) at all the time points evaluated.

Lanyan Fang, Ph.D.

Clinical Pharmacology Reviewer Date

Yow-Ming Wang, Ph.D.

Team Leader Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Review Summary

GATTEX® (teduglutide [rDNA origin]) powder for subcutaneous injection was approved on 12/21/2012 by the FDA for the treatment of adult patients with Short Bowel Syndrome (SBS). It is a 33–amino acid recombinant analog of the human glucagon-like peptide-2 (GLP-2), a peptide that is secreted primarily from the lower gastrointestinal tract. Teduglutide is used to improve intestinal permeability and thus absorption of fluid and nutrients.

The current submission is an efficacy supplement intending to update the currently approved product label based on the final reports from the below studies:

- A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome (CL0600-021, Up to 2 years)
- The Effects of Teduglutide on Postprandial Gallbladder Motility and Biliary Luminal Diameters in Healthy Volunteers (TED-C10-004)
- 104-Week Subcutaneous Injection Carcinogenicity Study with Teduglutide (ALX-0600) in Mice (P09-002)

Along with the final reports, the sponsor also submitted proposed revised label for GATTEX to include information from the above-noted studies and a modified REMS document.

The following sections of the proposed GATTEX label include updated information to reflect study findings:

6.1 Clinical Trials Experience (Based on long term safety results from CL0600-021)
6.1 Adverse Reactions of Special Interest (Based on long term safety results from CL0600-021)
6.2 Immunogenicity (Based on long term safety results from CL0600-021)
8.5 Geriatric Use (Add more subjects in the overall studied population, from 566 to 595 subjects).
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility (Based on P09-002)
14.1 Clinical Studies: Study 2 (Based on long term efficacy results from CL0600-021).

Because healthy subjects have normal gastric emptying and SBS subjects have disturbed gastric emptying, the data gained from healthy subjects after short-term treatment were irrelevant to SBS subjects and therefore were not used for labeling purpose in the original NDA review. Similarly, the relevance of gallbladder mobility data from healthy subjects to SBS subjects is questionable. Additionally, the applicant did not propose to include the specific PD effect evaluated in Study TED-C10-004 in the labeling. As such, Study TED-C10-004 will not be reviewed in this efficacy supplement.

Study CL0600-021 is an extension study to Study CL0600-020 to further study long-term safety and efficacy (up to 2 years). A total of 88 subjects received daily 0.05 mg/kg teduglutide (TED) treatment in Study CL0600-021, where these subjects were classified into three different groups based on their treatment history in Study CL0600-020:

- NT/TED group: 12 subjects were screened but not Randomized (i.e., not treated, NT) in Study CL0600-020,
- PBO/TED group: 39 subjects were treated with placebo (PBO) in Study CL0600-020
- TED/TED group: 37 subjects treated with teduglutide in Studies CL0600-020

The clinical pharmacology review of Study CL0600-021 will focus on assessing the long term efficacy and safety of teduglutide (specifically, immunogenicity incidence rate and its impact on PK/efficacy/safety).

The sponsor submitted a population PK (popPK) report incorporating PK data from Study CL0600-021. Since the popPK analysis was based on pooled datasets from different drug formulations which have different PK properties (refer to clinical pharmacology review of NDA 203441) and the popPK data were not intended to support any labeling change, the popPK report will not be reviewed in this efficacy supplement.

Information missing and needed for review:

It is noted that the PK dataset from Study CL0600-021 was not submitted. An information request will be conveyed to the applicant to request for an integrated dataset containing individual PK, immunogenicity and efficacy data to facilitate an independent assessment of the impact of immunogenicity on PK and efficacy.

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/s/

LANYAN FANG
10/18/2013

YOW-MING C WANG
10/18/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203441/S-002

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Final Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	June 24, 2014
Reviewer(s):	Nyedra Booker, PharmD, MPH, Risk Management Analyst Division of Risk Management (DRISK)
	Ana Tavakoli, MA, Health Communications Analyst, DRISK
Acting Team Leader:	Jamie Wilkins Parker, PharmD, DRISK
Acting Deputy Division Director:	Reema Mehta, PharmD, MPH, DRISK
Drug Name(s):	GATTEX (teduglutide)
Therapeutic Class:	Human glucagon-like peptide-2 (GLP-2) analog
Dosage and Route:	Injection for subcutaneous use
Application Type/Number:	NDA 203441/S-002
Applicant/sponsor:	NPS Pharmaceuticals, Inc.
OSE RCM #:	2013-2076

CONTENTS

EXECUTIVE SUMMARY

This is a review of NPS Pharmaceutical's proposed Risk Evaluation and Mitigation Strategy (REMS) modification for Gattex (teduglutide), NDA 203441/S-002, received on August 28, 2013 and amended February 10, 2014 and June 11, 2014.

(b) (4) In addition, the Applicant proposed revisions to three slides in the *Prescriber Education Slide Deck* based on findings from three clinical studies. Editorial revisions were also proposed to the REMS Supporting Document.

(b) (4) The Review Team agreed with the Applicant's proposed changes to the *Prescriber Education Slide Deck.* Furthermore, editorial updates were made to the REMS website and the *Patient and Caregiver Counseling Guide* was revised based on DRISK's review of the 1-Year Gattex REMS Assessment. The Applicant submitted an amended REMS modification proposal on June 11, 2014, and June 19, 2014.

DRISK finds the proposed Gattex REMS modification as submitted on June 19, 2014, to be acceptable.

1 INTRODUCTION

The purpose of this review is to provide the Division of Risk Management's assessment of the Applicant's proposed REMS modification for Gattex (teduglutide), NDA 203441/S-002, submitted by NPS Pharmaceuticals Inc., initially received June 11, 2014.

The proposed modifications to the REMS were submitted as part of an efficacy supplement (Supplement 002). The Applicant proposed revisions to the REMS included: (1) revisions to the Gattex REMS *Prescriber Education Slide Deck* to align with proposed changes to the label, which incorporated findings from the completion of three clinical studies; (b) (4) The modification impacts the REMS document and appended materials, and REMS Supporting Document.

1.1 PRODUCT BACKGROUND

Gattex is a human glucagon-like peptide-2 (GLP-2) analog approved for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support. Pharmacologic activity is achieved through the binding of Gattex to GLP-2 receptors in the intestine, resulting in increased intestinal and portal blood flow as well as decreased gastric acid secretion.

Gattex is available as a single-use vial containing 5 mg teduglutide as a powder for solution for subcutaneous injection. The recommended once daily dose of Gattex is 0.05mg/kg body weight, with a 50% dose reduction recommended in patients with moderate to severe renal impairment.

Serious adverse drug reactions have been associated with the use of Gattex including the following:

- *Increased risk for abnormal cell growth*- therapy should be discontinued in patients diagnosed with cancer of the bowel, liver, gallbladder or pancreas while on Gattex.
- *Polyp growth*- patients should have their colon checked for polyps within 6 months of starting Gattex therapy, at the end of the first year of using Gattex, and then at least every 5 years if no polyps are found. Any new polyps should be removed and Gattex discontinued if cancer is found in a polyp.
- *Blockage of the bowel (intestines)*- Gattex may need to be temporarily discontinued if a blockage is found.
- *Inflammation or blockage of the gallbladder or pancreas*-patients should have their gallbladder and pancreas function checked (e.g., bilirubin and lipase) within 6 months of starting Gattex and at least every 6 months for as long as treatment continues.

Due to the aforementioned risks, Gattex was approved with a REMS on December 21, 2012 that consists of a communication plan, elements to assure safe use (ETASU), and timetable for submission of assessments. The goal of the REMS is to inform prescribers and patients about the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with Gattex. The REMS accomplishes these goals through a communication plan that consists of letters to healthcare professionals and professional societies, and a training program that consists of a Prescriber Education Slide Deck, a Patient and Caregiver Counseling Guide, and a REMS website (ETASU), which is not linked to restricted distribution. The timetable for submission of assessments is annually from the date of approval.

In addition, Gattex may cause increased absorption of fluid. Patients (particularly those with cardiovascular disease) should be monitored closely for signs of fluid overload and parenteral support adjusted appropriately. The continued use of Gattex may need to be reassessed in patients experiencing fluid overload. This risk is mitigated by the prescribing information (PI) in the Warnings and Precautions section.

Gattex also has the potential to increase the absorption of certain concomitant oral medications including benzodiazepines. Close monitoring and possible dose adjustments of these medications may be necessary while a patient is on Gattex therapy. This risk is mitigated by the PI in the Warnings and Precautions section.

1.2 DISEASE BACKGROUND

Short Bowel Syndrome (SBS) is a condition that encompasses a group of GI issues related to poor nutrient absorption in patients who have had portions of their small intestine removed. The condition is more likely to occur in patients who have had more

than half of the small intestine removed. The small intestine plays a vital role in the digestion of food and absorption of nutrients, and people with SBS often experience difficulty in their body's ability to sufficiently absorb water, vitamins, minerals and other nutrients. Diarrhea is a major symptom of SBS.

Treatment for SBS varies and often depends on disease severity. In patients with mild SBS, dietary changes (eating small and frequent meals), use of nutritional supplements and use of medications to treat diarrhea are often sufficient. In patients with more severe SBS, the use of long-term parenteral nutrition may be required; intestinal transplantation has been used in patients who failed or experienced complications with long-term parenteral nutrition.

1.3 REGULATORY HISTORY

Gattex was approved on December 21, 2012 to treat adult patients with SBS who are dependent on parenteral support. Gattex was approved with a REMS to inform prescribers and patients about the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders. The REMS consisted of a communication plan, ETASU (prescriber training not linked to restricted distribution), and a timetable for submission of assessments.

On August 28, 2013, the Applicant submitted a Prior Approval Supplement-Labeling Change and proposed REMS Modification under NDA 203-441/S-002. Proposed REMS modifications under S-002 included revisions to three slides in the *Prescriber Education Slide Deck* (part of ETASU) to align with proposed changes to the label, which incorporated findings from three clinical studies.

(b) (4) which proposed the following modifications to the Gattex REMS:

1. (b) (4)
2. (b) (4)
3. *Elements to Assure Safe Use (ETASU)*:
   - Revised Prescriber Education Slide Deck to update 3 slides based on the completion of three clinical studies.
   - Added the following statement to the ETASU under healthcare prescriber training: "*Retraining will be made available to prescribers who have not written a prescription for Gattex within 12 months of completing REMS training*".
   - (b) (4)

[redacted] Therefore, Supplement 002 is the subject of this review.

On December 17, 2013, the first assessment report for Gattex was submitted by the Applicant. A review by DRISK of the 1 year REMS assessment report[1], covering the period December 21, 2012 to October 21, 2013, concluded that the REMS was not fully meeting all of its goals. This conclusion was based on the results from the patient survey that indicated improvements to understanding of key risk messages were needed. Patients were generally able to correctly identify the risk of potential cancerous growth, need for colon polyp removal before treatment initiation, need for regular colon exam, and symptoms of obstruction and possible gallbladder or pancreatic inflammation with Gattex. However, patients were less able to correctly identify that bowel obstruction and gall bladder/pancreatic disorders can be associated with Gattex.

[redacted]

On March 4, 2014, in response to the assessment findings DRISK requested the Applicant to provide a plan to address the deficiencies found in the patient survey. On April 11, 2014, the Applicant responded to the request with a plan to revise low scoring questions in the patient survey by utilizing their existing patient outreach infrastructure[3] to reinforce key risk messages in the Medication Guide and Patient and Caregiver Counseling Guide. These activities are conducted by the Applicant outside of the REMS.

[redacted] The Agency also informed the Applicant of recommended modifications to the Patient and Caregiver Counseling Guide tool (based on DRISK review of the 1-Year Gattex REMS Assessment), to focus the messages to the Gattex REMS key risk messages; DRISK determined that the approved tool was identical to the Medication Guide. Revisions also included renaming the *Patient*

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[1] Cvetkovich T. DRISK Review of 1-Year REMS Assessment for Gattex (teduglutide), dated February 25, 2014.

[2] Cao C. DPV Review of "Deaths, Fluid Overload and Increased Absorption of Concomitant Oral Medications" with Gattex (teduglutide), dated April 3, 2014.

[3] NPS Pharmaceuticals has a patient outreach program (launched in February 2013) in which a nurse makes an initial home visit to patients at the start of Gattex therapy, to review the risks outlined in the Medication Guide and Patient and Caregiver Counseling Guide and provide instruction on how to administer Gattex. Following this initial visit, the nurse makes follow-up phone calls on the following schedule: weekly for 3 months, monthly for 9 months beginning in month 4, then quarterly for 12 months beginning in year 2.

and Caregiver Counseling Guide to *What You Need to Know About Gattex Treatment: A Patient and Caregiver Counseling Guide*

The Applicant submitted an amended REMS modification proposal on June 11, 2014, and June 19, 2014.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

- August 28, 2013: Prior Approval Supplement-Labeling Change and proposed REMS Modification, Supplement 002
    - June 19, 2014: Amendment to Supplement 002/Submission of revised REMS documents
    - June 11, 2014: Amendment to Supplement 002/Response to REMS Interim comments
    - February 10, 2014: Amendment to Supplement 002/Response to Information Request and Resubmission of Proposed REMS Modification
- (b) (4)
- (b) (4)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- June 2, 2014: DRISK Interim Comments for the Gattex REMS
- April 3, 2014: Division of Pharmacovigilance (DPV I) Review for Gattex
- February 25, 2014: DRISK Review of 1-Year REMS Assessment for Gattex
- December 21, 2012: NDA Approval Letter for Gattex
- December 21, 2012: Prescribing information for Gattex
- December 17, 2012 (*Revised December 19, 2012*): DRISK Final REMS Review for Gattex
- November 30, 2012 (*Revised December 3, 2012*): DRISK Interim Comments on Amendments to the Gattex REMS

3 APPLICANT'S RATIONALE FOR PROPOSED REMS MODIFICATIONS

(b) (4)

(b) (4)

In addition, the Applicant proposed modifications to three slides in the *Prescriber Education Slide Deck* (part of ETASU) based on findings from the following clinical studies:

- Long-term, open-label study with teduglutide in subjects with parenteral support (PS) dependent short bowel syndrome (SBS) who completed previous clinical protocol[4],
- One-year, open-label study with teduglutide in subjects with PS-dependent SBS who completed the long-term, open-label study,
- 104-week mouse carcinogenicity study.

4 RESULTS OF REVIEW OF PROPOSED MODIFICATION FOR THE GATTEX REMS

(b) (4)

The Applicant was also provided a revised Patient and Caregiver Counseling Guide that focused the messages in the tool to the key risk messages in the Gattex REMS and improved readability. The revisions to the Patient and Caregiver Counseling Guide were based on DRISK review of the 1-Year Gattex REMS Assessment and a determination that the approved tool was identical to the Medication Guide.

NPS Pharmaceuticals Inc. submitted REMS modification amendments on June 11, 2014 and June 19, 2014, in response to Agency comments dated June 2, 2014 and June 18, 2014. The proposed modifications to the REMS goals and elements are described below:

4.1 GOALS

(b) (4)

REMS Goal:

- To inform prescribers and patients about the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with GATTEX.

Reviewer Comment: The Applicant revised the REMS Goal in accordance with Agency comments. The revisions applied to the REMS Goal returns it to the same as that approved on December 21, 2012 (the currently approved REMS) and is acceptable.

[4] Completion of a 24-week study of the efficacy and safety of teduglutide in subjects with PS-dependent SBS

4.2 REMS ELEMENTS

4.2.1 Communication Plan

Proposed revisions to the Gattex REMS communication plan are described below:

- (b) (4)
- Increased the prominence of the subject line in both the Dear Healthcare Professional and Dear Professional Society letters by bolding the word "**subject**" to further draw attention to the information.
- Replaced the bolded words "**must**" with **should** in the Dear Healthcare Professional and Dear Professional Society letters to be consistent with the PI.
- Revised the Dear Healthcare Professional and Dear Professional Society letters to reflect Agency proposed revisions to the name of the patient and caregiver counseling guide: "*What You Need to Know About Gattex Treatment: A Patient and Caregiver Counseling Guide*."

Reviewer Comment: The Applicant revised the REMS communication plan in accordance with Agency comments and is acceptable.

4.2.2 Elements to Assure Safe Use

4.2.2.1 REMS Document

(b) (4)

Reviewer Comment: The Applicant revised the REMS Document under the ETASU in accordance with Agency comments and is acceptable.

4.2.2.2 Prescriber Education Slide Deck

Proposed revisions to the Prescriber Education Slide Deck are described below:

1. Revised 3 slides in the Prescriber Education Slide Deck based on the completion of three clinical studies.
2. Revised the Prescriber Education Slide Deck by including a title and footer on the cover slide (see below):

   Slide title: GATTEX® (teduglutide [rDNA origin]) REMS Program: Prescriber Education

   Footer: (place on the bottom of the cover slide)
   A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. The GATTEX Prescriber Education Slide Deck is required by the FDA as part of the GATTEX REMS Program.

The Applicant revised the description of prescriber training to add a statement that "retraining is made available to prescribers who have not written a prescription for Gattex within 12 months of completing REMS training."

Reviewer Comment: The Applicant revised the Prescriber Education Slide Deck in accordance with Agency comments and is acceptable.

4.2.2.3 Patient and Caregiver Counseling Guide

The Applicant incorporated Agency recommendations for a revised Patient and Caregiver Counseling Guide that focused the messages in the tool to the key risk messages Gattex REMS and improved readability. Revisions also included renaming the *Patient and Caregiver Counseling Guide* to *What You Need to Know About Gattex Treatment: A Patient and Caregiver Counseling Guide*.

Of note, however, the Applicant maintained the statement "There is an increased risk that abnormal cells could become cancer" in the section **What Are the Most Serious Risks Related to GATTEX Treatment**, to be consistent with the Medication Guide and PI.[5]

Reviewer Comment: The statement "There is an increased risk that abnormal cells could become cancer" is consistent with language in the approved Medication Guide and PI. The Applicant's proposed What You Need to Know About Gattex Treatment: A Patient and Caregiver Counseling Guide is acceptable.

4.2.2.4 REMS Website

The Applicant revised the website landing page by replacing "RISK EVALUTION AND MITIGATION STRATEGY (REMS)" with: "GATTEX REMS (Risk Evaluation and Mitigation Strategy)."

Reviewer Comment: The Applicant revised the REMS website landing page in accordance with Agency comments and is acceptable.

4.3 TIMETABLE FOR SUBMISSION OF ASSESSMENTS

The timetable for submission of assessments of the REMS will remain the same as that approved on December 21, 2012.

4.4 REMS SUPPORTING DOCUMENT

The Applicant revised the REMS Supporting Document to be consistent with changes made to the REMS document, and to provide for updated safety information consistent with the proposed label.

In addition, the Applicant proposed editorial changes including the following changes to the company name and address block:

- Addition of "Inc" to NPS Pharmaceuticals, **Inc.**

[5] The Agency proposed modifying this text to state "There is a high risk that abnormal cells could become cancer."

- Revisions to the company address block: NPS Pharmaceuticals, 550 Hills Drive, 3rd Floor, Bedminster, NJ 07921 *to* NPS Pharmaceuticals, **Inc**, 550 Hills Drive, ~~**3rd Floor,**~~ Bedminster, NJ 07921
- Removal of the "nps pharmaceuticals" logo

Reviewer Comment: The Applicant's proposed revisions to the REMS Supporting Document are acceptable.

5 REMS ASSESSMENT PLAN

Based on the proposed modifications, the REMS assessment plan has not changed; the REMS assessment plan will remain the same as that described in the December 21, 2012 Approval letter.

6 DISUCSSION AND CONCLUSION

DRISK finds the proposed REMS modification for Gattex (teduglutide) as submitted on June 19, 2014 acceptable. The amended proposed modification to the Gattex REMS contains the agreed upon revisions to the REMS Document and appended materials, and REMS Supporting Document. The timetable for submission of assessments and assessment plan for the REMS will remain the same as that approved on December 21, 2012.

7 RECOMMENDATIONS

The Office of Surveillance and Epidemiology, DRISK recommends approval of the REMS Modification for Gattex (teduglutide) received on August 28, 2013 and last amended on June 19, 2014, and appended to this review.

ATTACHMENTS

Attachment A: Gattex REMS and appended materials

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/s/

NYEDRA W BOOKER
06/24/2014

REEMA J MEHTA
06/24/2014

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Interim Comments on Risk Evaluation and Mitigation Strategy (REMS) Set # 1

Date:	May 28, 2014
Reviewer(s):	Nyedra Booker, PharmD, MPH, Risk Management Analyst Division of Risk Management (DRISK) Ana Tavakoli, M.A., Health Communications Analyst, DRISK
Team Leader:	Reema Mehta, PharmD, MPH, DRISK
Division Director:	Claudia Manzo, PharmD, DRISK
Drug Name(s):	GATTEX (teduglutide)
Therapeutic Class:	Human glucagon-like peptide-2 (GLP-2) analog
Dosage and Route:	Injection for subcutaneous use
Application Type/Number:	NDA 203441
Applicant/sponsor:	NPS Pharmaceuticals, Inc.
OSE RCM #:	2013-2076

*** This document contains proprietary and confidential information that should not be released to the public. ***

1 INTRODUCTION

This purpose of this review is to provide interim comments by the Division of Risk Management (DRISK) on the proposed modification to the Risk Evaluation and Mitigation Strategy (REMS) for Gattex (teduglutide), NDA 203441, submitted by NPS Pharmaceuticals Inc., received on August 28, 2013 and amended February 10, 2014.

The proposed modifications to the REMS are submitted with an efficacy supplement, Supplement 002. The modification impacts the REMS document and appended materials, and REMS Supporting Document.

2 MATERIALS REVIEWED

2.1 SPONSOR'S SUBMISSION

- NPS Pharmaceuticals, Inc., Proposed REMS Modification for Gattex (teduglutide), including appended materials, received February 10, 2014.
- NPS Pharmaceuticals, Inc., Proposed REMS Modification for Gattex (teduglutide), including appended materials, received August 28, 2013.

2.2 ADDITIONAL MATERIALS INFORMING THE REVIEW

- Draft Labeling for Gattex, version dated May 19, 2014.
- Division of Pharmacovigilance I (DPV I), Pharmacovigilance Review for Gattex (C. Cao), dated April 3, 2014.

3 SUMMARY OF SPONSOR'S PROPOSED REMS MODIFICATIONS

NPS Pharmaceuticals Inc.'s February 10, 2014 submission included the following proposed REMS modifications:

REMS Goal:

- (b) (4)

REMS Elements

- (b) (4)

- *Elements to Assure Safe Use (ETASU)*:
  - Revised Prescriber Education Slide Deck to update 3 slides based on the completion of a Phase 3 open-label extension study and clinical pharmacology study.

  - Added the following statement to the ETASU under healthcare prescriber training: "*Retraining will be made available to prescribers who have not written a prescription for Gattex within 12 months of completing REMS training*".

- (b) (4)

4 SUMMARY OF AGENCY'S PROPOSED REMS MODIFICATIONS

(b) (4)

4.2 REVISED PATIENT AND CAREGIVER COUNSELING GUIDE

The first assessment report for Gattex was submitted by the Sponsor on December 17, 2013. A review by DRISK of the 1 year REMS assessment report, covering the period December 21, 2012 to October 21, 2013, concluded that the REMS was not fully meeting all of its goals. Results from the patient survey indicated that improvements to understanding of key risk messages were needed. Patients were generally able to correctly identify the risk of potential cancerous growth, need for colon polyp removal before treatment initiation, need for regular colon exam, and symptoms of obstruction and possible gallbladder or pancreatic inflammation with Gattex. Patients however, were less able to correctly identify bowel obstruction and gall bladder/pancreatic disorders that can be associated with Gattex.

DRISK provided comments to the Sponsor on March 4, 2014, requesting that they provide a plan to address the deficiencies found in the patient survey. The Sponsor provided a response to DRISK comments on April 11, 2014 with a plan to revise low scoring questions in the patient survey and utilize their existing patient outreach infrastructure[1] to reinforce key risk messages in the Medication Guide and Patient and Caregiver Counseling Guide. These activities are conducted by the Sponsor outside of the REMS.

Upon review of the approved Gattex REMS Patient and Caregiver Counseling Guide, DRISK determined that the tool was identical to the Medication Guide. Therefore, DRISK recommended modification to the tool to focus the messages to the Gattex REMS key risk messages. Formatting changes are also proposed to improve readability.

5 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the Gattex REMS Modification proposal be sent to the applicant. Please request that the applicant respond to these comments within 2 weeks, to facilitate further review.

The comments below are based on DRISK's preliminary review of the REMS Modification proposal for Gattex. Appended to this review is the REMS Modification proposal, Revised Patient and Caregiver Counseling Guide, Dear Healthcare Professional Letter, and Dear Professional Society Letter including our track changes (see Attachments A -D). The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

6 COMMENTS FOR THE SPONSOR

We have reviewed your REMS submission dated February 10, 2014 and have the following comments:

6.2 COMMUNICATION PLAN

[1] NPS Pharmaceuticals has a patient outreach program (launched in February 2013) in which a nurse makes an initial home visit to patients at the start of Gattex therapy, to review the risks outlined in the Medication Guide and Patient and Caregiver Counseling Guide and provide instruction on how to administer Gattex. Following this initial visit, the nurse makes follow-up phone calls on the following schedule: weekly for 3 months, monthly for 9 months beginning in month 4, then quarterly for 12 months beginning in year 2.

1. [redacted] (b) (4)

2. To be with consistent with the *Dear Health Care Provider Letters: Improving Communication of Important Safety Information* Guidance (January 2014, OMB Control No. 0910-0754), the Agency recommends increasing the prominence of the subject line in both the Dear Healthcare Professional and Dear Professional Society letters. For example, consider bolding the word **subject** to further draw attention to the information.

3. The Agency recommends replacing the bolded words "**must**" (see below) with (**should**) in the Dear Healthcare Professional and Dear Professional Society letters to be consistent with the PI.
    a. Colonoscopy of the entire colon with removal of polyps **must** be done within 6 months prior to starting treatment with GATTEX.
    b. For identification of the onset or worsening of gallbladder/biliary disease, patients **must** undergo laboratory assessment of bilirubin and alkaline phosphatase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed.
    c. For identification of onset or worsening of pancreatic disease, patients **must** undergo laboratory assessment of lipase and amylase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed.

6.3 ELEMENTS TO ASSURE SAFE USE

[redacted] (b) (4)

6.3.1 Prescriber Education Slide Deck

1. Your proposed revision to update 3 slides in the Prescriber Education Slide Deck based on the completion of a Phase 3 open-label extension study and clinical pharmacology study is acceptable.
2. The Prescriber Education Slide Deck does not communicate the fact that the distribution of this piece is a requirement of the REMS program, or that the piece is part of the REMS program. We recommend clearly communicating this information by including a title and footer on the cover slide (see below):

    Slide title: GATTEX® (teduglutide [rDNA origin]) REMS Program: Prescriber Education

    Footer: (place on the bottom of the cover slide)
    A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. The GATTEX Prescriber Education Slide Deck is required by the FDA as part of the GATTEX REMS Program.

6.3.2 Prescriber Training

Your proposed revision to add a statement that "Retraining will be made available to prescribers who have not written a prescription for Gattex within 12 months of completing REMS training" is acceptable.

6.3.3 Patient and Caregiver Counseling Guide

1. Rename the *Patient and Caregiver Counseling Guide* to *What You Need to Know About Gattex Treatment: A Patient and Caregiver Counseling Guide*.
2. See Appendix A for the revised *What You Need to Know About Gattex Treatment: A Patient and Caregiver Counseling Guide*. The content of the counseling guide has been revised to focus the messages to the Gattex REMS key risk messages. Additionally, formatting changes are recommended to improve readability.

6.4 REMS WEBSITE

On the website landing page, replace "RISK EVALUTION AND MITIGATION STRATEGY (REMS)" with: "GATTEX REMS (Risk Evaluation and Mitigation Strategy)"

6.5 GENERAL COMMENTS

1. Language in all REMS materials must reflect what is in the approved final labeling.
2. Resubmission Requirements and Instructions: Submit the revised proposed REMS for Gattex with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.
3. Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. 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 be in a single MS Word document.

7 REMS SUPPORTING DOCUMENT

The REMS Supporting Document must be consistent with all changes made to the REMS document.

ATTACHMENTS

Attachment A: REMS Document

Attachment B: Dear Healthcare Professional letter

Attachment C: Dear Professional Society letter

Attachment D: Revised Patient and Caregiver Counseling Guide

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/s/

NYEDRA W BOOKER
05/28/2014

REEMA J MEHTA
05/28/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203441/S-002

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 203441

Application Type: Efficacy Supplement 002

Name of Drug/Dosage Form: Gattex (teduglutide rDNA origin) for injection, for subcutaneous use

Applicant: NPS Pharmaceuticals, Inc.

Receipt Date: August 28, 2013

Goal Date: June 27, 2014

1. Regulatory History and Applicant's Main Proposals

Gattex (teduglutide rDNA origin) was originally approved in 2012 for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support. On August 28, 2013, NPS Pharmaceuticals, Inc. submitted an efficacy supplement to NDA 203441Gattex (teduglutide rDNA origin). Supplement 002 includes data in labeling supported by a final clinical study report ("A Long-term, Open-label Study with Teduglutide for Subjects with parenteral Nutrition Dependent Short Bowel Syndrome: Interim Report") and a final clinical pharmacology study report ("The Effects of Teduglutide on Postprandial Gallbladder Motility and Biliary Luminal Diameters in Healthy Volunteers"). The applicant's submission also included a modified Risk Evaluation and Mitigation Strategy (REMS) that was required to address the following risks: 1) possible acceleration of neoplastic growth and enhancement of colon polyp growth, which included a final report of a two year carcinogenicity study in rats, 2) gastrointestinal obstruction, 3) biliary and pancreatic disorders, 4) fluid volume overload and 5) increased absorption of concomitant oral medications.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by June 23, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

YES 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI

Selected Requirements of Prescribing Information

• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment:

N/A 13. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**"). The BW heading should be centered.

Comment:

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement "***See full prescribing information for complete boxed warning.***").

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013".

Comment:

N/A 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

N/A 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES 21. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement in Highlights

YES 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling"**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide"**

Comment:

Revision Date in Highlights

YES 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 9/2013**").

Comment:

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

YES 25. The TOC should be in a two-column format.

Comment:

YES 26. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS"**. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

NO 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment: *Section 6.3 Postmarketing Experience is missing from the TOC. This section is in the FPI, therefere needs to be added to the TOC.*

YES 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "FULL PRESCRIBING INFORMATION: CONTENTS" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]"* or *"*[*see Warnings and Precautions (5.2)*]".

Comment:

N/A 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 35. The following heading must be **bolded** and appear at the beginning of the FPI: "**FULL PRESCRIBING INFORMATION".** This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 36. In the BW, all text should be **bolded**.

Comment:

N/A 37. The BW must have a heading in UPPER CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**").

Comment:

CONTRAINDICATIONS Section in the FPI

YES 38. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 39. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment: *However, the sponsor has chosen to modify the statement. It reads as follows, "Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in clinical practice."*

YES 40. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

YES 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]
See full prescribing information for complete boxed warning.

- [text]
- [text]

----------RECENT MAJOR CHANGES----------
[section (X.X)] [m/year]
[section (X.X)] [m/year]

----------INDICATIONS AND USAGE----------
[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

----------DOSAGE AND ADMINISTRATION----------
- [text]
- [text]

----------DOSAGE FORMS AND STRENGTHS----------
[text]

----------CONTRAINDICATIONS----------
- [text]
- [text]

----------WARNINGS AND PRECAUTIONS----------
- [text]
- [text]

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- [text]
- [text]

----------USE IN SPECIFIC POPULATIONS----------
- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

JENNIFER S SARCHET
06/25/2014

BRIAN K STRONGIN
06/25/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Pediatric and Maternal Health Staff Memorandum

Date: May 22, 2014 **Date Consulted:** March 10, 2014

From: Miriam Dinatale, D.O., Medical Officer
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP, Team Leader
Pediatric and Maternal Health Staff

Lynne P. Yao, MD, OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Gattex (teduglutide [rDNA origin]) for injection, for subcutaneous use

NDA/BLA: 203441/S002

Applicant: NPS Pharmaceuticals , Inc

Subject: Pregnancy and Lactation labeling

Materials Reviewed: Gattex product labeling, Pharmacology/Toxicology Gattex Review 8/3/12

Consult Question:
"DGIEP requests your assistance with reviewing the label and updating regulatory language as needed (convert 8.1 and 8.3 to the hybrid PLLR format)."

INTRODUCTION

On August 28, 2013, NPS Pharmaceuticals submitted a new efficacy supplement for Gattex (teduglutide) injection (NDA/BLA 203441/S002), which is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support. This supplement includes data in labeling supported by a final clinical study report ("A Long-term, Open-label Study with Teduglutide for Subjects with parenteral Nutrition Dependent Short Bowel Syndrome: Interim Report") and a final clinical pharmacology study report ("The Effects of Teduglutide on Postprandial Gallbladder Motility and Biliary Luminal Diameters in Healthy Volunteers"). The applicant's submission also included a modified Risk Evaluation and Mitigation Strategy (REMS) that was required to address the following risks: 1) possible acceleration of neoplastic growth and enhancement of colon polyp growth, which included a final report of a two year carcinogenicity study in rats, 2) gastrointestinal obstruction, 3) biliary and pancreatic disorders, 4) fluid volume overload and 5) increased absorption of concomitant oral medications.

Gattex is a glucacon-like peptide-2 (GLP-2) that was originally approved by the FDA on December 21, 2012. Teduglutide was granted Orphan Drug designation on June 29, 2000. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) on March 10, 2014 to revise and update the pregnancy and nursing mothers subsections of Gattex labeling. See Appendix A for the applicant's currently approved pregnancy and nursing mothers labeling.

BACKGROUND

Short Bowel Syndrome (SBS) can result from surgical resection, congenital defect, or disease-associated loss of absorption of some or all of the small or large intestine. If SBS is extensive, it can cause malabsorption of protein, fluids, electrolytes and micronutrients. Following surgery, it may take up to two years for compensatory increase in bowel absorptive capacity. If after two years the patient still requires total parenteral nutritional (TPN) support, it is not likely that they will be completely weaned from TPN. TPN is associated with complications that include malnutrition, diarrhea, dehydration, nutrient deficiencies, electrolyte imbalance, intestinal obstruction, intestinal polyps, gallbladder, pancreatic/liver disease, sepsis and blood clots.[1]

Teduglutide is a 33-amino acid recombinant analog of GLP-2, a peptide secreted in the lower gastrointestinal tract. Teduglutide increases villus height and crypt depth of intestinal epithelium and results in an increased absorptive capacity of the intestine.[2] Due to adverse reactions observed in clinical trials, data from animal studies, as well as the drug's mechanism of action, a REMS was required at approval to ensure that the benefits of Gattex outweigh the risks noted above. The Gattex REMS includes a communication plan to support REMS implementation and elements necessary to assure safe use (ETASUs) to mitigate the risk of the possible gastrointestinal adverse reactions associated with the drug. ETASUs include

[1] Korvick, Joyce. Division Safety Deputy Director Review: GATTEX (teduglutide [rDNA]) for injection, for subcutaneous use. DARRTS 12/20/2012. Page 3,14
[2] He, Ruyi. Cross-Discipline Team Leader Review: NDA 203411. DARRTS 11/13/2012. Page 1

training for health care providers who prescribe Gattex and appropriate risk information for patient education.

REVIEW OF DATA

No evidence of impaired fertility, teratogenicity, or fetotoxicity was observed in animal reproduction studies with the administration of subcutaneous teduglutide to rats and/or rabbits during organogenesis at doses up to 1000 times the recommended human intravenous dose. [3]

A search of published literature was performed. There were no studies with teduglutide conducted in pregnant women.

The Drugs and Lactation Database (LactMed)[4] was searched for available lactation data on the use of Gattex, and no information was found. Current approved Gattex Nursing Mothers labeling provides language suggesting that teduglutide is present in rat milk and that there is a potential for tumorigenicity shown for teduglutide in mice and rats. It is unknown whether teduglutide is excreted in human milk. This information is based on data from submitted animal pre-and post-natal development studies that was reviewed by the FDA.[5]

DISCUSSION

PREGNANCY AND NURSING MOTHERS LABELING

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing Mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. A brief description of an available pregnancy exposure registry or pregnancy surveillance program that monitors or evaluates pregnancy outcomes with exposure of a drug during pregnancy should be placed in the pregnancy subsection. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in human milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.

---

[3] Chakraborti, Tamal. Pharmacology/Toxicology NDA/BLA Review and Evaluation, DARRTS August 3, 2012.

[4] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[5] Chakraborti, Tamal. Pharmacology/Toxicology NDA/BLA Review and Evaluation, DARRTS August 3, 2012.

PMHS-MHT notes that pregnancy categories will be eliminated with the publication of the PLLR and replaced with clinically relevant information to assist prescribers with benefit/risk decision making for using a drug during pregnancy.

CONCLUSION
A pregnancy category B is the appropriate classification for Gattex labeling since animal reproduction studies failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.[6] Additionally, a literature search revealed no human pregnancy data with the use of this product. The pregnancy subsection of Gattex labeling was structured in the spirit of the proposed PLLR, while complying with the current pregnancy labeling regulations (see 21 CFR 201.57(c)(9)(i). Minor editorial revisions were made to the nursing mothers subsection of Gattex labeling for consistency with language in the proposed PLLR, while complying with the current nursing mothers pregnancy labeling regulations (see 21 CFR 201.57(c)(9)(iii)..

PMHS-MHT GATTEX (TEDUGLUTIDE) INJECTION LABELING
PMHS-MHT recommends the following revision to the Pregnancy and Nursing Mothers sections of Gattex. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

HIGHLIGHTS OF PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Category B

Risk Summary
Adequate and well controlled studies with GATTEX have not been conducted in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of subcutaneous teduglutide at doses up to 1000 times the recommended human dose in both rats and rabbits. Because animal reproduction studies are not always predictive of human response, GATTEX should be used during pregnancy only if clearly needed.

Data
Animal data
In animal studies, no effects on embryo-fetal development were observed in pregnant rats given subcutaneous teduglutide at doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg) or pregnant rabbits given subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg). A pre- and postnatal development study in rats showed no evidence of any adverse

[6] Pregnancy Category B: Animal reproduction studies have not shown an adverse effect on the fetus and there are no adequate and well-controlled studies in pregnant women, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no adequate and well controlled studies in humans

effect on pre- and postnatal development at subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg).

8.3 Nursing Mothers

It is not known whether GATTEX is present in human milk. Teduglutide is excreted in the milk of lactating rats, and the highest concentration measured in milk was 2.9% of the plasma concentration following a single subcutaneous injection of 25 mg/kg. Because many drugs are present in human milk, because of the potential for serious adverse reactions to nursing infants from GATTEX and because of the potential for tumorigenicity shown for teduglutide in mice and rats, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother *[*see *NonclinicalToxicology (13.1)]*.

APPENDIX A- Current Approved Gattex Pregnancy and Nursing Mothers Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Pregnancy Category B
Reproduction studies with teduglutide have been performed in pregnant rats at subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg) and in rabbits at subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to teduglutide. A pre- and postnatal development study in rats showed no evidence of any adverse effect on pre- and postnatal development at subcutaneous doses up to 50 mg/kg/day (about 1000 times the recommended daily human dose of 0.05 mg/kg). There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, teduglutide should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers
It is unknown whether teduglutide is excreted in human milk. Teduglutide is excreted in the milk of lactating rats, and the highest concentration in the milk was 2.9% of the plasma concentration following a single subcutaneous injection of 25 mg/kg. Because many drugs are excreted in human milk; because of the potential for serious adverse reactions to nursing infants from teduglutide and because of the potential for tumorigenicity shown for teduglutide in rats, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. *[*see *NonclinicalToxicology (13.1)]*

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

/s/

MIRIAM C DINATALE
05/22/2014

JEANINE A BEST
05/22/2014

LYNNE P YAO
05/23/2014

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

Pharmacovigilance Review

Date:	April 03, 2014
Reviewers:	Christian Cao, MPAS, PA-C, Safety Evaluator Division of Pharmacovigilance I (DPV I)
Team Leaders:	Eileen Wu, PharmD, Safety Evaluator Team Leader DPV I
Acting Division Director:	Min Chen, RPh, MS, Acting Director DPV I
Product Name:	Gattex (teduglutide [rDNA origin])
Subject:	Deaths, Fluid Overload and Increased Absorption of Concomitant Oral Medications
Application Type/Number:	NDA 203441
Applicant/Sponsor:	NPS Pharmaceuticals Inc.
OSE RCM #:	2014-519

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates and summarizes post-market cases of fluid overload and increased absorption of concomitant oral medications with the use of Gattex (teduglutide). (b) (4)

[redacted]

DPV reviewed the cases submitted by NPS and retrieved from the FAERS database. There are 16 cases of fluid overload and one case of increased absorption of oral concomitant drugs reported since approval of teduglutide on December 21, 2012.

Of the 16 cases of fluid overload, the most commonly reported symptoms were weight increased, abdominal distension, and fluid retention. Patients experienced fluid overload-associated symptoms 1 to 63 days after starting teduglutide with a median time to onset of 9 days. In the 9 cases that reported an intervention, adjustment of parenteral nutrition and teduglutide dosage were consistent with labeling recommendation. One patient died while taking teduglutide; it is unknown whether the parenteral nutrition was adjusted. The patient had a complex medical history that included coronary artery disease and chronic pelvic infection related to complications of colorectal surgery, which may contribute to the fluid retention. Another two cases also reported that the patient had a history of cardiovascular disease: coronary artery disease (n=1) and atrial fibrillation (n=1). No cases of CHF or new onset CHF, however, were reported.

There was one case of increased absorption of oral concomitant drugs (Vicodin, zolpidem, citalopram, and cyclobenzaprine) that also reported the patient died. The patient had a history of alcoholic liver cirrhosis that may have contributed to higher zolpidem, citalopram, cyclobenzaprine, and Vicodin drug levels because of reduced drug-metabolism.

The role of teduglutide in the development of fluid overload or increase absorption of oral concomitant drugs cannot be excluded in the two fatal cases. Both patients in these cases, however, had very complex medical histories that may contribute to the adverse events and death.

Based on the information, DPV did not identify any new safety concern related to fluid overload or increased absorption of oral concomitant drugs with teduglutide use.

DPV recommends that NPS submit all reports of fluid overload and increased absorption of oral concomitant drugs with a serious outcome as 15-day alert reports to FDA.

1 INTRODUCTION

This review evaluates and summarizes post-market cases of fluid overload and increased absorption of concomitant oral medications with the use of Gattex (teduglutide). (b) (4)

[redacted]

2 BACKGROUND

2.1 REGULATORY HISTORY[2,3]

The FDA approved Gattex (teduglutide) on December 21, 2012 for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support. As part of the approval, the FDA required a REMS to ensure the benefits of teduglutide outweigh the potential risks. Teduglutide is an analog of glucagon-like peptide-2 (GLP-2), which is secreted in the distal intestine. Endogenous GLP-2 increases intestinal and portal blood flow while inhibiting gastric acid secretion and reducing gastric motility, thereby reducing intestinal losses and improving intestinal absorption. Teduglutide binds and activates GLP-2 receptors, resulting in release of mediators including insulin-like growth factor (IGF)-1, nitric oxide, and keratinocyte growth factor (KGF).

The goal of the Gattex REMS is to inform prescribers and patients about the following risks:

1. Possible acceleration of neoplastic growth and enhancement of colon polyp growth while on Gattex
2. Gastrointestinal obstruction while on Gattex
3. Biliary and pancreatic disorders while on Gattex and the need to have laboratory assessments done before starting Gattex and repeated every 6 months while on Gattex to monitor gallbladder and biliary functions

A Gattex REMS 12-Month Assessment Report from NPS was completed on December 12, 2013.[4] In this report, NPS identified two additional important safety messages:

4. Increased absorption of fluids leading to fluid overload disease
5. Increased absorption of oral concomitant medication

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[1] NDA 203441 S002 GATTEX® (Teduglutide [rDNA origin]) for Injection: Risk Evaluation and Mitigation Strategy (REMS). (\\cdsesub1\evsprod\nda203441\0081\m1\us\risk-mgmt-plan.pdf)
[2] Gattex: Risk Evaluation And Mitigation Strategy (REMS). Food and Drug Administration. Approved December 21, 2012.
[3] Gattex: Label. NPS Pharmaceuticals. Approved December 21, 2012.
[4] Gattex® (Teduglutide [rDNA origin]) for Injection Safety and Use Information RISK EVALUATION and MITIGATION STRATEGY (REMS) 12-MONTH ASSESSMENT. NPS Pharmaceuticals, Inc. December 12, 2013 (\\cdsesub1\evsprod\nda203441\0081\m1\us\risk-mgmt-plan.pdf)

(b)

NPS included all five aforementioned risks in the Communication Plan directed to health care providers (HCPs) and Patient and Caregiver Counseling Guide. The Gattex REMS assessment evaluated the prescribers' as well as patients' knowledge of the five risks. Overall, most HCPs were knowledgeable about all the risks, but assessment of the patients' knowledge identified some deficiencies in patients' understanding of the safe use of Gattex. Just more than half of the respondents correctly identified too much fluid in the body (*fluid overload;* 59.3%) and were aware of the potential for adverse events when using Gattex with other medications (53.7%) as possible adverse events of Gattex therapy.

The REMS 12-Month Assessment Report also provided an analysis of the post-market safety data for cases related to these five risks. NPS identified 36 reports related to the risk of acceleration of neoplastic growth and enhancement of colon polyp growth (n=1), gastrointestinal obstruction (n=8), pancreatic disorders (n=4), biliary disorders (n=4), and fluid volume overload (n=19). There were 8 cases with a fatal outcome. In six cases, the outcomes were unrelated to Gattex. In two cases, the contribution of the drug to the development of fluid overload or increased absorption of concomitant oral drugs could not be excluded.

2.2 Clinical Trial Data[5]

Risk of fluid overload and increased absorption of oral concomitant drugs were identified in the clinical trials for teduglutide. There were 4/39 (6.8%) reports of fluid overload in the group receiving teduglutide 0.05 mg/kg/day with 1 serious adverse event (SAE) of congestive heart failure (CHF). In the group that received teduglutide 0.10 mg/kg/day, there were 9/77 (11.7%) reports of fluid overload. There were no reports of fluid overload in the placebo group. Although an evaluation of the study sub-population of patients who used concomitant benzodiazepine did not show a significantly higher proportion with "Cognition and attention disorders and disturbances" in the treatment groups (teduglutide 0.05 mg/kg/day and 0.10 mg/kg/day) than the placebo group, 14% and 21% vs. 20%, respectively, the mechanism of action of the drug made the risk still a potential.

2.3 Product Labeling

In Section 5 Warnings and Precautions, the FDA approved label for Gattex lists the following:

1. **Acceleration of Neoplastic Growth, Colorectal Polyps and Small Bowel Neoplasia**
   Based on the pharmacologic activity and findings in animals, GATTEX has the potential to cause hyperplastic changes including neoplasia. In patients at increased risk for malignancy, the clinical decision to use GATTEX should be considered only if the benefits outweigh the risks. In patients with active gastrointestinal malignancy (GI tract, hepatobiliary, pancreatic), GATTEX therapy should be discontinued. In patients with

[5] NDA 203-441 Gattex (teduglutide) Clinical Review. John Troiani, MD, PhD. October 31, 2012

active non-gastrointestinal malignancy, the clinical decision to continue GATTEX should be made based on risk-benefit considerations.

Colorectal polyps were identified during the clinical trials. Colonoscopy of the entire colon with removal of polyps should be done within 6 months prior to starting treatment with GATTEX. A follow-up colonoscopy (or alternate imaging) is recommended at the end of 1 year of GATTEX. Subsequent colonoscopies should be done every 5 years or more often as needed. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of diagnosis of colorectal cancer, GATTEX therapy should be discontinued.

Based on benign tumor findings in the rat carcinogenicity study, patients should be monitored clinically for small bowel neoplasia. If a benign neoplasm is found, it should be removed. In case of small bowel cancer, GATTEX therapy should be discontinued

2. **Intestinal Obstruction**
   Intestinal obstruction has been reported in clinical trials. In patients who develop intestinal or stomal obstruction, GATTEX should be temporarily discontinued while the patient is clinically managed. GATTEX may be restarted when the obstructive presentation resolves, if clinically indicated.

3. **Biliary and Pancreatic Disease**
   Gallbladder and Biliary Tract Disease
   Cholecystitis, cholangitis, and cholelithiasis, have been reported in clinical studies. For identification of the onset or worsening of gallbladder/biliary disease, patients should undergo laboratory assessment of bilirubin and alkaline phosphatase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed. If clinically meaningful changes are seen, further evaluation including imaging of the gallbladder and/or biliary tract is recommended; and the need for continued GATTEX treatment should be reassessed.

4. **Pancreatic Disease**
   Pancreatitis has been reported in clinical studies. For identification of onset or worsening of pancreatic disease, patients should undergo laboratory assessment of lipase and amylase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed. If clinically meaningful changes are seen, further evaluation such as imaging of the pancreas is recommended; and the need for continued GATTEX treatment should be reassessed.

5. **Fluid Overload**
   Fluid overload and congestive heart failure have been observed in clinical trials, which were felt to be related to enhanced fluid absorption associated with GATTEX. If fluid overload occurs, parenteral support should be adjusted and GATTEX treatment should be reassessed, especially in patients with underlying cardiovascular disease. If significant cardiac deterioration develops while on GATTEX, the need for continued GATTEX treatment should be reassessed.

6. **Increased Absorption of Concomitant Oral Medication**
   Altered mental status in association with GATTEX has been observed in patients on benzodiazepines in clinical trials. Patients on concomitant oral drugs (e.g.,

benzodiazepines, phenothiazines) requiring titration or with a narrow therapeutic index may require dose adjustment while on GATTEX.

3 METHODS AND MATERIALS

3.1 CASE DEFINITION

3.1.1 Fluid Overload

One of the following satisfies the inclusion criteria:

1. Any case reporting any of the following diagnosis:
   - Fluid overload
   - Hypervolemia
   - New onset or worsening congestive heart failure
2. Any case reporting one of the following signs or symptoms:
   - Mental status changes
   - Peripheral edema (e.g., swelling of hands, feet, or ankles)
   - Increase in weight
   - Ascites
   - Pulmonary edema with or without dyspnea
   - Pleural effusion with or without dyspnea
   - Hypokalemia
   - Hyponatremia
   - Cardiac arrhythmia
   - Jugular venous distention

   OR

3. Any case reporting one of the following treatments:
   - Diuresis (e.g., furosemide)
   - Teduglutide discontinuation or dose(s) held
   - Adjustment of parenteral nutrition (PN)

3.1.2 Increased Absorption of Oral Concomitant Drugs

One of the following satisfies the inclusion criteria:

1. Any case reporting a diagnosis of drug overdose or supratherapeutic response
2. Any case reporting a concomitant oral drug

   AND

   Signs or symptoms related to drug overdose or supratherapeutic response (e.g., cognition and attention disorders and disturbances with a benzodiazepine or bleeding with warfarin).

3.2 CASES SUBMITTED BY NPS PHARMACEUTICALS INC.

An Information Request (IR) was submitted to NPS for MedWatch reports of the cases of fluid overload (n=19) and deaths (n=8) that were reviewed in the Gattex REMS 12-Month Assessment Report.[6]

3.3 FAERS SEARCH STRATEGY

To retrieve additional reports not identified by NPS, the FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1 for all events.

Table 1. FAERS Search Strategy*	
Date of search	February 27, 2014
Time period of search	December 21, 2012 ^ - February 26, 2014
Product Terms	Product name: Gattex Active Ingredient: teduglutide
Event Terms	None were selected.

*See Appendix A for description of the FAERS database.
^ US approval date.

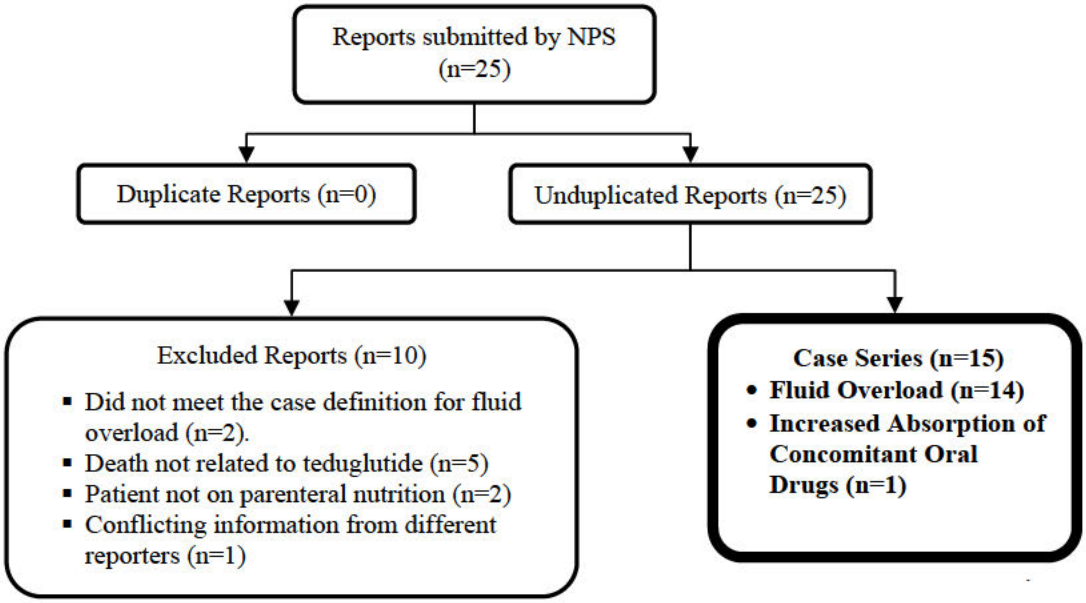
4 RESULTS

4.1 CASES SUBMITTED BY NPS PHARMACEUTICALS INC.

FDA received 25 total case reports from NPS. After applying the case definition in Section 2 and accounting for duplicate reports, 15 cases were included in the case series of fluid overload (n=14) and increased absorption of concomitant oral drugs (n=1) with teduglutide use (see Figure 1).

[6] These cases were not submitted to FAERS at the time of this review because they reported labeled events and were included in the biannual Periodic Benefit-Risk Evaluation Report (PBRER) for Gattex. NPS was granted a waiver for the biannual submission of the PBRER on October 25, 2013.

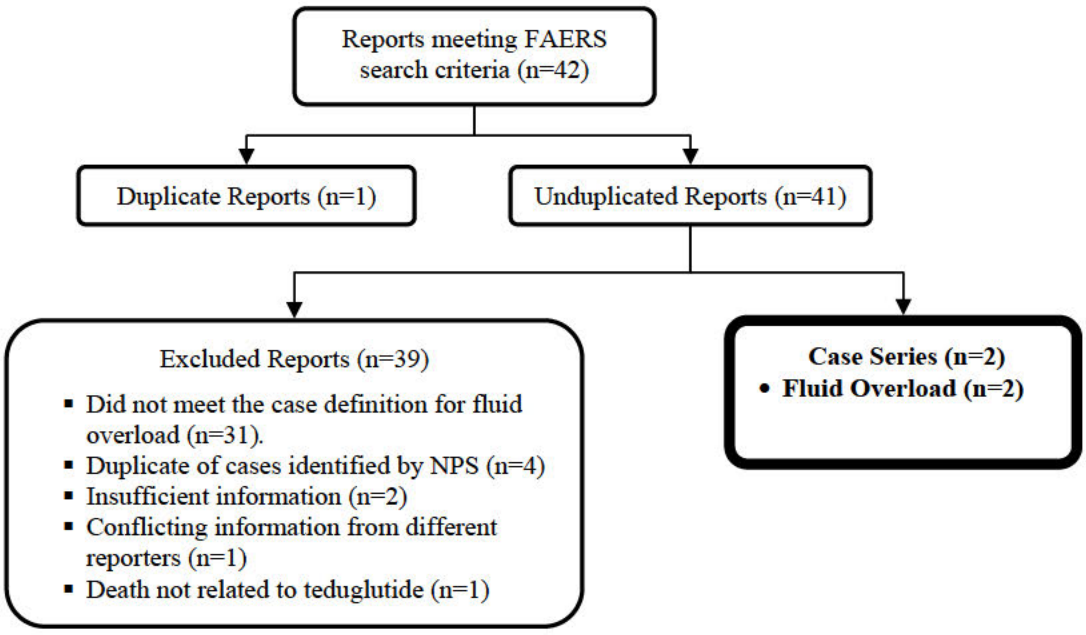
Figure 1. NPS Provided Case Selection



4.2 FAERS CASE SELECTION

The FAERS search retrieved 42 reports. After applying the case definition in Section 2 and accounting for duplicate reports and cases submitted by NPS, additional 2 cases of fluid overload were identified (see Figure 2).

Figure 2. FAERS Case Selection



4.3 COMBINED CASE SELECTION FROM NPS PHARMACEUTICALS INC. AND FAERS DATABASE

There are 16 cases of fluid overload and one case of increased absorption of oral concomitant drugs reported since approval of teduglutide on December 21, 2012.

Table 2 summarizes the 16 cases of fluid overload reported with teduglutide use. Case vignettes for one case of fluid overload and the 2 deaths, which include one case of fluid overload and the one case of increased absorption of oral concomitant drugs are provided below.

Appendix B lists all the FAERS case numbers, FAERS version numbers, and Manufacturer Control numbers for the 16 cases of fluid overload and one case of increased absorption of oral concomitant drugs.

Table 2. Descriptive characteristics of Fluid Overload reported with Teduglutide use (December 21, 2012 ^ - February 26, 2014)
(N=16)*

Age	Mean	59 years
	Median	48 years
	Range	39-71 years
Sex	Female	13
	Male	3
Event Date (month-year), n=15	May-13	2
	Jun-13	2
	Jul-13	3
	Aug-13	2
	Sep-13	4
	Oct-13	1
	Nov-13	1
Country	USA	16
	Foreign	0
Outcome	Deaths	2
	Hospitalization	2
	Other	12
Reporter	Consumer	7
	Allied healthcare professional	5
	Physician	4
Time to Onset (TTO), n=14	Median	9 days
	Range	1-63
Coded Preferred Term	Weight increased	9
	Abdominal distension	4
	Fluid retention	4
	Dyspnoea	2
	Local Swelling	2
	Oedema peripheral	2
	Fluid overload	1
	Generalised oedema	1
	Oedema	1
Cardiovascular history, n=3	Coronary artery disease	2
	Atrial fibrillation	1

Intervention†	Teduglutide held	4
	PN Adjusted	4
	Diuresis	2
	Teduglutide discontinued	2
	Not reported	7
Dechallenge, n=6	Positive	3
	Negative	2
	Not reported	1

*N=16 unless otherwise noted
†Not mutually exclusive: one case reported teduglutide discontinued, diuresis, and IV fluid adjusted; another case reported diuresis and iv fluid adjusted

Representative Case of Fluid Overload

- **Case#** US-000730 (NPS, domestic, June 2013): A registered nurse reported that a 68-year-old female patient who initiated Gattex 0.25 ml subcutaneously daily on 18Jun2013 experienced swelling of her face, legs and eye lids and abdominal bloating on the morning of 19Jun2013. Patient has been PN dependent since 15Oct2012. The patient weighed 107 pounds one day prior to initiating Gattex. On 21Jun2013, the patient weighed 112 pounds (5 pound weight gain); the patient later reported a total weight gain of 9 pounds and itching all over her body as of 23Jun 2013. The nurse noted that the patient's PN had been increased from 1350 ml twice a week to 1300 ml, three times a week prior to starting Gattex on 14Jun2013. Patient discontinued Gattex on 22Jun2013 based on her gastroenterologist's advice. She was treated with antihistamine and furosemide. The reported events subsequently resolved. Patient's medical history includes history of fluid retention (but reported as less severe) and coronary artery disease managed by a cardiologist. Patient resumed Gattex on 4Jul2013 and on day 5, she experience nausea, headache, diarrhea, cold like symptoms ("ears cloggy"), swelling of the face, hands, both ankles, intestinal swelling and pain; bloating of the stomach and lower back pain. At follow-up, physician reported the patient had improved without further recurrence of the events.

Fatalities (n=2)

- **Case# US-000859** (NPS, domestic, Nov. 2013): A physician reported that a 50-year-old female patient with alcoholic liver cirrhosis died while receiving Gattex for treatment of parenteral nutrition dependent short bowel syndrome. Her short bowel syndrome was related to ischemia. The patient took multiple concomitant drugs including **zolpidem, citalopram, cyclobenzaprine, and Vicodin**. The patient was prescribed Vicodin 500 mg every 4 hours prn, for treatment of back pain related to a spinal vertebral fracture. While in an assisted living facility for rehabilitation after the fracture, the patient was found nonresponsive at 2-3 AM on routine nightly check-up on (b) (6) There were no complaints of any problems from the patient in the prior day. No autopsy was performed. The Gattex was started on October 1, 2013 at 0.27 mL SC once daily and the last dose was on (b) (6).

  Comment: This case is included in the case series for Increased Absorption of Concomitant Oral Drugs. The patient's history of alcoholic liver cirrhosis may have

contributed to higher zolpidem, citalopram, cyclobenzaprine, and Vicodin drug levels because of reduced drug-metabolism.

- **Case# US-000806** (NPS, domestic, Sept. 2013): A dietitian and physician reported that a 60-year-old male patient with a history of coronary artery disease and chronic pelvic infection related to complications of colorectal surgery died while receiving Gattex for treatment of parenteral nutrition dependent short bowel syndrome. The patient reportedly started Gattex (dose not reported) on September 26, 2013. On approximately (b) (6) , the patient was brought to the emergency department due to loss of consciences and '**fluid retention**' where he died. The patient was not evaluated prior to starting the Gattex and it is unknown whether the PN was adjusted.

  Comment: This case is included in the case series for Fluid Overload. The patient has a complicated medical history which may contribute to the fluid retention.

5 DISCUSSION

Of the 16 cases of fluid overload, the most commonly reported symptoms were weight increased, abdominal distension, and fluid retention. Patients experienced fluid overload-associated symptoms 1 to 63 days after starting teduglutide with a median time to onset of 9 days. In the 9 cases that reported an intervention, adjustment of parenteral nutrition and teduglutide dosage were consistent with labeling recommendation. One patient died while taking teduglutide; it is unknown whether the parenteral nutrition was adjusted. The patient had a complex medical history that included coronary artery disease and chronic pelvic infection related to complications of colorectal surgery, which may contribute to the fluid retention. Another two cases also reported that the patient had a history of cardiovascular disease: coronary artery disease (n=1) and atrial fibrillation (n=1). No cases of CHF or new onset CHF, however, were reported.

There was one case of increased absorption of oral concomitant drugs (Vicodin, zolpidem, citalopram, and cyclobenzaprine) that also reported a death outcome. The patient had a history of alcoholic liver cirrhosis that may have contributed to higher zolpidem, citalopram, cyclobenzaprine, and Vicodin drug levels because of reduced drug-metabolism.

The role of teduglutide in the development of fluid overload or increase absorption of oral concomitant drugs cannot be excluded in the two fatal cases. Both patients in these cases, however, had very complex medical histories that may contribute to the adverse events and death.

6 CONCLUSION AND RECOMMENDATION

DPV did not identify any new safety concern related to fluid overload or increased absorption of oral concomitant drugs with teduglutide use**.**

DPV recommends the following:

> Request NPS to submit all reports of fluid overload and increased absorption of oral concomitant drugs with a serious outcome[7] as 15-day alert reports to FDA.

[7] Serious outcomes include death, hospitalization, life-threatening, disability, congenital anomaly and/or other serious outcome.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 APPENDIX B. FAERS CASE NUMBERS, FAERS VERSION NUMBERS, AND MANUFACTURER CONTROL NUMBERS

FAERS CASE ID	Version	MCN
Fluid Overload (n=16)		
		US-000711
		US-000713
		US-000730
		US-000739
		US-000740
9454519	1	US-000746
		US-000766
		US-000770
		US-000781
		US-000790
		US-000798
		US-000806*
		US-000815
		US-000862
		US-000871
9389167	1	US-AMGEN-USASP2013039867
Increased Absorption Of Concomitant Oral Drugs (n=1)		
		US-000859*

*Cases with a fatal outcome (n=2)

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

/s/

CHRISTIAN T CAO
04/03/2014

EILEEN WU
04/03/2014

MIN CHU CHEN
04/03/2014

Office of Prescription Drug Promotion

Internal Consult

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Anahita Tavakoli, Senior Drug Risk Analyst, DRISK

From: Meeta Patel, Regulatory Review Officer, OPDP

CC: Kathleen Klemm, Team Leader, OPDP
Phong Do, SRPM, OSE
Reema Mehta, Team Leader, DRISK
Kate Heinrich Oswell, Health Communications Analyst, DRISK
Carole Broadnax
CDER-OPDP-RPM
Michael Wade

Date: March 25, 2014

Re: NDA 203441
GATTEX® (teduglutide [rDNA origin]), for injection, for subcutaneous use
Comments on draft Risk Evaluation and Mitigation Strategies (REMS) Materials (Submission date: February 12, 2014)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for GATTEX:

- Healthcare Professional (HCP) REMS Materials:
  - Dear Healthcare Professional letter
  - Dear Professional Society Leader letter
  - Prescriber Education Slide Deck

The version of the draft REMS materials used in this review were obtained from the eRoom on March 18, 2014, and are attached to the end of this review. As per the email from Anahita Tavakoli on March 18, 2014, the other REMS materials are not being updated and will not be reviewed at this time.

The version of the draft REMS materials used in this review can be found at: http://eroom.fda.gov/eRoom/CDER3/CDERDivisionofGastroenterologyProducts/0_41cb0

OPDP offers the following comments on these draft REMS materials for GATTEX.

General Comments

Please remind NPS Pharmaceuticals, Inc., that REMS materials are not appropriate for use in a promotional manner.

OPDP is concerned that the proposed Prescriber Education Slide Deck does not communicate the fact that the distribution of this piece is a requirement of the REMS program, or that the piece is part of the REMS. We recommend clearly communicating this information.

Additionally, to be with consistent with the *Dear Health Care Provider Letters: Improving Communication of Important Safety Information* guidance (January 2014, OMB Control No. 0910-0754), OPDP recommends increasing the prominence of the subject line in both the Dear Healthcare Professional and Dear Society Leader letters. For example, consider placing the subject line within a border, text box, or in bold type to further draw attention to the information.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Dear Healthcare Professional letter
- Dear Professional Society Leader letter
- Prescriber Education Slide Deck

Specific Comments

OPDP considers the following statements promotional in tone and recommends revising or deleting them from the REMS piece:

- Dear Healthcare Professional (DHCP) letter

    - The proposed DHCP letter states the following (emphasis added) (in pertinent part):

        > The purpose of this letter is to **remind** you about serious risks associated with GATTEX. . .

        OPDP is concerned that the use of the word, "remind" minimizes the risks presented in the letter by not adequately conveying that the letter includes new REMS risk information. Specifically, the risks pertaining to fluid overload and increased absorption of concomitant oral medications were not presented in the original DHCP letter. Therefore, this presentation is misleading and we recommend that it be revised.

    - The proposed DHCP letter states the following (emphasis added) (in pertinent part):

        > Colonoscopy of the entire colon with removal of polyps **must** be done within 6 months prior to starting treatment with GATTEX.

        We recommend revising this statement to be consistent with the full Prescribing Information (PI). Specifically, the PI states the following (emphasis added) (in pertinent part):

        > Colonoscopy of the entire colon with removal of polyps **should** be done within 6 months prior to starting treatment with GATTEX.

    - The proposed DHCP letter states the following (emphasis added) (in pertinent part):

        > For identification of the onset or worsening of gallbladder/biliary disease, patients **must** undergo laboratory assessment of bilirubin and alkaline phosphatase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed.

        We recommend revising this statement to be consistent with the PI. Specifically, the PI states the following (emphasis added) (in pertinent part):

        > For identification of the onset or worsening of gallbladder/biliary disease, patients **should** undergo laboratory assessment of bilirubin and alkaline phosphatase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed.

- The proposed DHCP letter states the following (emphasis added) (in pertinent part):

  > For identification of onset or worsening of pancreatic disease, patients **must** undergo laboratory assessment of lipase and amylase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed.

  We recommend revising this statement to be consistent with the PI. Specifically, the PI states the following (emphasis added) (in pertinent part):

  > For identification of onset or worsening of pancreatic disease, patients **should** undergo laboratory assessment of lipase and amylase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed.

- OPDP is concerned that the removal of the statement, "This letter is not a complete description of the risks associated with GATTEX," minimizes the risks associated with this drug. Specifically, removing this statement implies that the DHCP letter contains a comprehensive risk presentation, when this is not the case. We recommend that this statement be included back in the DHCP letter.

- Dear Professional Society Leader letter

  - Please apply our comments from the DHCP letter to the same or similar claims presented in the Dear Professional Society Leader letter.

- Prescriber Education Slide Deck

  - We have no comments on the Prescriber Education Slide Deck at this time.

Thank you for your consult.

25 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

MEETA N PATEL
03/25/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 203441 BLA#	NDA Supplement #:S- 002 BLA Supplement #	Efficacy Supplement Type SE- 8
Proprietary Name: GATTEX Established/Proper Name: teduglutide [rDNA origin] Dosage Form: powder for subcutaneous injection Strengths: 5 mg		
Applicant: NPS Pharmaceuticals Agent for Applicant (if applicable): NA		
Date of Application: 8-28-13 Date of Receipt: 8-28-13 Date clock started after UN: NA		
PDUFA Goal Date: 6-28-14	Action Goal Date (if different):	
Filing Date: 10-27-13	Date of Filing Meeting: 10-17-13	
Chemical Classification: (1,2,3 etc.) (original NDAs only) NA		
Proposed indication(s)/Proposed change(s): NA, approved indication is Treatment of adult with Short Bowel Syndrome (SBS) who are dependent on parenteral support		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults –*** RPM Comment: OCP was consulted when the original NDA was submitted. It is not necessary to involve OCP for this supplement.		☒ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*): NA	
List referenced IND Number(s): 058213	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	☒	☐		No fee necessary as this has orphan designation #99-1269

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☐	☒	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs***	☐	☐	☒	
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	☒	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug***	☐	☒		

Designations and Approvals list at: *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*				
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?	☐	☐	☒	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	☒	☐		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	Sponsor has committed to submit this information in a timely manner
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."***	☒	☐		

If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant				
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☐	☐	☒	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be*	☐	☒		Orphan drug, therefore, PREA is not triggered

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

reviewed by PeRC prior to approval of the application/supplement.				
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	☐	☐	☒	
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	☐	☐	☒	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	☐	☐	☒	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☐	☐	☒	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☒	☐	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL	☒	☐		

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

format? ***If no, request applicant to submit SPL before the filing date.***				
Is the PI submitted in PLR format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	☒	☐	☐	OPDP to be consulted after successful filing.
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	☐	☒	☐	This supplement does not include changes to patient labeling, therefore, DRISK review of labeling not necessary.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	☐	☒	☐	This supplement does not include changes to container/carton or relevant sections of the PI.
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging, and current approved Rx PI (if	☐	☐	☐	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

switch) sent to OSE/DMEPA?				
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☒	☐	☐	Carc stats consult sent 9-18-13. Others to be determined.
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***	☐	☒		
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 17, 2013

BLA/NDA/Supp #: 203441/S002

PROPRIETARY NAME: Gattex

ESTABLISHED/PROPER NAME: teduglutide

DOSAGE FORM/STRENGTH: powder for subcutaneous injection/5 mg

APPLICANT: NPS Pharmaceuticals, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): no proposed changes to the current indication: "GATTEX® (teduglutide [rDNA origin]) for injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support."

BACKGROUND: GATTEX (teduglutide [rDNA origin]) for injection was approved under NDA 203441 on December 21, 2012. GATTEX is an orphan drug (designation #99-1269). Supplement 002, received August 28, 2013, includes the following proposed changes:

Revisions to the PI

- Assorted minor editorial changes
- Revision of 6.1 to incorporate additional patient exposures from the TED study and results from the complete study report for Study 021.
- Revision of 8.5 to reflect additional exposures
- Revision of 13.1 to incorporate final results of 2-year mouse carcinogenicity study
- Revision of 14.1 to incorporate results from the complete study report for Study 021

Revisions to the REMS

- Revision of the Prescriber Education Slides (7, 9, 11) to incorporate results from the complete study report for Study 021.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matthew Scherer	y
	CPMS/TL:	Wes Ishihara	n
Cross-Discipline Team Leader (CDTL)	Ruyi He		y
Clinical	Reviewer:	John Troiani	n

	TL:	Ruyi He	y
Clinical Pharmacology	Reviewer:	Lanyan Fang	y
	TL:	Yow-Ming Wang	y
Biostatistics	Reviewer:	Behrang Vali	y
	TL:	Freda Cooner	y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Emmanuel Akinshola	y
	TL:	Sushanta Chakder	y
Statistics (carcinogenicity)	Reviewer:	TBD	n
	TL:	Karl Lin	n
Product Quality (CMC)	Reviewer:	Anamitro Banerjee	y
	TL:	Marie Kowblansky	y
Facility Review/Inspection	Reviewer:	TBD	n
	TL:	TBD	n
OSE/DRISK (REMS)	Reviewer:	Nyedra Booker	y
	TL:	Kendra Worthy	n
OC/OSI/DSC/PMSB (REMS)	Reviewer:	TBD	n
	TL:	TBD	n
Bioresearch Monitoring (OSI)	Reviewer:	TBD	n
	TL:	TBD	n
Other reviewers	none		n
Other attendees	Donna Griebel		y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed	☒ Not Applicable ☐ YES ☐ NO

drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., BA/BE studies):	☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: submission appears acceptable	☐ Not Applicable
CLINICAL **Comments**: electronic datasets to be requested	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain: interim results from Study 021 (the key clinical study supporting the proposed labeling changes) have already been reviewed and incorporated into the label. Additional inspections not expected to be necessary.	☐ YES ☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☒ NO ☐ To be determined Reason: changes to the label are not significant. The new data does not appear to raise any significant new issues with GATTEX.
• Abuse Liability/Potential	☒ Not Applicable ☐ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**: analysis dataset to be requested to facilitate independent analysis of immunogenicity results from Study 021	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: Biostats review not expected to be necessary.	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

PRODUCT QUALITY (CMC) **Comments**: CMC review not necessary.	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: sponsor has agreed to submit request categorical exclusion	☐ YES ☒ NO – see comment ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	☒ Not Applicable ☐ Review issues for 74-day letter

APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☒ N/A
• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?	☐ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☐ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☐ YES ☐ NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Division Director

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): Not a program NDA

21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Not included

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:

☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): electronic datasets to be requested to support clinical and clinical pharmacology reviews Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☒	Other: consult OPDP to review labeling

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MATTHEW C SCHERER
10/25/2013

RICHARD W ISHIHARA
10/25/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 203441/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203441 SUPPL # 002 HFD #

Trade Name Gattex

Generic Name teduglutide[rDNA origin]

Applicant Name NPS Pharmaceuticals, Inc

Approval Date, If Known June 27, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

The sponsor provided a proposed revised label for GATTEX and corresponding modified REMS document.

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question is YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 203441 Gattex

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study CL 0600-021

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 Study CL 0600-021 YES ☒ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Study CL 0600-021 NDA 203441 Gattex

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 Study CL 0600-021 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

The initial NDA 203441 (Sequence 0001, November 30, 2011) submission which included an interim clinical study report CL0600-021 entitled, "A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome: Interim Report." The interim report was prepared to support the initial marketing application review. The Study CL0600-21 has been relied on by the agency to demonstrate the effectiveness of NDA 20441 Gattex. As agreed with the Division, the final clinical study report would be submitted following study completion. This supplement included final study report of Study CL0600-021.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 58,213 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Jennifer Sarchet, RN, BSN, Regulatory Project Manager
Ruyi He, MD, CDTL, Clinical Team Lead

Date: 6/17/2014

Name of Office/Division Director signing form: Joyce A. Korvick, MD, MPH
Title: Deputy Director for Safety

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

JENNIFER S SARCHET
06/25/2014

JOYCE A KORVICK
06/26/2014

From:	Diane Fiorenza
To:	Barley, Stacy
Cc:	Sarchet, Jennifer
Subject:	Re: NDA 203441/Supplement 002; Gattex; Medication Guide
Date:	Wednesday, June 25, 2014 9:46:15 PM
Attachments:	image001.png

Hi Stacy,
Yes we are in agreement on the below IFU revisions. I confirm your below edits.

Sent from my iPhone

On Jun 25, 2014, at 9:03 PM, "Barley, Stacy" <Stacy.Barley@fda.hhs.gov> wrote:

> Hello Diane,
>
> Thank you for your submission. I was also looking at your Instructions for Use (IFU) and wanted to ask if you want me to keep the "distributed by" address (located on the last page) consistent with your revisions made to the Medication Guide "distributed by" address. You deleted "3rd floor" and change the copyright year to 2014. If you are in agreement, you do not need to make a formal submission of the IFU.
>
> **Please confirm via email that you agree with the following revisions to the last page of the IFU:**
>
> Distributed by:
> NPS Pharmaceuticals, Inc.
> 550 Hills Drive~~, 3rd Floor~~
> Bedminster, NJ 07921
> U.S.A.
>
> ©201~~2~~4 NPS Pharmaceuticals
>
> **Revised**~~Issued~~: June 2014
>
> Thank you!
>
> ***Stacy Barley, RN, M.S.N., M.S.H.A.***
> ***CDR, USPHS Commissioned Corps***
> ***Senior Regulatory Project Manager***
> ***Division of Gastroenterology/Inborn Errors Products***
> ***Office of Drug Evaluation III***
> ***CDER/FDA***
> ***(301) 796-2137 (office)***
> ***(301) 796-9905 (fax)***
> ***stacy.barley@fda.hhs.gov***
>

From: Diane Fiorenza [mailto:DFiorenza@npsp.com]
Sent: Wednesday, June 25, 2014 4:35 PM
To: Sarchet, Jennifer
Cc: Barley, Stacy
Subject: RE: NDA 203441/Supplement 002; Gattex; Medication Guide
Importance: High

Dear Jennifer,

Reference is made to NDA 203441 approved on 21 December 2012 for GATTEX® (teduglutide [rDNA origin]) for injection, for subcutaneous use indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.
Additional reference is made to:

- Prior Approval Supplement - NDA 203441/S002 submitted August 28, 2013 (Sequence No. 0074) for a proposed revised label for GATTEX and corresponding modified REMS document
- Email communication from the FDA Project Manager on June 25, 2014

At this time, NPS Pharmaceuticals is providing the attached WORD file of the Gattex Medication Guide.

This information will also be provided to the FDA in an official sequence submission. The documents are being simultaneously handled by the Sponsor's publishing vendor. When NPS Pharmaceuticals receives confirmation that the submission has cleared the FDA Gateway, the FDA Project Manager will be notified by NPS Pharmaceuticals.

Thank you!

Diane

Kind Regards,
Diane C. Fiorenza, BS, RAC
Senior Director, Regulatory Affairs
NPS Pharmaceuticals Inc.
550 Hills Dr
Bedminster, NJ 07921
(908) 450 5520 - Office
(908) 450 3808 - Mobile
(908) 450 5506 – Fax
<image001.png>

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Wednesday, June 25, 2014 3:13 PM
To: Diane Fiorenza
Subject: NDA 203441/Supplement 002; Gattex; Medication Guide
Importance: High

Diane,

We noticed you did not submit a Medication Guide with supplement 002. Although no revisions were made during this review, please send us a copy of the Medication Guide in word format. Please remember to place the month and year at the end of the document. In addition, also include your U.S. license number. This needs to be submitted formally to the application today.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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

/s/

STACY R BARLEY
06/26/2014

From: Sarchet, Jennifer
To: "Diane Fiorenza"
Subject: RE: NDA 203441/Supplement 002; Gattex; Label
Date: Tuesday, June 24, 2014 7:13:30 AM
Attachments: image001.png

Hello Diane,

It is not necessary to submit a formal submission at this time. Thank you for asking.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

From: Diane Fiorenza [mailto:DFiorenza@npsp.com]
Sent: Monday, June 23, 2014 12:09 PM
To: Sarchet, Jennifer
Subject: RE: NDA 203441/Supplement 002; Gattex; Label

Hi Jennifer,
Thanks so much for your email. We will have the below edits completed by end of day today. (We had also identified the spacing issue and are just confirming the corrections). Would you prefer that I email the label to you as well as a formal sequence submission? Please advise.

Regards,
Diane C. Fiorenza, BS, RAC
Senior Director, Regulatory Affairs
NPS Pharmaceuticals Inc.
550 Hills Dr
Bedminster, NJ 07921

(908) 450 5520 - Office
(908) 450 3808 - Mobile
(908) 450 5506 – Fax

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Monday, June 23, 2014 11:39 AM
To: Diane Fiorenza
Subject: NDA 203441/Supplement 002; Gattex; Label

Hello Diane,

We have additional revisions for the label for NDA 203441/Supplement 002; Gattex.

In reference to your Highlights please delete the bullets from the following sections: Contradictions, Drug Interactions and Use In Specific Populations. A bullet is not needed if there is only a single statement.

Under the Table of Contents, please add 6.3 Postmarketing Experience.

In addition, please verify the spacing throughout the label.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
06/26/2014

From:	Sarchet, Jennifer
To:	"Diane Fiorenza"
Subject:	NDA 203441/Supplement 002; Gattex; Returned REMS
Date:	Wednesday, June 18, 2014 10:09:31 PM
Attachments:	Gattex_rems_Agency_clean.doc Gattex_rems_Agency_trackchange.doc Gattex_rems_Agency_clean.pdf Gattex_rems_Agency_trackchange.pdf

Dear Diane,

For NDA 203441/Supplement 002, Gattex please see that attached track change and clean versions (in word and PDF format) of the REMS documents. The remaining changes are editing/formatting. Since the last changes are such, do you anticipate being able to submit a clean version to the Gateway by COB tomorrow, June 19, 2014? Please let me know.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
06/18/2014

From:	Sarchet, Jennifer
To:	"Diane Fiorenza"
Subject:	NDA 203441/Supplement 002; Gattex; June 6 2014 Returned Label to NPS
Date:	Friday, June 06, 2014 1:21:15 PM
Attachments:	Label as of June 6 2014 NDA 203441 Supplement 002 Gattex.pdf Label as of June 6 2014 NDA 203441 Supplement 002 Gattex.doc NDA 203441 Supplement 002 Gattex Immunogenicity data listing.pdf
Importance:	High

Dear Diane,

In reference to the prior approval supplement NDA 203441/Supplement 002 submitted on August 28, 2013, please see the following two documents (attached):

1. The returned USPI label changes in WORD format and PDF format.
2. A supporting document to the label titled, "NDA 203441 Supplement 002 Gattex Immunogenicity Data Listing."

Please let me know if you have any questions and when you can expect your revisions, if any returned back to us.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
06/06/2014

June 24, 2014

Only the attachment to the e-mail in the below correspondence was originally entered into DARRTS. The e-mail itself was originally not included. Jennifer Sarchet requested to have the e-mail added as a cover note.

From:	Sarchet, Jennifer
To:	"Diane Fiorenza"
Subject:	NDA 203441/Supplement 002; Gattex; Returned Label to NPS on June 2, 2014
Date:	Monday, June 02, 2014 7:34:42 AM
Attachments:	NDA 203441 Supplement 2; Gattex; May 30 2014 Label to NPS.docx NDA 203441 Supplement 2 Gattex May 30 2014 Label to NPS.pdf

Hello Diane,

I have attached a WORD version and a PDF version of the current changes to the label for NDA 203441/Supplement 002; Gattex.

Please let me know if you have any questions and when you anticipate having the label back to us so I can let the team know.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
06/02/2014

From: Sarchet, Jennifer
To: "Diane Fiorenza"
Subject: NDA 203441/Supplement 002; Gattex; REMS Interim Comments
Date: Monday, June 02, 2014 9:40:19 AM
Attachments: AppendixA_rems-tracked-changes from Agency.doc
AppendixB_healthcare-provider-letter-tracked-changes from Agency.doc
AppendixC_professional-society-letter-tracked-changes from Agency.doc
AppendixD_What You Need to Know About GATTEX Treatment A Patient Guide 4 (2).doc

Hello Diane,

For NDA 203441/Supplement 002; Gattex: The REMS interim comments are below and attached. As a reminder the REMS Supporting Document must be consistent with all changes made to the REMS document. Please respond by Wednesday, June 11, 2014. As always, please do not hesitate to contact me with any questions you may have.

1 COMMENTS TO NPS

We have reviewed your REMS submission dated February 10, 2014 and have the following comments:

(b) (4)

[redacted]

1.2 COMMUNICATION PLAN

(b) (4)

[redacted]

2. To be with consistent with the *Dear Health Care Provider Letters: Improving Communication of Important Safety Information* Guidance (January 2014, OMB Control No. 0910-0754), the Agency recommends increasing the prominence of the subject line in both the Dear Healthcare Professional and Dear Professional Society letters. For example, consider bolding the word **subject** to further draw attention to the information.

The Agency recommends replacing the bolded words "**must**" (see below) with (**should**) in the Dear Healthcare Professional and Dear Professional Society letters to be consistent with the PI.

a. Colonoscopy of the entire colon with removal of polyps **must** be done within 6 months prior to starting treatment with GATTEX.

b. For identification of the onset or worsening of gallbladder/biliary disease, patients **must** undergo laboratory assessment of bilirubin and alkaline phosphatase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed.

c. For identification of onset or worsening of pancreatic disease, patients **must** undergo laboratory assessment of lipase and amylase within 6 months prior to starting GATTEX, and at least every 6 months while on GATTEX; or more frequently if needed.

1.3 ELEMENTS TO ASSURE SAFE USE

(b) (4)

1.3.1 Prescriber Education Slide Deck

Your proposed revision to update 3 slides in the Prescriber Education Slide Deck based on the completion of a Phase 3 open-label extension study and clinical pharmacology study is acceptable.

The Prescriber Education Slide Deck does not communicate the fact that the distribution of this piece is a requirement of the REMS program, or that the piece is part of the REMS program. We recommend clearly communicating this information by including a title and footer on the cover slide (see below):

> Slide title: GATTEX® (teduglutide [rDNA origin]) REMS Program: Prescriber Education
>
> Footer: (place on the bottom of the cover slide)
>
> A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. The GATTEX Prescriber Education Slide Deck is required by the FDA as part of the GATTEX REMS Program.

1.3.2 Prescriber Training

Your proposed revision to add a statement that "Retraining will be made available to prescribers who have not written a prescription for Gattex within 12 months of completing REMS training" is acceptable.

1.3.3 Patient and Caregiver Counseling Guide

Rename the *Patient and Caregiver Counseling Guide* to *What You Need to Know About Gattex Treatment: A Patient and Caregiver Counseling Guide*.

See Appendix A for the revised *What You Need to Know About Gattex Treatment: A Patient and Caregiver Counseling Guide*. The content of the counseling guide has been revised to focus the messages to the Gattex REMS key risk messages. Additionally, formatting changes are recommended to improve readability.

1.4 REMS WEBSITE

On the website landing page, replace "RISK EVALUTION AND MITIGATION STRATEGY (REMS)" with: "GATTEX REMS (Risk Evaluation and Mitigation Strategy)"

1.5 GENERAL COMMENTS

Language in all REMS materials must reflect what is in the approved final labeling.

Resubmission Requirements and Instructions: Submit the revised proposed REMS for Gattex with attached materials and the REMS Supporting Document. Provide a MS Word document with track changes and a clean MS Word version of all revised materials and documents. Submit the REMS and the REMS Supporting Document as two separate MS Word documents.

Format Request: Submit your proposed REMS and other materials in MS Word format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single MS Word document. 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 be in a single MS Word document.

2 REMS SUPPORTING DOCUMENT

The REMS Supporting Document must be consistent with all changes made to the REMS document.

ATTACHMENTS

Attachment A: REMS Document
Attachment B: Dear Healthcare Professional letter
Attachment C: Dear Professional Society letter
Attachment D: Revised Patient and Caregiver Counseling Guide

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

telephone at 240-402-4275. Thank you.

11 Page(s) has been Withheld in Full as b4 (CCI/ TS) immediately following this page

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/s/

JENNIFER S SARCHET
06/02/2014

June 24, 2014

Only the attachment to the e-mail in the below correspondence was originally entered into DARRTS. The e-mail itself was originally not included. Jennifer Sarchet requested to have the e-mail added as a cover note.

From:	Sarchet, Jennifer
To:	"Diane Fiorenza"
Subject:	NDA 203441/Supplement 002; Gattex; Returned Label and Pending Information Requests
Date:	Wednesday, May 14, 2014 2:28:13 PM
Attachments:	Signed DARRTS NDA 203441 Supplement 2 Label to Sponsor May 14 2014.pdf NDA 203442 Label Sponsor Revisions (JS) for SharePoint.doc image001.png Signed DARRTS NDA 203441 Supplement 002 Gattex Information Request.pdf

Hello Diane,

Please see the returned label for NDA 203441/Supplement 002; Gattex. I have attached a PDF copy and a word copy.

Please let me know when you anticipate getting this back to us.

Also, I know the team is looking forward to the data for the two pending information requests. Can they still expect the information on May 16 (the full list of 51 subjects, etc.) and May 30 the second information request (analysis of concentration samples, etc.)?

Thanks so much.

Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

From: Diane Fiorenza [mailto:DFiorenza@npsp.com]
Sent: Tuesday, May 06, 2014 3:30 PM
To: Sarchet, Jennifer
Subject: RE: NDA 203441 (S002) Label - Sequence 0089

Hi Jennifer,

The below submission has been assigned sequence number 0089. Our publishing vendor has indicated that it has gone through the FDA gateway today, Tuesday, May 6, 2014. Please let me know if you have any questions or concerns with the transmission. Thank you!

Regards,

Diane C. Fiorenza, BS, RAC
Senior Director, Regulatory Affairs
NPS Pharmaceuticals Inc.
550 Hills Dr
Bedminster, NJ 07921
(908) 450 5520 - Office
(908) 450 3808 - Mobile
(908) 450 5506 – Fax

From: Diane Fiorenza
Sent: Friday, May 02, 2014 4:17 PM
To: 'Sarchet, Jennifer'
Subject: RE: NDA 203441 (S002) Label
Importance: High

Dear Jennifer,

Reference is made to NDA 203441 approved on 21 December 2012 for GATTEX® (teduglutide [rDNA origin]) for injection, for subcutaneous use indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.
Additional reference is made to:

- Prior Approval Supplement - NDA 203441/S002 submitted August 28, 2013 (Sequence No. 0074) for a proposed revised label for GATTEX and corresponding modified REMS document
- Updated USPI label changes received by email from the FDA Project Manager on April 28, 2014

At this time, NPS Pharmaceuticals is providing the attached response document and a proposed updated USPI label.

- Response Document - PDF file
- USPI - WORD file in tracked changes

This information will also be provided to the FDA in an official sequence submission. The documents are being simultaneously handled by the Sponsor's publishing vendor. When NPS Pharmaceuticals receives confirmation that the submission has cleared the FDA Gateway, the FDA Project Manager will be notified by NPS Pharmaceuticals.

For ease of review the USPI is color coded in tracked changes as follows:

- NEW edits proposed by NPS is highlighted in green and is in tracked changes
- NPS edits proposed in the sNDA but not yet edited by FDA remains unhighlighted and is in tracked changes

Please call me if you have any questions navigating through the documents. I look forward to continue working with you throughout this sNDA and thank you for your continued collaboration on the Gattex program.

Diane

Kind Regards,
Diane C. Fiorenza, BS, RAC
Senior Director, Regulatory Affairs
NPS Pharmaceuticals Inc.
550 Hills Dr
Bedminster, NJ 07921
(908) 450 5520 - Office
(908) 450 3808 - Mobile
(908) 450 5506 – Fax

Regards,
Diane C. Fiorenza, BS, RAC
Senior Director, Regulatory Affairs
NPS Pharmaceuticals Inc.
550 Hills Dr
Bedminster, NJ 07921
(908) 450 5520 - Office
(908) 450 3808 - Mobile
(908) 450 5506 – Fax

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Wednesday, April 30, 2014 2:16 PM
To: Diane Fiorenza
Subject: RE: NDA 203441 (S002) Label

Hello Diane,

Yes, please accept or delete **FDA track changes** that you are in agreement or disagreement with as appropriate. If the FDA did not previously accept or delete your original proposed track changes, leave that specific text in track change format for FDA review. In other words, do not accept your own track changes.

My apologies as I think this was an issue from when it switched project manager's.

Thanks again,
Jennifer

From: Diane Fiorenza [mailto:DFiorenza@npsp.com]
Sent: Wednesday, April 30, 2014 12:39 PM
To: Sarchet, Jennifer
Subject: RE: NDA 203441 (S002) Label

Hi Jennifer,
I should have a response by end of day for targeting an email submission to you by end of day this Friday with a follow-up sequence submission. In preparing the edits to the USPI, I was planning on "accepting" the changes to all agreed text within the document. That would allow the agency to clearly see the outstanding tracked changes that need further discussion. Is this acceptable? We are trying to make it as clean as possible to your review. Thanks for your continued support.

Regards,
Diane C. Fiorenza, BS, RAC
Senior Director, Regulatory Affairs
NPS Pharmaceuticals
550 Hills Dr, 3rd Floor
Bedminster, NJ 07921
(908) 450-5520 - Office
(908) 450 3808 - Mobile
(908) 450 5351 - Fax

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Wednesday, April 30, 2014 10:19 AM
To: Diane Fiorenza
Subject: RE: NDA 203441 (S002) Label

Hello Diane,

Thank you for responding so quickly. If it works out that you can e-mail me a tracked changes version earlier and later submit the same version officially that would be much appreciated. Let me know your thoughts and anticipated timing for planning purposes!

Thanks again,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

From: Diane Fiorenza [mailto:DFiorenza@npsp.com]
Sent: Wednesday, April 30, 2014 8:55 AM
To: Sarchet, Jennifer
Subject: RE: NDA 203441 (S002) Label

Hi Jennifer,
Our internal team met yesterday to go over the agency's comments. We were targeting a submission to you next week. Can you tell me if this will need to be an official sequence submission or would a tracked changes version via email be acceptable? If the latter is acceptable we can shave off publishing time and try to expedite. Let me know and I will try to push for an earlier turn around on my end.

Regards,
Diane C. Fiorenza, BS, RAC
Senior Director, Regulatory Affairs
NPS Pharmaceuticals
550 Hills Dr, 3rd Floor
Bedminster, NJ 07921
(908) 450-5520 - Office
(908) 450 3808 - Mobile
(908) 450 5351 - Fax

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Wednesday, April 30, 2014 8:26 AM
To: Diane Fiorenza
Subject: RE: NDA 203441 (S002) Label

Hello Diane,

Thank you for confirming receipt. Our team would like to have a meeting on Monday to go over the changes to the label. Is there any way you could have the label back to us on Friday by 1200?

Let me know…

Thanks,
Jennifer

From: Diane Fiorenza [mailto:DFiorenza@npsp.com]
Sent: Monday, April 28, 2014 2:15 PM
To: Sarchet, Jennifer
Subject: RE: NDA 203441 (S002) Label

Hi Jennifer,
I am confirming receipt of your email and label. We are currently assembling our internal team. I will get back to you as soon as I have more information regarding our responses. Thank you for your continued collaboration on the Gattex program.

Regards,
Diane C. Fiorenza, BS, RAC
Senior Director, Regulatory Affairs
NPS Pharmaceuticals
550 Hills Dr, 3rd Floor
Bedminster, NJ 07921
(908) 450-5520 - Office
(908) 450 3808 - Mobile
(908) 450 5351 - Fax

From: Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
Sent: Monday, April 28, 2014 12:51 PM
To: Diane Fiorenza
Subject: NDA 203441 (S002) Label

Hello Diane,

Attached is a courtesy copy in word and the PDF version of the current changes to the label for NDA 203441 (S002); Gattex.

Please let me know if you have any questions and when you anticipate having it back to us so I can let the team know. We had a little trouble with the track changes from the hand-off from Matt but I believe this is resolved in the current format and should better be able to track changes between NPS and us.

Thank you again,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
05/14/2014

From: Sarchet, Jennifer
To: "Diane Fiorenza"
Subject: NDA 203441/Supplement 002; Gattex; Information Request
Date: Monday, May 12, 2014 1:34:19 PM

Dear Diane,

We have the following information request for NDA 203441/Supplement 002; Gattex:

> Based on your 5/6/2014 response to our information request dated 04/28/14, it appears that one subject (Patient ID 0203-1003) might have been counted twice in the total number of subjects who were tested for neutralizing antibody. Please submit the full list of the 51 subjects who were tested for neutralizing antibody as proposed in your labeling. For each subject, submit study ID, patient ID, the protocol specified time points of the tested samples (including date and time), and teduglutide concentration of the samples that were already analyzed.
>
> We request a response to this information request by close of business EST 5/16/14. We also remind you of your planned 05/30/14 submission of results of the ongoing analysis of the teduglutide concentration in the samples that have not been analyzed.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
05/12/2014

June 24, 2014

Only the attachment to the e-mail in the below correspondence was originally entered into DARRTS. The e-mail itself was originally not included. Jennifer Sarchet requested to have the e-mail added as a cover note.

From:	Sarchet, Jennifer
To:	"DFiorenza@npsp.com"
Subject:	NDA 203441 (S002) Label
Date:	Monday, April 28, 2014 12:51:05 PM
Attachments:	Signed DARRTS Copy Use This For Labeling Updates for NDA 203441 S002 sponsor label revision and IFU 2 12 14 (2).pdf Use This For Labeling Updates for NDA 203441 S002 sponsor label revision and IFU 2.12.14.doc

Hello Diane,

Attached is a courtesy copy in word and the PDF version of the current changes to the label for NDA 203441 (S002); Gattex.

Please let me know if you have any questions and when you anticipate having it back to us so I can let the team know. We had a little trouble with the track changes from the hand-off from Matt but I believe this is resolved in the current format and should better be able to track changes between NPS and us.

Thank you again,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
04/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**PEDIATRIC AND MATRERNAL HEALTH STAFF REQUEST FOR CONSULTATION**	
TO: CDER Pediatric and Maternal Health Staff *(please check)* Pediatrics ☐ Maternal Health ☒ Both ☐			FROM *(Name, Office/Division, and Phone Number of Requestor)*: Jennifer Sarchet/DGIEP 240-402-4275	
DATE 3/10/2014	IND NO.	NDA/BLA NO. 203441/S002	TYPE OF DOCUMENT Supplement with REMS	DATE OF DOCUMENT 8/28/2013
NAME OF DRUG Gattex (teduglutide [rDNA origin]) for injection, for subcutaneous use, 5 mg.	NAME OF FIRM NPS Pharmaceuticals		CLASSIFICATION OF DRUG Micellaneous GI: glucagon-like peptide-2 (GLP-2) analog	PDUFA Goal Date 6/27/2014
Requested Consult Completion Date: May 23, 2014 (for revisions to the label) Official review should be completed NLT June 6, 2014	☐ Urgent* (< 14 days)		☒ Priority (14-29 days)	☐ Routine ≥ 30 days

*Note: Any consult requests with a desired completion date of < 14 days from receipt must receive prior approval from PMHS team leaders. Also, please check one of the three boxes above and also put in a due date.

REASON FOR REQUEST

Pediatrics:	Maternal Health Team:
☐ Labeling Review ☐ Written Request/PPSR ☐ PREA PMR/General Regulatory Question ☐ SPA ☐ Action Letter Review ☐ 30-day IND Review ☐ Other Protocol Review ☐ Meeting Attendance ☐ PeRC Preparation Assistance ☐ Other (please explain):	☒ Labeling Review ☐ Pregnancy Exposure Registry (protocol or report) ☐ Clinical Lactation Study (protocol or report) ☐ Pregnancy PK (protocol or report) ☐ 30-day IND Review ☐ Risk Management – Pregnancy Prevention and Planning ☐ Evaluation of possible safety signal ☐ Guidance development ☐ Other (please explain):
Link to electronic submission (if available): The share point link for the label is pending and will be made available to the assigned reviewer.	Materials to be reviewed: label

1. Please briefly describe the submission including drug's indication(s):

DGIEP is reviewing NDA 203441/S002, a new efficacy supplement that includes a revised REMS and final report of a 2 year carcinogenicity study in mice. "GATTEX® (teduglutide [rDNA origin]) for injection is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support."

2. Describe in detail the reason for your consult. Include specific questions:

DGIEP requests your assistance with reviewing the label and updating regulatory language as needed (convert 8.1 and 8.3 to the hybrid PLLR format).

3. Meeting dates: Labeling Meetings: April 2, 8, 21, 28 and May 7. Two additional team meetings pending.

4. DARRTS Reference ID # for Prior Peds or Maternal Health consults for this product (within the last 3 years):

Reference ID: 3447909 (2/14/2014)

Review team: Project Manager: Jennifer Sarchet and Stacy Barely Clinical reviewer & Team Leader: Ruyi He CDTL (serving also as clinical reviewer) Pharmacology/Toxicology reviewer & Team Leader: Babatunde Akinshola/Sushanta Chakder Clinical Pharmacology reviewer & Team Leader: Lucy Fang/Sue Chih Lee Other: CMC reviewer & Team Leader: Marie Kowblansky (serving also as CMC reviewer)	
PRINTED NAME or SIGNATURE OF REQUESTOR: Jennifer Sarchet Regulatory Project Manager	METHOD OF DELIVERY (Please check) ☒ DARRTS ☐ EMAIL ☐ HAND ☐ OTHER

Version: DARRTS 06/01/2011

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/s/

JENNIFER S SARCHET
03/10/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203441/S002

INFORMATION REQUEST

NPS Pharmaceuticals, Inc.
Attention: Diane Fiorenza, BS, RAC
Sr. Director, Regulatory Affairs
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Ms. Fiorenza:

Please refer to your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gattex (teduglutide [rDNA origin]) for injection, for subcutaneous use indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are depending on parenteral support.

We also refer to your August 28, 2013 submission, containing Risk Evaluation and Mitigation Strategy (REMS) modifications.

We are reviewing the REMS modifications of your submission and have the following comments and information requests. We request a prompt written response by March 12, 2014 in order to continue our evaluation of your supplemental NDA.

1. Submit a word version (and in track change format if revisions were made), for the Patient and Caregiver Counseling Guide and the REMS website screenshot.

If you have any questions, please contact me at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Jennifer Sarchet, RN, BSN
LCDR, USPHS
Regulatory Project Manager

Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JENNIFER S SARCHET
03/07/2014

From: Sarchet, Jennifer
To: "DFiorenza@npsp.com"
Cc: Barley, Stacy; Do, Phong
Subject: NDA 203441 Gattex Supplement 2
Date: Friday, February 21, 2014 1:13:39 PM

Dear Ms. Fiorenza,

Please refer to your New Drug Application (NDA) 203441 Gattex Supplement 2 submitted on August 28, 2013, under section 505(b) of Federal Food, Drug, and Cosmetic Act.

We are reviewing the clinical information for your product and have the following requests for information. We request that you provide your response by February 25, 2014, if possible.

Please submit reports of the cases below on Form FDA Med Watch 3500A and provide a MS Excel file with the data below for each report.

Case with Fluid Overload	Case with Fatalities
• US-000683 • US-000711 • US-000713 • US-000714 • US-000730 • US-000739 • US-000740 • US-000758 • US-000766 • US-000770 • US-000781 • US-000790 • US-000798 • US-000806 • US-000815 • US-000817 • US-000856 • US-000862 • US-000871	• US-000706 • US-000764 • US-000770 • US-000773 • US-000806 • US-000822 • US-000832 • US-000859

MS Excel Data Columns

- Mfr report #
- Suspects Product(s)
- Therapy Start Date
- Therapy End Date
- Gattex Dose, Frequency, & Route Used
- Diagnosis for Use (Indication)
- Concomitant Therapy
- Adverse Event Terms (MedDRA Preferred Term)
- Date of Event
- Outcome

- Sex
- Age(Yrs)
- Relevant History or Concomitant Disease
- Country
- Report Source
- Narrative

If you have any questions, please do not hesitate to contact me.

Thank you,
Jennifer

Thank you,

Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

JENNIFER S SARCHET
02/21/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-OPDP-RPM	Ana Tavakoli; Health Communications Analyst

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
2/12/14		203441	REMS Materials

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
GATTEX (teduglutide)			March 7, 2014

NAME OF FIRM:	
NPS	PDUFA Date: June 28, 2014

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

For OSE USE ONLY
- X☐ REMS

EDR link to submission:
url:gs:IAAAAAUBAAqmrgKudIIAAIMBrgKDAQAAAAECAgEAAgADFVJpc2sgTWFuYWdlbWVudCBQbGFucwYyMDM0NDEDbmRhAA%3d%3d

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS: Please review the REMS materials for Gattex to ensure they are not promotional in nature.
Materials as follows:

Provider:
Dear Healthcare Professional Letter
Dear Professional Society Letter
Prescriber Education Slide Deck
REMS Website Screenshots

Consumer:
Patient and Caregiver Counseling Guide
REMS Website Screenshots

Mid-Cycle Meeting: [Insert Date] Labeling Meetings: [Insert Dates] Wrap-Up Meeting: [Insert Date]	
SIGNATURE OF REQUESTER	
SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) X☐ eMAIL ☐ HAND

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/s/

PHONG DO
02/12/2014

From: Barley, Stacy
To: "DFiorenza@npsp.com";
cc: Sarchet, Jennifer;
Subject: NDA 203441 Gattex: Urgent request
Date: Wednesday, February 05, 2014 2:08:00 PM

Hello Ms. Fiorenza,

As you are aware, Matt Scherer will be away from our Division for the next 2 months. We are in the process of reviewing your NDA 203441 Gattex Supplement 2 [redacted] (b) (4) and request the following:

[redacted] (b) (4)

2) Please submit any labeling and REMS changes in track change format as well as a clean version. **We request a word version of track change and clean versions**.

I request that the items listed above are completed by COB Friday February 7, 2014 if possible. Please notify me if you have any questions. Thank you!

Stacy Barley, RN, M.S.N., M.H.A.
CDR, USPHS Commissioned Corps
Senior Regulatory Project Manager
Division of Gastroenterology/Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
(301) 796-2137 (office)
(301) 796-9905 (fax)
stacy.barley@fda.hhs.gov

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/s/

STACY R BARLEY
02/05/2014

Scherer, Matthew

From: Scherer, Matthew
Sent: Wednesday, January 08, 2014 1:46 PM
To: 'Diane Fiorenza'
Subject: NDA 203441/S002 (Gattex) - Information Request re: carcinogenicity datasets

Attachments: Carci Data Format and Stat Guidance Info Sheets 11-12-13.pdf

Dear Ms Fiorenza,

We are currently reviewing the mouse carcinogenicity data that was included in NDA 203441/S002 and have the following request. Please respond as soon as possible so may continue to review these data. The dataset(s) submitted omitted some important variables, including organcod, tumorcod, organnam, tumornam and organexm. Please review the attached Guidance and resubmit the data so they conform to the required format.

Carci Data Format and Stat Gui...

Kind Regards,

Matthew C. Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
CDER/OND/ODEIII
Ph: 301-796-2307
Fax: 301-796-9904

10903 New Hampshire Avenue
Building 22, Room 5139
Silver Spring, MD 20993

Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies

(The electronic data format is for two-year studies as well as transgenic mouse studies using all except the TgAC mouse models)

Revised 11/12/2013

The statistical reviewer responsible for the review of the carcinogenicity studies of this NDA/IND submission requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's April 2008 guidance document entitled "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*". The guidance document can be found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf. The cover page of the document is attached to this information sheet (Attachment A).

In Section III.D.3 of the above document the Agency gives a general description of the data formats for the pharmacology and toxicology datasets and refers readers to the associated document "*Study Data Specifications*" for more information about the format specifications of the data submission. This associated document can be found at the FDA website http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf. At this time, we are only requesting the tumor dataset in the format described on pages 9 and 10 (APPENDIX 1) of the associated document. The table containing the format for tumor data in the document is attached to this information sheet (Attachment B).

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Note that the draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available on the FDA web site at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079272.pdf
. Sponsors are urged to use the statistical methods recommended in the guidance to analyze the carcinogenicity study data in their IND or NDA submissions. The cover page of the document is also attached to this information sheet (Attachment C).

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 4677, Building 21, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, karl.lin@fda.hhs.gov.

(Attachment A)

Cover page of "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*"

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

June 2008
Electronic Submissions

Revision 2

(Attachment B)

Data format table on page 7 (APPENDIX 1) of the associated document "*Study Data Specifications*"

Tumor Dataset For Statistical Analysis[1,2] (tumor.xpt)				
Variable	**Label**	**Type**	**Codes**	**Comments**
STUDYNUM	Study number	char		[3]
ANIMLNUM	Animal number	char		[1,3]
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		[3,4]
TUMORNAM	Tumor name	char		[3,4]
ORGANCOD	Organ/tissue code	char		[3,5]
ORGANNAM	Organ/tissue name	char		[3,5]
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	[4]
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	[4]
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

[1] Each animal in the study should have at least one record even if it does not have a tumor.

[2] Additional variables, as appropriate, can be added to the bottom of this dataset.

[3] ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

[4] A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unusable or not examined.

[5] Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

(Attachment C)

Cover page of *"Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals"*

Guidance for Industry

Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability.

For questions regarding this draft document contact (CDER) Karl K. Lin, Ph.D., 301-796-0943, e-mail link.lin@fda.hhs.gov or link@cder.fda.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2001

Pharm/Tox

C:\Data\My Documents #1 A-M\Guidance04232001NncyDerr.DOC
11/22/05

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/s/

MATTHEW C SCHERER
01/08/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM	Matthew Scherer, RPM, DGIEP, 6-2307

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
11-20-13		203441/S002	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Gattex (teduglutide)	standard	Misc GI drug	5/17/14

NAME OF FIRM:	
NPS Pharmaceuticals	PDUFA Date: 6-28-14

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
X PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
☐ CARTON/CONTAINER LABELING
☐ MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
☐ ORIGINAL NDA/BLA
☐ IND
X EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
X INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: \\CDSESUB1\evsprod\NDA203441\203441.enx

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: TBD – target 1-28-14
Labeling Meetings: TBD – expected mid May 2014
Wrap-Up Meeting: TBD – target 5-31-14

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check all that apply) ☐ eMAIL ☐ DARRTS ☐ HAND

06/18/2013

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/s/

MATTHEW C SCHERER
11/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203441/S-002

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

NPS Pharmaceuticals, Inc.
Attention: Diane Fiorenza, BS, RAC
Senior Director Regulatory Affairs
550 Hills Drive 3rd Floor
Bedminster, NJ 07921

Dear Ms. Fiorenza:

Please refer to your Supplemental New Drug Application (sNDA) dated and received August 28, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for GATTEX (teduglutide [rDNA origin]) for injection, 5 mg.

We also refer to your amendment dated October 28, 2013.

This supplemental application proposes the following changes:

- Revision of the package insert to include results from 1) a completed long-term open-label study, 2) a study of the effects of teduglutide on postprandial gallbladder motility and biliary luminal diameters in healthy volunteers, and 3) a 2-year carcinogenicity study in mice.

- Modifications of REMS materials based on the final report of the long-term open-label study.

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your supplemental application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is June 28, 2014.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during

the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 31, 2014.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

- Provide an analysis dataset to facilitate an independent analysis of the immunogenicity impact on the pharmacokinetics (PK) and efficacy of teduglutide. The dataset should contain at least each individual's teduglutide concentrations, anti-drug antibody (ADA) status, percent and absolute change in weekly PN/I.V. volume, and binary response status (response defined as the achievement of at least a 20% reduction from baseline in weekly PN/I.V. volume) at all the time points evaluated.

- Provide the clinical/tabulation datasets and corresponding data definition file for Study CL-0600-021.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

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.

If you have any questions, call Matthew Scherer Regulatory Project Manager, at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Donna Griebel, MD
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

RICHARD W ISHIHARA
11/06/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Division of Biometrics VI Attn: Karl Lin	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Matthew Scherer, RPM, DGIEP, x6-2307

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9-18-13	Corresponding IND is 58213	203441/S002	New efficacy supplement	8/28/13

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Gattex (teduglutide)	standard	Misc GI	January 18, 2014

NAME OF FIRM: NPS Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☒ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: DGIEP is reviewing NDA 203441/S002, a new efficacy supplement that includes a final report of a 2 year carcinogenicity study in mice. DGIEP requests your assistance for the carc stats review. The Nonclinical reviewer is Babatunde (Emmanuel) Akinshola, the Team Leader is Sushanta Chakder and the RPM is Matthew Scherer.

This is an electronic submission that can be accessed through DARRTS or the following link:
\\CDSESUB1\evsprod\NDA203441\203441.enx

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MATTHEW C SCHERER
09/18/2013