CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203441Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE of New Drugs III
Division of Gastroenterology and Inborn Errors Products

NDA #:	203441
Products:	GATTEX (teduglutide [rDNA origin]) for injection
APPLICANT:	NPS Pharmaceuticals
FROM:	Victoria Kusiak, MD.
DATE:	12/19/2012

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

GATTEX is a 33 amino acid recombinant analog of the human glucagon-like peptide-2 (GLP2), a peptide that is secreted primarily from the lower gastrointestinal tract and increases absorptive capacity. GATTEX is indicated for the treatment of adult patients with short bowel syndrome (SBS) who are dependant on parenteral support (parenteral nutrition/intravenous hydration [TPN]). After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for GATTEX (teduglutide [rDNA origin]) for injection to ensure that the benefits of the drug outweigh the risks of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disorders associated with GATTEX (teduglutide [rDNA origin]) for injection. In reaching this determination, we considered the following:

A. The number of patients in the United States requiring total parenteral nutrition (TPN) is approximately 40,000 In the Oley Foundation Home TPN Registry, 26% of TPN patients had SBS, which suggests that the number of patients with SBS requiring TPN is approximately 10,000.[1] FDA granted Orphan Designation (on June 29, 2000) to the recombinant human

[1] Oley Foundation. North American home parenteral and enteral nutrition patient registry annual report, 1994

glucagon-like peptide-2 formulation for subcutaneous injection for the proposed treatment of SBS (adults).

B. Short Bowel Syndrome (SBS) results from surgical resection of some or all of the small or large intestine. Conditions that can result in bowel resection include Crohn's disease, malrotation, volvulus, intussusception, necrotizing enterocolitis, mesenteric vessel thrombosis, trauma, and others. Loss of the small intestine, if extensive, leads to malabsorption of protein, fluid, electrolytes, and micronutrients. According to the 2006 consensus statement:

> "Short-bowel syndrome results from surgical resection, congenital defect, or disease-associated loss of absorption and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet." [2]

The clinical presentation of SBS varies depending on the length and anatomy of the excised bowel as well as concomitant illness and medication. The loss of intestine can lead to malabsorption with consequent fluid imbalance, weight loss, anemia, and malnutrition. Depending on severity, malabsorption might be overcome by increasing oral intake. When increasing oral intake fails to provide sufficient nutrition, antimotility agents can be given to prolong nutrition-mucosa contact time to improve absorption. When both of these treatment modalities fail, patients become dependent on TPN therapy. It is this latter group of patients to whom teduglutide is targeted.

Following bowel resection in SBS, compensatory increases in bowel absorptive capacity by the remaining bowel can take up to two years to occur. In many cases it is insufficient to compensate fully for the lost intestine. If after two years the SBS patient still requires TPN support, it is unlikely the patient will be completely weaned from such support.[3] For many patients SBS is a lifelong disease associated with significant increases in morbidity and mortality

Although lifesaving, TPN itself is associated with clinical complications. These complications can include malnutrition, diarrhea, dehydration, nutrient deficiencies, electrolyte imbalance, recurrent intestinal obstruction, intestinal polyps, intestinal obstruction, gallbladder/pancreatic/hepatic disease, sepsis, liver injury, and blood clots. Thus both SBS and TPN supplementation are associated with multiple long-term multi-organ system derangements ranging from mild to life threatening. In addition, being tethered to the infusion apparatus required for TPN is a significant quality of life issue that directly affects mobility and lifestyle. TPN therapy is typically given for 10 or more hours a day for 5-7 days a week. Consequently, weaning from TPN is a cornerstone of clinical management in SBS.

C. GATTEX (teduglutide [rDNA origin]) for injection increases villus height and crypt depth of the intestinal epithelium. The applicant proposes that teduglutide accelerates intestinal adaptation and enhances barrier function in the small intestine, thus enhancing absorption of

[2] O'Keefe SJD, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J, Short bowel syndrome and intestinal failure: Consensus definitions and overview. Clinical Gastroenterology and Hepatology. 2006; 4:6-10
[3] Buchman AL. The clinical management of short bowel syndrome: steps to avoid parenteral nutrition. 1997. Nutrition. 13(10): 907-13.

fluids. In the pivotal 24-week trial, the primary efficacy endpoint was based on a clinical response, defined as a subject achieving at least 20% reduction in weekly TPN volume from Baseline (immediately before randomization) to both Weeks 20 and 24. The percentages of treatment group responders were compared in the intent-to-treat population. Sixty-three percent (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 TPN 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 TPN support. An uncontrolled extension study demonstrated continued reduction in fluid requirements. Six patients were weaned off TPN in theses studies. There were two additional supportive studies which demonstrated similar effects.

D. The expected use of this product is for the treatment of Short Bowel Syndrome in adult patients who rely on TPN therapy. Although some patients who responded to therapy with GATTEX were able to be completely weaned from TPN to oral intake, for the majority of patients, therapy with GATTEX is likely to be life long.

E. Adverse events that are the subject of this REMS and are listed in the Warnings and Precautions section of product labeling include "Acceleration of Neoplastic Growth" (Colorectal Polyps, Small Bowel Neoplasia), "Intestinal Obstruction", and "Biliary and Pancreatic Disease". Acceleration of neoplastic growth may result from the putative mechanism of action of GATTEX (teduglutide [rDNA origin]) for injection; in fact, intestinal mucosal hypertrophy has been documented in human subjects and, in non clinical studies, hypertrophic/hyperplastic changes have been observed in the mucosa of the large and small intestine and the gall bladder. The background rates for these events in patients with SBS are acknowledged to be higher than those seen in the general population (secondary to SBS as well as to administration of TPN).

Intestinal obstruction, biliary disease and pancreatic disease are all increased in the SBS population compared to the general population. The increase is due in part to the underlying residual anatomy of the patients who have variable lengths and or absence of small intestine or colon; variable surgical anastomoses; presence or absence of stomas; variable duration of disease before and after surgery; as well as variable underlying disease etiologies. Because of the number of variables and the relatively small number of patients with SBS, exact incidences are difficult to determine.

The following are listings of the events as described in labeling.

"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, 6 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 4 polyp cases occurred in the extension studies--two colorectal villous adenomas (onset at 6 and 7 months in GATTEX 0.10 and 0.05 mg/kg/day dose groups, respectively), one hyperplastic polyp (onset 6 months in GATTEX 0.10 mg/kg/day dose group), and one 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 7 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 studies, 1 subject required endoscopic dilation and none 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, 3 subjects had an episode of acute cholecystitis; 2 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."

Other potential SAES that are listed in the Warnings and Precautions section of the labeling include: fluid overload, and increased absorption of concomitant oral medication.

F. GATTEX (teduglutide [rDNA origin]) for injection is a new molecular entity.

The elements of the REMS will be: Communication Plan, elements to assure safe use (health care providers who prescribe GATTEX (teduglutide [rDNA origin]) for injection will have training regarding the risks and safe use of GATTEX)and a timetable for submission of assessments of the REMS.

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

/s/

VICTORIA KUSIAK
12/19/2012

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

Review of Final Amendments to the Proposed Risk Evaluation and Mitigation Strategy (REMS) for GATTEX in Short Bowel Syndrome

Date:	December 17, 2012; *Revised December 19, 2012*
Reviewer(s):	Scientific Lead, Carolyn L. Yancey, M. D., F.A.A.P., Senior Medical Officer, Division of Risk Management (DRISK) Ana Tavakoli, M.A., Health Communications Analyst, DRISK
Team Leader:	Kendra Worthy, Pharm. D., DRISK
Division Director	Claudia Manzo, Pharm. D., DRISK
Drug Name(s):	GATTEX® (teduglutide)
Therapeutic Class:	Glucagon-like Peptide (GLP-2) Receptor Analog
Dosage and Route:	0.5 mg/kg body weight administered by subcutaneous injection
Application/Numbers:	NDA 203-441/Amendments to the REMS are in submissions: Supplement 45 (Sequence 49); Supplement 46 (Sequence 50); Supplement 47 (Sequence 51); Supplement 50, (Sequence 55); Supplement 51 (Sequence 54); Supplement 53 (Sequence 57); Supplement 54 (Sequence 58); Supplement 56 (Sequence 60)
Subject:	Review of Final Amendments to the Proposed REMS for GATTEX for Small Bowel Syndrome
Applicant/sponsor:	NPS Pharmaceuticals, Limited (NPS)
OSE RCM #:	2012-046

CONTENTS

EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review evaluates the amendments to the proposed Risk Evaluation and Mitigation Strategy (REMS) for GATTEX for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support to improve intestinal absorption of fluid and nutrients. Based on the serious risks associated with teduglutide (possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disease), the Agency determined that a REMS is required to ensure that the benefits of teduglutide outweigh the risks. The original proposed REMS was received on November 30, 2011 and amendments to the proposed REMS and appended materials were received on August 3; September 5; October 31; November 30; December 6, 7, 12, 13, 17, and 18, 2012.

The amended proposed GATTEX REMS is comprised of a goal, a communication plan (directed to prescribers and professional societies, prescriber training as an element to assure safe use (ETASU) and a timetable for submission of assessments. Prescriber training will not be linked to distribution of GATTEX.

Based upon internal discussions including a REMS Oversight Committee meeting (August 15, 2012) and a Gastrointestinal Drugs Advisory Committee meeting (October 16, 2012), the applicant incorporated final revisions to the REMS Document, appended REMS materials, and the REMS website. [1, 2] The amendments to the proposed GATTEX REMS (Amendments to REMS are in Supplements 45, 46, 47, 50, 51, 53, 54, and 56) incorporate all of the Agency's revisions and comments to the REMS Document and appended materials including the REMS website, and the REMS supporting document (including a revised REMS assessment plan) and are acceptable to the DRISK. The DRISK recommends that the GATTEX REMS be approved.

1 INTRODUCTION

This is a review of the final amendments to the proposed REMS for GATTEX for SBS, appended REMS materials, REMS website landing page and screenshots, and the revised REMS assessment plan.

1.1 BACKGROUND

Teduglutide is an analog of naturally occurring human glucagon-like peptide-2 (GLP-2), a peptide secreted by L-cells of the distal intestine. Teduglutide preserves mucosal integrity by promoting repair and normal growth of the intestine through an increase in villous height and crypt depth and accelerates intestinal adaptation after bowel resection and enhances selective barrier function in the small intestine. The indication for teduglutide is stated above in the **Executive Summary**.

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[1] See DRISK Review, Interim Comments to Amendments to the Proposed REMS for GATTEX for SBS, Set # 1 (dated November 20, 2012) written by Carolyn L. Yancey, M.D., F.A.A.P., DRISK

[2] See ADDENDUM: Comments and Revisions To Be Sent to the Applicant (dated December 3, 2012) written by Carolyn L. Yancey, M.D., F.A.A.P., DRISK

Short Bowel Syndrome

Short Bowel Syndrome (SBS) is a serious life-threatening malabsorption disorder caused by the surgical removal of the small intestine, or rarely, due to the complete dysfunction of a large segment of bowel. Although some children are born with a congenital short bowel, most cases of SBS are acquired. Unless more than two-thirds of the small intestine is removed, development of SBS is uncommon. The applicant cites that there are between 10,000 and 15,000 adults in the United States with SBS who are dependent on parenteral nutrition (PN) and intravenous fluids (iv).

Complications associated with SBS are malabsorption of vitamins and minerals, such as deficiencies of vitamins A, D, E, K and B12, Calcium, magnesium, iron, folic acid, and zinc. These may appear as anemia, hyperkeratosis, easy bruising, muscle spasms, poor clotting and bone pain. Many of the complications and mortality with SBS is secondary to complication of the total parental nutrition (TPN), especially chronic liver disease, infection and thrombosis.

See the DRISK Interim Comments Review (Set 1) for details about teduglutide as a glucagon-like peptide (GLP-2) receptor analog. The DRISK Addendum to *and* the Interim Comments Review (Set 1) include details of the REMS Oversight Committee discussion and recommendations (August 15, 2012), the Gastrointestinal Drugs Advisory Committee meeting (October 16, 2012), and subsequent internal discussion that led to the proposed REMS elements presented in the **Executive Summary** of this review. Approved products for SBS are presented in the *REMS Oversight Committee Briefing Summary* in the Appendix to the Interim Comments Review (Set 1). [1]

1.2 REGULATORY HISTORY

The regulatory history below in regard to the proposed GATTEX REMS [under New Drug Application (NDA) 203-441 received on November 30, 2011] refers to milestones since November 9, 2012. See past DRISK GATTEX REMS Reviews for earlier regulatory history. [1, 2]

- November 20, 2012: The Office of Regulatory Policy (ORP) and the Office of General Counsel (OGC) held a teleconference with the DRISK to discuss final track changes to the REMS Document (including a communication plan and the addition of an ETASU for healthcare provider training (*non-mandatory*).
- November 20, 2012: Teleconference with the applicant, DGIEP and the DRISK to discuss Chemistry Manufacturing and Controls issues, post-marketing requirement, post-marketing commitment, and any questions about the amendments to the proposed REMS.
- December 3, 2012: The DRISK completed an "Addendum: with Comments and Revisions" to the Interim Comments on Amendments to the Proposed REMS for GATTEX in SBS Review. Addendum comments included revisions to the *Prescriber Education Slide Deck* and *Patient and Caregiver Counseling Guide.*
- December 14, 2012: The Regulatory Project Manager, DGIEP, contacted the applicant to request submission of a revised *Patient and Caregiver Counseling Guide*

that reflects required changes per the Agency (teleconference with the applicant on November 20, 2012).

- December 14, 2012: The DRISK issued written comments to the applicant that supplemented the ADDENDUM (see December 3 entry above). Comments included revisions to the proposed REMS Document, REMS website landing page and screenshots, Patient and Caregiver Counseling Guide and the REMS supporting document (revised REMS assessment plan).
- December 17, 2012: Two teleconferences with the applicant, the DGIEP/RPM, and the DRISK were held to clarify the applicant's questions about REMS amendment submissions including the final GATTEX REMS Document, appended materials (including the REMS website) and the revised REMS supporting document.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

The following materials submitted for review under the GATTEX REMS for SBS (NDA 203-441 GATTEX (Teduglutide [r-DNA]) are in regard to the proposed REMS:

- November 20, 2012: Applicant's substantially final proposed labeling (Supplement 43/Sequence 47)
- November 30, 2012: Division of Medical Policy Programs (DMPP) Patient Labeling Review: Medication Guide and Instructions for Use written by Latonia M. Ford, R.N., B.S.N., M.B.A., DMPP
- November 30, 2012: Office of Prescription Drug Promotion (OPDP) Consult Review on Labeling for GATTEX for Injection written by Kendra Y. Jones, Regulatory Review Officer, Division of Consumer Drug Promotion (DCDP)
- Amendments to the proposed REMS (and appended materials) submitted by the applicant follow:
  - November 30, 2012: Amendment: Updated REMS with Attached Communication letters and REMS Supporting Document (Supplement 45/Sequence 49)
  - December 6, 2012: Amendment: Updated REMS with Attached Communication letters; Updated Prescriber Education Slide Deck (Supplement 46/Sequence 50)
  - December 7, 2012: Amendment: Updated REMS Supporting Document and Post-training Knowledge Assessment Slides; Replacement REMS website landing page screenshots (Supplement 47/Sequence 51)
  - December 12, 2012: Amendment: Updated Proposed Package Insert; Medication Guide, Instructions for Use, and *Patient and Caregiver Counseling Guide* (Supplement 50/Sequence 55)

- December 12, 2012: Amendment: REMS Supporting Document – Resubmission from Amendment in Supplement 45 (Sequence 49) [See Supplement 51/Sequence 54]
- December 13, 2012: Amendment: Replacement file for *Patient and Caregiver Counseling Guide* (Supplement 53/Sequence 57)
- December 17, 2012: Amendment: Updated REMS and REMS Supporting Document. This submission includes clean final versions of the following: *Dear Healthcare Professional letter, Dear Professional Society letter,* Prescriber Education slide Deck, *Patient and Caregiver Counseling Guide,* REMS website landing page screen shots, and the Post-training Knowledge Assessment Questions. The REMS supporting document includes a revised REMS assessment plan. (Supplement 54/Sequence 58)
- December 18, 2012: Amendment: Updated REMS and REMS supporting document (Supplement 56/Sequence 60)

- December 14, 2012: Office of Prescription Drug Promotion (OPDP) Consult Review on the GATTEX *Patient and Caregiver Counseling Guide* written by Kendra Y. Jones, Regulatory Review Officer, Division of Consumer Drug Promotion (DCDP)
- December 18, 2012: (Supplement 55/Sequence 59) USPI Label and Medication Guide

2.2 ANALYSIS TECHNIQUES

Amendments to the proposed REMS for GATTEX for SBS were reviewed for conformance with the Agency's comments and revisions (including track changes) sent to the applicant on the REMS Document and appended REMS materials, and a revised REMS assessment plan.

3 RESULTS OF REVIEW

3.1 OVERVIEW OF CLINICAL PROGRAM

The NDA 203-441 (Supplement 02/Sequence 001) for teduglutide (TED) includes two Phase 3 multinational clinical trials in SBS as randomized (R), double-blind (DB), placebo-controlled (PBO-C), Study 004 and Study 020, conducted in the US, Canada and Europe. Both trials include open-label (OL) extension studies, Study 005 and Study 021, respectively.[3]

[3] Overview of the Clinical Program and Safety are summarized from the applicant's NDA 203-441 in Supplement 02, the Gastrointestinal Drugs Advisory Committee Background Package, internal discussions with the DGIEP, and substantially final labeling for GATTEX (teduglutide).

- Study 004: R, DB, PBO-C; TED with 3 treatment arms (0.05 mg/kg/day, 0.10 mg/kg/day, and PBO); 24- weeks duration; male and female adult patients who require PN at least 3 times/week
- Study 020: R, DB, PBO-C; TED with 2 treatment arms (0.05 mg/kg/day, PBO); duration 24 weeks; patients (same as above)
- Extension Study 005: OL, TED with 1 treatment arm (0.05 mg/kg/day); duration 24 months; patients who completed or stopped dosing [due to an adverse drug reaction (ADR)] in Study 004; long-term safety
- Extension Study 021: OL, TED with 2 treatment arms (0.05 mg/kg/day and 0.10 mg/kg/day); patients who completed or stopped dosing due to an ADR in Study 020; long-term safety

Efficacy

Two caveats apply to understanding efficacy results in this NDA:

- Study 004 and Study 020 were conducted sequentially. Preliminary results of Study 004 were available during discussions of the design of the primary endpoint and statistical analysis of Study 020.
- Though both studies are similar in design, there are key differences between the two studies:
  - Study 004 had a different fluid optimum stabilization algorithm to guide clinicians in selecting PN/IV fluid administered during the trial: Study 004 allowed only 10% fluid reduction at key time points, contrasted with Study 020 allowed a 30% reduction in fluid. Hence, the absolute change in volume during the study period for Study 004 appears to be smaller than that of Study 020.

Efficacy Endpoints and Efficacy Results

- Study 004: The primary efficacy endpoint is ordered categorical graded response related to PN volume reduction and duration
  - Primary Efficacy Results: Not statically significant ($p = 0.161$). This analysis concludes formal statistical testing for Study 004.
  - Secondary Efficacy Results: Secondary endpoints trended in favor of TED 0.05 mg/kg/day (to-be-marketed dosage) over PBO with the following clinically meaningful outcomes: Change in PN/IV volume; at least 1-Day reduction in PN/IV; and, complete weaning off PN by Week 24 (2 of 35 patients treated with TED and zero treated with PBO)
- Study 020: The percentage of patients who had a reduction of 20% to 100% in PN volume at Weeks 20 and 24 compared to baseline.
  - Primary Efficacy Results: TED 0.05 mg/kg/day treatment group: 27 / 43 (62.8%) and PBO treatment group: 13/ 43 (30.2%); $p = 0.002$
  - Secondary Efficacy Results: Trended in favor of TED (0.05 mg/kg/day) with the absolute change in PN/IV volume from Baseline to Week 24: TED 0.05

mg/kg/day treatment group: - 4.4 L/week versus PBO treatment group: - 2.3 L/ eek; at least one-day reduction in PN/IV demonstrated as 21/39 (53.8%) versus 9/39 (23.1%); and cmplete weaning off PN by Week 24: zero patients

- Study 005 and 021: Long-Term Extension Studies Efficacy: complete weaning off PN/IV was achieved as follows:
  - Study 005 (TED 0.05 mg/kg/day): 1 new patient weaned off PN/IV; 2 patients weaned off PN/IV in Study 004 continued with clinical response without requiring re-starting PN/IV
  - Study 021 (TED 0.05 mg/kg/day): 12 new patients weaned of PN, to-date (November 2012)

3.2 SAFETY

Based on data in animal models of SBS and studies in normal animals, TED therapy in humans is expected to produce increase in intestinal absorption through increases in the intestinal surface area. [4, 5] The non-clinical data that is consistent with the serious clinical risks associated with teduglutide treatment described below.

Clinical Exposure

Clinical safety for TED in SBS patients is based on controlled Studies 004 and 020, and OL extension Studies 005 and 021. Across 15 clinical studies in the clinical development program, 566 patients were treated with TED and 198 patients were treated with PBO. Of 566 TED-treated patients, 299 patients participated in clinical pharmacology studies, 173 patients were treated across two Phase 3 trials, and 94 patients were treated in other clinical trials (Crohn's disease).

Of 566 TED-treated patients, 135 patients (23.9%) were exposed to TED for at least 6 months, and 75 patients (13.3%) were exposed to TED for at least 12 months. The mean duration of exposure to TED was 15.5 weeks with total person years (pt-yrs) of 168 pt-yrs. The greatest duration of exposure to TED (defined as pt-yrs) occurred in the SBS efficacy and safety studies for 141.86 pt-yrs.

The serious risks associated with TED (that are included in the REMS goal) follow:

3.2.1 Possible acceleration of neoplastic growth and enhancement of colon polyp growth

Possible acceleration of neoplastic growth and enhancement of colon polyp growth is the primary safety concern with use of GATTEX. In OL extension studies, three (3) cases of malignancy were observed in SBS in patients treated with TED (0.05 mg/kg/day). No malignancies were observed in the controlled-portion of the clinical trials.

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[4] P B Jeppesen et al, Ted, a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, *Gut* 2005; 1224-1231

[5] P B Jeppesen, Growth Factors in Short-Bowel syndrome Patients, *Gastroenterol Cllin N Am*, 36 (2007); 119-121

- 3 patients were diagnosed with malignancy in the clinical studies, all of whom were male and received GATTEX 0.05 mg/kg/day in the extension studies:
    - 1 patient 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
    - 2 patients 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.

Causality for each of these 3 cases was not attributed to TED. Due to TED's mode of action, promoting growth and repair of gastrointestinal epithelium, it is possible that long-term treatment with TED could accelerate growth of intestinal neoplasms.

3.2.2 Gastrointestinal Obstruction

Gastrointestinal obstruction is inherent to and a well-known complication of SBS. Based on the mode of action of TED, gastrointestinal obstruction observed in the TED clinical development program follows:

- PBO-C Studies: Twelve (12) patients experienced one or more episodes of intestinal obstruction/stenosis: 6 in SBS PBO-C studies and 6 in OL studies. The 6 patients in the PBO-C trials were all treated with TED: 3/77 (3.9%) on TED 0.05 mg/kg/day and 3/32 (9.4%) on TED 0.10 mg/kg/day. No cases of intestinal obstruction occurred in the PBO group. Onsets ranged from 1 day to 6 months.
- OL Studies: 6 additional patients (all on TED 0.05 mg/kg/day) were diagnosed with intestinal obstruction/stenosis with onsets ranging from 6 days to 7 months.
    - 2 of 6 patients from the PBO-C trials experienced recurrence of obstruction in the OL studies. Of all 8 patients with an episode of intestinal obstruction/stenosis in the OL studies, 1 patients required endoscopic dilatation and none required surgical intervention.

3.2.3 Biliary and Pancreatic Disease

Gallbladder, biliary and pancreatic disease are known complications of SBS and are considered causally related serious adverse events with TED treatment. In PBO-C studies, there were 4 cases of cholecystitis observed with TED treatment.

- PBO-C studies, for gallbladder, biliary and pancreatic disease:
    - 3 patients were diagnosed with cholecystitis, all of whom had prior history of gallbladder disease and were in the TED 0.05 mg/kg/day dose group. No cases were reported in the PBO 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.
    - For pancreatic disease in PBO-C studies, 1 patient (TED 0.05 mg/kg/day dose group) had a pancreatic pseudocyst diagnosed after 4 months of TED.
- OL studies::

- 3 patients were diagnosed with cholecystitis, each of whom had prior history of an episode of acute cholecystitis; 2 patients had new-onset cholelithiasis; and 1 patient experienced cholestasis secondary to an obstructed biliary stent.
- For pancreatic disease in OL studies, 1 patient was diagnosed with chronic pancreatitis; and 1 patient was diagnosed with acute pancreatitis.

3.2.3 Other Adverse Event of Special Interest

Additional adverse events of special interest associated with TED therapy (included in proposed labeling but *not included in the goals of the REMS* follow:

Fluid Overload

Fluid overload and congestive heart failure were observed in the SBS clinical trials. Fluid overload considered related to enhanced fluid absorption is associated with the mode of action of TED.

- PBO-C group: 4 of 39 patients (6.8%) experienced observed fluid overload.
  - TED (0.05 mg/kg/day) treatment group 9 of 77 patients (11.7%) experienced fluid overload (2 cases of congestive heart failure (CHF), one of these 2 cases was considered a serious adverse event (SAE) on Day 186. Patient history included undiagnosed hypothyroidism (history of thyroidectomy) and/or cardiac dysfunction.

Increased Absorption of Concomitant Medication

Altered mental status in association with TED was 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 during TED therapy.

Immunogenicity

Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of TED may trigger development of antibodies. In the R, DB, PBO-C, parallel-group, multi-center, clinical trial (Study 1) in adults with SBS, the incidence of anti-TED antibody was 0% (0/16) at Week 12 and 18% (6/34) at Week 24 in patients who received sc administration of 0.05 mg/kg TED once daily. Anti-TED antibodies were cross-reactive to native glucagon-like peptide (GLP-2) in 5 of the 6 patients (83%) who had anti-TED antibodies.

In OL studies, the immunogenicity incidence rate increased over time to 27% (14/51) at 12 months and 38% (13/34) at 18 months. Anti-TED antibodies appear to have no impact on short-term (up to 1.5 years) efficacy and safety although the long-term impact is unknown.

See the substantially final proposed labeling for GATTTEX (teduglutide) for additional details of the above safety information in Section 3, in this review.

3.3 APPLICANT'S PROPOSED REMS

NPS proposes an amended GATTEX REMS that includes the following agreed upon components and appended materials. The final formatted REMS for GATTEX submitted

on December 18, 2012 as an amendment to the REMS (in Supplement 56) is attached to this review (see **Attachments** at the end of this review).

The proposed goal of the GATTEX REMS is:

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

3.3.1 REMS ELEMENTS

The REMS for GATTEX is comprised of a communication plan, an element to assure safe use, specifically Prescriber Training and Education, and a Timetable for Submission of Assessments.

Comment:

The applicant accepted all revisions (in track changes) as stipulated by the Agency.

3.3.1.1 Communication Plan

As a REMS element, the communication plan includes:

- A *Dear Healthcare Professional letter* targeted to gastroenterologists, colorectal and gastrointestinal tract surgeons. This initial letter will be distributed within 60 days of approval of GATTEX or at the time of product launch, whichever is sooner, and will be sent at 12 and 24 months after product approval. NPS will indentify and send the DHCP letter to all other GATTEX prescribers within 60 days of the date of initial prescription, and again at 12 and 24 months after their initial prescription.
- A *Dear Professional Society letter* to the leadership of the professional organizations as listed in the final formatted REMS for GATTEX will request that the letter be provide to the members of these professional organizations. The Dear Professional Society letter will be disseminated via direct mail or electronic delivery within 60 days of approval of GATTEX, or at the time of product launch.

Comment:

The applicant accepted all revisions (in track changes) as stipulated by the Agency.

3.3.1.2 Element to Assure Safe Use

The applicant will ensure that training and education materials will be available for completion by healthcare providers who prescribe GATTEX for SBS via the GATTEX REMS website and available as hard copy, upon request. The training and education will be targeted to the physicians targeted to receive the *Dear Healthcare Professional letter*. NPS will identify non-targeted HCPs who prescribe GATTEX to receive the DHCP letter with information about the training as not all patients with SBS are cared for by a subspecialist, for example, gastroenterologist and/or colorectal/gastrointestinal surgeon.

The program comprises the following:

- *Prescriber Educational Slide Deck*
- *Patient and Caregiver Counseling Guide*

Comments:
NPS is committed to identify any non-target prescribers of GATTEX to receive the DHCP letter with directions on how to access training materials online or to receive hard copy. The Agency concurred with NPS on their commitment to reach out to non-target prescribers of GATTEX for the training and education materials for reasons cited above in this review.

3.3.1.3 Timetable for Submission of Assessments

The timetable for submission of assessments is annually from the date of approval of the REMS.

Comment:

The Agency believes that a 12-month assessment report will provide adequate time for ample data from survey testing of GATTEX prescribers and patients taking GATTEX therapy for their understanding of the serious risks associated with this product.

3.3.2 REMS ASSESSMENT PLAN

The REMS assessment plan includes the following:

1. Date(s) the Dear Healthcare Professional letter mailing(s) were sent and number of healthcare professionals that were sent this letter
    a. Number of mailings returned
    b. Sources of the recipient lists
2. Date(s) the Dear Professional Society mailing(s) were sent and number of societies that were sent this letter
3. Number of HCPs who completed the Post-training Knowledge Assessment Questions via the NPS REMS website or through mailing
    a. Demographics of prescribers (by specialty type) that completed the post-training knowledge assessment questions, to the extent possible
    b. Summary of the method used to complete the Post-training Knowledge Assessment Questions (on-line, fax/mail);
    c. Number of prescribers who completed each knowledge assessment question correctly and the number of prescribers who did not complete each post training knowledge assessment question correctly
4. Number of prescribers identified through specialty pharmacy dispensing data to have dispensed a patient prescription who did not complete the Post-training Knowledge Assessment Questions (during the reporting period and cumulative)
        a. Number of prescribers who did not complete the Post-training Knowledge Assessment Questions who were contacted by NPS and then, who completed the Post-training Knowledge Assessment Questions

5. KAB surveys of prescribers' and patients' understanding of the potential risks associated with use of GATTEX for Short Bowel Syndrome, their understanding of the recommended monitoring during, and after treatment with GATTEX.
6. Narrative summary of adverse events of interest including the risks of acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction and biliary and pancreatic disorders reporting from spontaneous sources, published literature, regulatory agencies, clinical studies and trials (clinical serious adverse events/SAEs) and solicited sources for entry into the NPS drug safety database
7. The requirement for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified

Comments:

The Agency accepts that these reports and data will be based on monitoring from NPS and that some of these data will be identified through a contract pharmacy vendor.

3.4 PROPOSED POSTMARKETING STUDIES

The approval of GATTEX will include one postmarketing requirement (PMR) and one postmarketing commitment (PMC). Brief summary follows of the information about the PMR and PMC that will be included in the Approval letter:

PMR (# 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. 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.

PMC (#1978-2):

Elemental Impurities specifications will be expanded to include limits and testing for all metals as recommended in the substantially final USPI.

See the Approval letter from the DGIEP for additional details and the final timetables for the PMR and PMC.

4 DISCUSSION

GATTEX for the treatment of adult patients with SBS dependent on parenteral support carries the serious risks of possible acceleration of neoplastic growth and enhancement of colon polyps, gastrointestinal obstruction, and biliary and pancreatic disorders. Because of these serious risks with GATTEX, FDA required a REMS for the indication in adult

patients with SBS to ensure that the benefits of GATTEX (teduglutide) outweigh the risks.

Labeling includes these key risks and three additional serious risks (fluid overload, increased absorption of concomitant medications, and immunogenicity), recommended pre-treatment screening colonoscopy and ongoing monitoring (including colonoscopy no less frequently than every 5 years and laboratory tests) during and after stopping GATTEX therapy. The REMS includes educational materials directed to prescribers under a communication plan and specific training materials directed to prescribers and for prescribers to use to educate patients about the serious risks associated with GATTEX under an ETASU.

The Agency considered *requiring* prescriber training as a requirement for prescribing GATTEX; however, in view of the expertise of the subspecialists who most often manage patients with SBS, the Agency agreed to include a non-mandatory ETASU for prescriber training. FDA believes that the communication plan and ETASU for prescriber training in the proposed REMS are sufficient to support safe use of GATTEX. The GATTEX REMS assessment plan will require annual submission of assessment reports.

The amendment to the proposed REMS for GATTEX in SBS (received on December 18, 2012) includes all required revisions (to the REMS Document, appended REMS materials including the REMS website and the REMS supporting document with the REMS assessment plan) based upon the Agency's comments. The DRISK finds the amendments to the proposed REMS for GATTEX to be acceptable.

The proposed postmarketing studies (described in **Section 3.4**) aim to assist in providing data that may not be discerned from the REMS assessments.

5 CONCLUSION

In conclusion, the amended proposed REMS for GATTEX (teduglutide) for adult patients with SBS received on December 18, 2012 contains the agreed upon revisions to the REMS Document, appended REMS prescriber training and educational materials, and the REMS website. The proposed REMS assessment plan incorporates the additional components included in the Advice letter (to be dated December 21, 2012) and is acceptable to the DRISK.

6 RECOMMENDATIONS TO THE DIVISION OF GASTROINTESTINAL AND INBORN ERRORS PRODUCTS

The DRISK recommends approval of the REMS for GATTEX in SBS and requests that the REMS assessment plan be included in the Approval letter.

ATTACHMENTS

The final REMS Document and appended REMS materials (*Dear Healthcare Professional letter, Dear Professional Society letter*) are attached to this review in individual clean WORD version. The other final REMS appended training and educational materials (*Prescriber Education Slide Deck, Patient and Caregiver and Counseling Guide, GATTEX REMS website landing page screenshot*) are in PDF format and with the DGIEP.

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/s/

CAROLYN L YANCEY
12/19/2012
Final GATTEX REMS Review_19Dec2012

CLAUDIA B MANZO
12/19/2012
concur

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

ADDENDUM: Comments and Revisions To Be Sent To the Applicant

Interim Comments on Amendments to the Proposed Risk Evaluation and Mitigation Strategy for GATTEX in Short Bowel Syndrome

Date:	November 30, 2012: *Revised December 3, 2012*
Reviewer(s):	Scientific Lead, Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK) Ana Tavakoli, M.A., Health Communication Analyst, DRISK
Team Leader:	Kendra Worthy, Pharm. D., DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Subject:	Comments on two additional appended REMS materials in the proposed GATTEX REMS for Short Bowel Syndrome
Drug Name(s):	GATTEX (teduglutide [recombinant-Deoxyribonucleic Acid (DNA) origin]) powder for subcutaneous injection
Therapeutic Class:	Glucagon-like Peptide (GLP-2) Receptor Analog
Dosage and Route:	0.5 mg/kg body weight administered by subcutaneous injection
NDA/Supplement:	NDA 203-441/Supplement 044/Sequence 040
Applicant:	NPS Pharmaceuticals, Limited (NPS)
OSE RCM #:	2012-046

ADDENDUM

This Division of Risk Management (DRISK) Addendum provides comment and required revisions to the *Prescriber Education Slide Deck* and the *Patient and Caregiver Counseling Guide* submitted as a REMS Amendment (dated October 31, 2102/ Supplement 044/ Sequence 040) to the proposed GATTEX REMS for Short Bowel Syndrome (SBS). The applicant submitted a *Prescriber Education Slide Deck* to enhance prescriber education about the serious risks associated with GATTEX and a *Patient and Caregiver Counseling Guide* for prescribers to use to educate patients with Short Bowel Syndrome (SBS) considering GATTEX therapy. These education materials will be included under the ETASU for Prescriber Training. Refer to the DRISK review (dated November 20, 2012) for comments on the proposed GATTEX REMS and supporting document.[1]

Materials Reviewed

- October 31, 2012: The applicant submitted a GATTEX REMS Amendment with additional required education material (specifically, a *Prescriber Education Slide Deck* and a *Patient and Caregiver Counseling Guide*) to be placed under the ETASU for Prescriber Training
- November 9, 2012: Consult from the Division of Consumer Drug Promotion (DCDP) in the Office of Prescription Drug Promotion (OPDP) with recommends to remove numerous promotional claims and/or presentations, and comment that this proposed material (*Patient and Caregiver Counseling Guide)* does not represent material appropriate for use in the proposed GATTEX REMS

Recommendations for Review Division

The DRISK requests that the below comments and revisions to the new proposed appended REMS education materials (submitted October 31, 2012/Sequence 040) be sent to the applicant as soon as possible. As some revisions to these education materials are substantial, the DRISK is available for a teleconference with the applicant and DGIEP, if requested.

Comments To Be Sent to Applicant

The following are required revisions to the *Prescriber Education Slide Deck* and *Patient and Caregiver Counseling Guide)* submitted on October 31, 2012/Supplement 044/ Sequence 040) that must be incorporated into your appended REMS education materials for the GATTEX REMS to be acceptable to the Agency. Submit these revised REMS education materials incorporating the Agency's comments by close of business on December 7, 2012. If this is not possible, notify the Agency as soon as possible as to the expected submission date of these revised materials.

See the comments and revisions to the proposed *Prescriber Education Slide Deck* and *Patient and Caregiver Counseling Guide* appended REMS materials corresponding to the comments below:

[1] See DRISK Interim Comments Review (Set 1) written by Carolyn L. Yancey, M.D. on November 20, 2012.

A. Proposed Prescriber Education Slide Deck

1. Slide 1: Acceptable
2. Slide 2:
   - In the Table of Contents (TOC), 1st Topic, delete [redacted] and replace it with "Indication"
   - In the 2nd Topic, insert the word, "Serious" in front of "Adverse Events of Special Interest"
   - In the 3rd Topic, insert the word, "Possible" in front of "Acceleration of Neoplastic Growth"
   - In the 4th Topic, insert the word, "Possible" in front of "Enhanced Growth of Colorectal Polyps"
   - In the 5th Topic, delete, [redacted] Obstruction" and replace it with, "Gastrointestinal"
   - In the 7th Topic, delete, [redacted] and replace it with, "Fluid Overload"
3. Slide 3:
   - Delete the title, [redacted] and all proposed text related to this Topic.
   - Replace the slide title with, "Indication"
   - Insert the following text in the slide, "GATTEX (teduglutide) is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support."
4. Slide 4:
   - In the title, insert the word, "Serious" in front of "Adverse Events of Special Interest"
   - Delete the [redacted] at the end of the title and [redacted]
   - Delete the word, [redacted] in the first bullet point header; replace it with "Possible" in front of "Acceleration of neoplastic growth and enhanced growth of colorectal polyps"
   - In the 2nd sub-bullet, delete, [redacted] obstruction" and replace it with , "Gastrointestinal"
5. Slide 5:
   - In the title, insert the word "Possible" in front of "Acceleration of Neoplastic Growth"
   - [redacted]

- In the 3rd bullet point, remove the extra space between "3 patients" and "on"
- [redacted]

6. Slide 6:
   - In the title, insert the word "Possible" in front of "Acceleration of Neoplastic Growth"
   - Delete [redacted]
   - Insert the following text below sub-header, "Possible Acceleration of Neoplastic Growth":
     - Based on the pharmacologic activity and findings in animals, GATTEX has the potential to cause hyperplastic changes including neoplasia
     - 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.
     - 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
     - In patients at increased risk for malignancy, the clinical decision to use GATTEX should be considered only if the benefits outweigh the risks
7. Slide 7:
   - In the title, delete the word, [redacted] and replace it with "Possible"
   - Revise 1st sub-bullet, [redacted] to read as "2 villous adenomas"
   - Revise 2nd sub-bullet text, [redacted] to read "2 hyperplastic"
   - [redacted]
8. Slide 8:
   - Insert the word, "Possible" in front of "Enhanced Growth of colorectal Polyps"
   - Delete [redacted] from sub-header, "Colorectal Polyps"
   - Insert the following text below the sub-header:

- Colonoscopy of the entire colon with removal of polyps must 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

9. Slide 9:
   - In the title, delete "(b) (4) Obstruction" and replace it with, "Gastrointestinal"
   - (b) (4)
   - Delete all proposed text in this slide and replace it with following text:
     - 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, 0.05 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
       - Of all of these patients, 1 patient required endoscopic dilatation; and none required surgical intervention

10. Slide 10:
    - Delete the title, (b) (4) Obstruction" and replace it with, "Gastrointestinal Obstruction"
    - Delete (b) (4) from sub-header, "Intestinal Obstruction"
    - Delete the proposed content under the sub-header and replace it with the following text:
      - 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

11. Slide 11:
    - [redacted]
    - Content in this slide is, otherwise, acceptable
12. Slide 12:
    - Delete [redacted] in the sub-header, "Gallbladder and Bile Duct Diseases"
    - Content in this slide is otherwise, acceptable
13. Slide 13:
    - [redacted]
    - In the 1st sub-bullet, insert [redacted] to read as, "All 3…"
    - Delete 2nd sub-bullet proposed text and replace it with, "None of these events resulted in study withdrawal"
14. Slide 14:
    - Delete, [redacted] in the sub-header, "Pancreatic Diseases"
    - Content is, otherwise, acceptable
15. Slide 15:
    - Delete the proposed title and replace it with "Fluid Overload"
    - [redacted]
    - Under the 2nd major bullet, delete all text [redacted].
16. Slide 16: Delete this slide and figure.
17. Slide 17: Acceptable.
18. Slide 18:
    - Delete the proposed title and replace it with "Fluid Overload"
    - Delete [redacted] from sub-header, "Cardiovascular Disease"
19. Slide 19:
    - [redacted]
    - Content is, otherwise, acceptable
20. Slide 20:
    - Delete [redacted] from sub-header
    - Delete proposed text and insert the following text:
        - 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, etc.) requiring titration or with a narrow

therapeutic index may require dose adjustment while on GATTEX.

B. Proposed Patient and Caregiver counseling Guide

1. Front Cover: Remove the [redacted] (b) (4) from the front cover

2. Page 2: Remove the title, [redacted] (b) (4) and all text below the heading.

3. Page 3: Entitled, **Understanding the Risk of GATTEX**, text should focus only on the safety risks and important safety information per the substantially final proposed labeling that includes a Medication Guide.

4. Page 4: Entitled, [redacted] (b) (4) remove the entire heading and all text below the heading.

5. Page 5: Entitled, **The GATTEX Discussion**, text should focus only on the safety risks and important safety information per the substantially final proposed labeling that includes a Medication Guide.

[redacted] (b) (4)

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/s/

CAROLYN L YANCEY
12/03/2012
Addendum to Interim Comments Review (Set 1) of Amendments to the Proposed GATTEX REMS

KENDRA C WORTHY
12/03/2012

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 Amendments to the Proposed Risk Evaluation and Mitigation Strategy for GATTEX in the Treatment of Short Bowel Syndrome (Set # 1)

Date:	October 27, 2012; *Revised November 20, 2012*
Reviewer(s):	Scientific Lead, Carolyn L. Yancey, M.D., F.A.A.P., Senior Medical Officer, Risk Management Analyst, Division of Risk Management (DRISK) Ana Tavakoli, M.A., Health Communication Analyst, DRISK
Team Leader:	Kendra Worthy, Pharm. D., DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Subject:	Interim Comments on amendments to the proposed Risk Evaluation and Mitigation Strategy for GATTEX for Short Bowel Syndrome
Drug Name(s):	GATTEX (teduglutide [recombinant-Deoxyribonucleic Acid (DNA) origin]) powder for subcutaneous injection
Therapeutic Class:	Glucagon-like Peptide (GLP-2) Receptor Analog
Dosage and Route:	0.5 mg/kg body weight administered by subcutaneous injection
NDA/Supplements:	NDA 203-441 (Original Supplement 02/Sequence 001), Amendement (Supplement 029/Sequence 026), Amendement (Supplement 032/Sequence 029), Amendement (Supplement 044/Sequence 040)
Applicant:	NPS Pharmaceuticals, Limited (NPS)
OSE RCM #:	2012-046

CONTENTS

1 INTRODUCTION

This Division of Risk Management (DRISK) Interim Comments Review evaluates and communicates required revisions to the amendment (submitted on September 5, 2012) to the original proposed Risk Evaluation and Mitigation Strategy (REMS) for GATTEX for the treatment of Short Bowel Syndrome (SBS) (submitted on November 30, 2011/ Supplement 02/Sequence 001). The serious risks with teduglutide are the risk of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disease.

2 BACKGROUND

Teduglutide (GATTEX) is a new molecular entity (NME) that is a recombinant analogue of human glucagon-like peptide-2 (GLP-2). The proposed indication is for the treatment of adult patients with SBS to improve intestinal absorption of fluid and nutrients. The to-be-marketed product is a sterile, single-use, 3 mL glass vial containing 5 mg of teduglutide as a white lyophilized powder for reconstitution with 0.5 mL sterile water for subcutaneous (sc) injection (solvent provided in a pre-filled syringe). The recommended once daily dose teduglutide is 0.05 mg/kg body weight.

Original Proposed REMS for GATTEX

The applicant submitted the original proposed REMS for GATTEX with a Medication Guide (MG), communication plan, ETASUs[1], implementation plan, and Timetable for Submission of Assessments.

REMS Oversight Committee Meeting

The DRISK presented the serious risks with teduglutide [2] that require a risk mitigation strategy beyond labeling (and pharmacovigilance) and the applicant's original proposed REMS for GATTEX with ETASUs to the REMS Oversight Committee (ROC) on August 15, 2012.

The ROC agreed with the Review Team that the proposed ETASUs were not necessary for GATTEX based on the following rationale:

- Target prescribers for teduglutide will most likely be specialty physicians, specifically, gastroenterologists and colorectal surgeons who have expertise in the complex management of adult patients with SBS post-surgical resection.
- Target subspecialty physicians are trained to manage complications of SBS including dehydration, diarrhea, chronic weight loss, and life-threatening complications of gastrointestinal obstruction, sepsis, blood clots, and ongoing risks of hepatobiliary disease. These subspecialists understand the potential and

[1] The proposed ETASUs formed a tightly restricted drug distribution program for access to GATTEX with the following requirements: Prescriber Certification, Pharmacy Certification, Documentation of Safe Use Conditions, Patient Monitoring, and a GATTEX Patient Registry.

[2] Serious risks with teduglutide that require risk mitigation beyond labeling are the risk of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disease.

known serious risk with teduglutide, some of which are inherent complications of SBS.

- A collaborative team approach led by a gastroenterologist is used in many settings for care of patients with SBS. Other team providers may include nutritionists, clinical pharmacists, nurse practitioners, and/or physician assistants. Follow-up requires frequent doctor visits and monitoring to avoid septic episodes and treatment of small bowel bacterial overgrowth.
- Long-term care burden for patients with SBS is substantial including chronic parenteral nutrition. The added burden of required participation in a restricted distribution program for access to a potentially beneficial product will likely be excessive in the hands of target subspecialty physicians.

The ROC agreed that the broad scope of the restricted ETASUs did not appear aligned with the serious risks with teduglutide in SBS patients managed by subspecialists with expertise in the management of the serious and ongoing complications of SBS.

The Agency held a teleconference with the applicant (on August 23, 2012) to request re-evaluation of the proposed ETASU REMS due to the burden ETASUs create for patients, barriers to access for these complex patients, and in consideration of target subspecialists' expertise in the management of serious complications inherent to SBS.

The applicant's amendment (dated September 5, 2012) to the original proposed REMS incorporates revised REMS elements (a communication plan and timetable for submission of assessments). In a teleconference with the applicant on October 5, 2012, the Agency required that a Prescriber Education Slide Deck and patient education material (for prescribers to use to educate patients) about the serious risks with GATTEX be added to the communication plan education materials to further support prescriber and patient education about the serious risks with GATTEX. The applicant submitted these two new education materials to the Agency on October 29, 2012.

See **Section 8**, **APPENDICES**, in this review, for the **ROC Briefing Document.**

3 REGULATORY HISTORY

The regulatory history that relates to the GATTEX REMS proposal under NDA 203-441 is summarized below:

- June 29, 2000: Orphan Drug designation granted to teduglutide for adult patients with SBS.
- April 25, 2011: Pre-NDA Meeting (under IND 058-213) held for teduglutide in SBS. The applicant provided a Risk Management Plan (RMP) based on the European Union (EU) format with modifications for the FDA REMS requirements. The initial proposed REMS elements included a communication plan and timetable for submission of assessments.
- November 30, 2011: The applicant submitted the original NDA 203-441 for GATTEX (teduglutide) for adult patients with SBS and included a proposed REMS (with a Medication Guide, communication plan, ETASUs, implementation plan, and timetable for submission of assessments).

- August 3, 2012: The applicant submitted an amendment to the original proposed REMS for GATTEX that provided tabular summary of the risk management plan with proposed pharmacovigilance activities described in each proposed ETASUs forming a restricted distribution program. The proposed ETASUs in this amendment are *unchanged* from the ETASUs in the original proposed REMS (Prescriber Certification, Pharmacy Certification, Documentation of Safe Use Conditions, Patient Monitoring, and a GATTEX Patient Registry) submitted on November 30, 2011. The amendment (dated August 3, 2012) was in response to email exchanges between the applicant and the DGIEP in which the DGIEP suggested that NPS might consider re-evaluating the REMS elements (ETASUs) in the context of the teduglutide review by the Committee for Medicinal Products for Human Use (CHMP) on June 21, 2012. The CHMP did not recommend restricted product distribution for teduglutide for the proposed treatment of SBS. The applicant was informed of the upcoming internal REMS Oversight Committee meeting (see entry for August 15, 2012) and had not yet removed the ETASUs from the proposed REMS for GATTEX.
- August 10, 2012: The PDUFA goal date (September 30, 2012 for NDA 203-441) extended by three months was to provide time for full review of the amendment to the original proposed REMS for GATTEX received on August 3, 2012. The extended user fee goal date is December 30, 2012.
- August 15, 2012: The Agency held a ROC meeting to discuss the original proposed GATTEX REMS with ETASUs. See **Section 8, Appendices: ROC Briefing Document,** in this review.
- August 23, 2012: The Agency held a teleconference with the applicant to discuss re-evaluation of the REMS elements and appended educational materials. The Agency recommended that the applicant add a prescriber education slide deck and patient education material for prescribers to use to educate a patient (considering GATTEX therapy) about the serious risks associated with GATTEX.
- October 4, 2012: The Agency held a teleconference with the applicant to clarify non-REMS educational material (specifically, the SBS Registry) included in the applicant's slides for the GDAC meeting (October 16, 2012).
- October 16, 2012: the Agency held a Gastrointestinal Drugs Advisory Committee meeting to discuss the efficacy and safety of teduglutide based on two pivotal Phase 3 clinical trials in adults with SBS and the proposed REMS for GATTEX.

Gastrointestinal Drugs Advisory Committee Summary

A Gastrointestinal Drugs Advisory Committee (GDAC) meeting was held on October 16, 2012 to discuss the efficacy and safety of GATTEX (teduglutide) proposed for treatment of adults with SBS as well as the proposed REMS for this product.

The GDAC accepted the new primary efficacy endpoints employed in the pivotal clinical trials and accepted the primary efficacy results as clinically meaningful (for patients with SBS) with a favorable vote of 12 - YES, 0 - NO and 0 - Abstain. There was robust discussion and agreement on the serious risks associated with use of teduglutide (risk of possible acceleration of neoplastic growth and enhancement of colon polyp growth, gastrointestinal obstruction, and biliary and pancreatic disease).

See **Section 8, APPENDICES**, for summary of the GDAC discussion about the efficacy and safety of teduglutide.

REMS

The committee voted 11 - YES, 0 - NO, and 1 - Abstain that the proposed REMS elements (a communication plan and timetable for submission of assessments) are acceptable. The DRISK explained that a MG does not have to be required as a REMS element, particularly, if the MG is included in proposed labeling (as is the case with GATTEX). The committee supported the proposed communication plan educational materials directed to prescribers and to patients (for prescribes to use to educate patients) about the serious risks with GATTEX.

The committee requested clarification from the Agency to understand that the applicant's proposed SBS registry is external to the proposed REMS elements. The committee recommended that a SBS registry be considered as a post-marketing requirement for teduglutide, if approved in SBS.

One committee member voiced concern that the REMS assessment does not include surveys to assess patients' understanding of the serious risks with GATTEX or understanding of the recommended screening colonoscopy, follow-up colonoscopy, and laboratory monitoring. This committee member further inquired if the applicant or the Agency plans to collect data to monitor the behavioral aspect of adherence to the treatment recommendations. The Agency responded that we seek the committee's feedback on a monitoring approach without using restricted drug access for patients and burdening stakeholders in the healthcare system.

This same committee member recommended more frequent REMS assessments (than 18 months, 3 years and 7 years) at every 6 months based on the serious risks with teduglutide that may occur during early exposure. This same committee member inquired if the applicant will conduct pre-testing of the education materials. The applicant confirmed that pre-testing of some of the proposed education materials will be completed via a vendor prior to launch, if GATTEX is approved.

Following the GDAC meeting, the review team decided to include an assessment of patients' understanding of the serious risks ad recommended screening and monitoring during GATTEX therapy. However, based on feedback from the Office of Regulatory Policy on November 6, 2012, a communication plan only REMS cannot include survey assessment of patients' understanding of the serious risks associated with GATTEX because, under FDAAA, the communication plan materials only target prescribers. The REMS assessment, for a communication only REMS, can only assess prescribers' understanding of serious risks, not patients' understanding. A REMS element that includes educational material directed specifically to patients must be included in the REMS elements in order for a patient survey assessment to be required in the REMS assessment plan.

In order to be responsive to the GDAC feedback (to the Agency) to include survey assessment of patients' understanding of the serious risks associated with GATTEX, an ETASU for Prescriber Training (that includes patient educational material) will replace the communication plan element in the proposed GATTEX REMS. The proposed

communication plan materials will be limited to the *DHCP letter* and the *Dear Professional Society letter,* and the *Prescriber Education Slide Deck* and the *Patient and Caregiver Counseling Guide* will be included under the ETASU for Prescriber Training. The REMS assessment will include survey assessment of patients' understanding of the serious risks associated with GATTEX based on the safety risk information in the *Patient and Caregiver Counseling Guide.*

Based on further internal discussions, the communication plan will remain as an element in the proposed GATTEX REMS and will include the *DHCP letter* and *Dear Professional Society letter*. The ETASU for Prescriber Training will include the *Prescriber Education Slide Deck*, *Patient and Caregiver Counseling Guide,* and the GATTEX REMS website landing page.

4 MATERIALS REVIEWED

The following materials, listed by document date, reviewed from NDA 203-441/ Supplement 02 for GATTEX in SBS, are in regards to the proposed REMS:

- November 30, 2011: Original NDA 203-441 for GATTEX (teduglutide) proposed for the treatment of SBS and included a proposed REMS. See **Sections 2** and **3**, in this review for details of this submission.
- August 3, 2012: REMS Amendment to the original proposed REMS with added details in the REMS Supporting Document and revised proposed labeling (Supplement 029/Sequence 026). See **Section 3, Regulatory History**, in this review.
- September 5, 2012: REMS Amendment to the original proposed REMS with revised elements (communication plan with a *Dear Healthcare Professional letter* and *Dear Professional Society letter*) and timetable for submission of assessments, REMS Supporting Document (Supplement 032/Sequence 029).
- October 29, 2012: REMS Amendment submitted with new communication plan materials (*Prescriber Education Slide Deck* and *Patient and Caregiver Counseling Guide*) (Supplement 044/Sequence 040).
- November 15, 2012: Revised substantially and complete proposed labeling for GATTEX per the Agency.
- November 18, 2012: The applicant submitted revised proposed labeling.

5 SUMMARY OF THE APPLICANT'S AMENDMENTS TO THE PROPOSED REMS FOR GATTEX IN SHORT BOWEL SYNDROME

The applicant submitted an amendment (dated September 5, 2012) to the original proposed REMS for GATTEX in SBS (dated November 30, 2011) in response to the Agency's comments on August 23, 2012. The proposed goal and GATTEX REMS elements include the following based on subsequent Agency comments to the applicant on October 5, 2012:

1. In the **REMS Document**, the original proposed goals are revised to a single goal:

I. Goal

To inform prescribers 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 is required to add "*and patients*" to the goal of "informing prescribers *and patients* about the serious risks associated with use of GATTEX to the goals of the GATTEX REMS. See the **REMS Elements** below with a communication plan and addition of an element to assure safe use (ETASU) for Prescriber Training.

II. REMS Elements

A. Communication Plan

NPS Pharmaceuticals will implement the following elements of the communication plan:

1. A *Dear Health Care Professional (DHCP) letter* (b) (4)

2. A *Dear Professional Society letter* (b) (4)

    - American Society for Parenteral and Enteral Nutrition
    - American Gastrointestinal Association
    - American College of Gastroenterology
    - Society for Surgery of the Alimentary Tract
    - American Society of Colon and Rectal surgery

The *Dear Healthcare Professional letter* and *Dear Professional Society letter* are part of the GATTEX REMS and are appended (b) (4).

(b) (4)

Reviewer Comments:

1. To be responsive to the GDAC feedback (to the Agency) to include an assessment of patients' understanding of the serious risks associated with GATTEX in the REMS assessment plan, the applicant is required to add an element to assure safe use (ETASU) for Prescriber Training. This ETASU will include prescriber training materials, specifically, the *Prescriber Education Slide Deck* and the *Patient and Caregiver Counseling Guide*. The communication plan will remain as an element in the proposed REMS and be limited to the DHCP letter and Dear Professional Society letter to the leadership of professional societies for dissemination to their members.
2. The applicant is required to add the following physicians to the target healthcare providers:
   - Internal Medicine, Family Practice, and General Surgeons who are likely to prescribe or care for patients' with SBS
3. The applicant must incorporate the Agency's track changes to the following communication plan materials:
   - *Dear Healthcare Professional letter* (See **Attachments** to this review)
   - *Dear Professional Society letter* (See **Attachments** to this review)
4. The applicant will be required to revise the dissemination of the DHCP letter as follows: "This initial letter will be distributed within 60 days of approval of GATTEX or at the time of product launch, whichever is sooner. The letter will be sent again at 12 and 24 months after product approval."

5. The Dear Healthcare Professional letter and the Dear Professional Society letter will be provided to MedWatch at the same time they are provided to the healthcare professional and the professional society leadership.
6. Comments to the applicant's proposed *Prescriber Educational Slide Deck* and the *Patient and Caregiver Counseling Guide* (submitted on October 29, 2012) will follow the DGIEP completion of the substantially revised proposed labeling for GATTEX. The Agency will require that an ETASU for Prescriber Training be added to the proposed GATTEX REMS elements. The applicant should include information in the *Prescriber Education Slide Deck* about the revised recommendations for screening and monitoring of patients taking GATTEX. The applicant must explain in the REMS supporting document how they will introduce and make the training material available to prescribers, how they plan to use the training material, and in what venue(s) they plan to use the training material for prescribers.
7. The applicant will be required to develop and submit post-training knowledge assessment questions (4 to 5 questions) about the content of the Prescriber Education Slide Deck. The post-training knowledge assessment questions must be available in hard copy and on the GATTEX REMS website for prescribers to complete. NPS will maintain a list of all healthcare providers who have completed the Prescriber Education Slide Deck and the post-training knowledge assessment questions (see REMS Assessment Plan).
8. The applicant is required to develop and submit a GATTEX REMS-specific website (www.GATTEXREMS.com) landing page with any screen shots. NPS must ensure that all FDA-approved appended REMS materials will be available through the GATTEX REMS-specific website, www.GATTEXREMS.com.

B. Timetable for Submission of Assessments

NPS will submit REMS assessments to FDA at 18 months, 3 years and 7 years from the date of initial approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. NPS will submit each assessment so that it is received by FDA on or before the due date.

Reviewer Comment:

1. Based on internal discussion and recommendations from the GDAC meeting about monitoring the proposed GATTEX REMS assessments based on the serious risks with teduglutide in SBS, the applicant is required to change the timetable for submission of assessments to:
   - Submit REMS assessments to FDA 12 months from the date of initial approval of the REMS and annually, thereafter.

REMS Assessment Plan

NPS will assess the effectiveness of the proposed GATTEX REMS through knowledge, attitude and behavior surveys of GATTEX prescribers. The proposed REMS assessment

will include an evaluation of the effectiveness of the REMS and recommendations on any areas for program improvements or modifications, as appropriate.

NPS proposes to report on the following:

1. Evaluation of prescribers' understanding of the potential risks associated with GATTEX and the importance of appropriate patient selection and monitoring to be conducted by prescriber Knowledge, Attitude, and Behavior (KAB) surveys. The survey instrument will include questions assessing whether HCPs understand the key risk messages in the REMS educational materials.
    - Surveys will be conducted with a random sample of prescribers as identified in market research in order to assess their awareness and understanding of the risks with GATTEX.
    - Assessment protocol and survey instruments will be submitted to the FDA at least 90 days before the assessments are conducted.
    - Results of the prescriber surveys will be included in REMS Assessment Reports beginning at 18 months after the REMS approval; subsequent reports will be submitted at 3 years and 7 years after the REMS approval.

Reviewer Comment:

1. Results of the prescriber surveys and all other required monitoring and data will be submitted under the revised timetable for submission of assessments.
2. Based on feedback from the GDAC, the applicant is required to add survey assessment of patients' understanding of the serious risks associated with GATTEX to the REMS assessment plan (see above). Following submission of the survey methodology (for prescribers and patients), the Agency will communicate to the applicant that patient survey questions need to focus on patients' understanding of the safety information included in the *Patient and Caregiver Counseling Guide*.
3. The applicant will be required to maintain and report on a list of all healthcare providers who complete the Prescriber Education Slide Deck and the post-training knowledge assessment questions.

6 RECOMMENDATIONS FOR THE REVIEW DIVISION

The DRISK requests that the comments and revisions to the REMS Document and appended REMS educational materials in **Section 7**, **Comments To Be Sent To The Applicant,** in this review, be sent to the applicant as soon as possible.

Appended to this review are **Attachments** including required track changes that the applicant must accept to the proposed REMS for GATTEX including the REMS Document and appended REMS materials. The comments below are based on internal discussions, the GDAC recommendations to the proposed REMS for GATTEX, and consistency with the revised proposed labeling (as of November 18, 2012).

7 COMMENTS TO BE SENT TO THE APPLICANT

The following are required revisions to the proposed REMS dated September 5, 2012 (Supplement 032/Sequence 029) and October 29, 2012 (Supplement 044/Sequence 040) that must be incorporated into your REMS proposal for the REMS to be acceptable to the Agency. Submit your revised REMS proposal incorporating the Agency's comments by close of business on November 30, 2012. If this is not possible, notify the Agency as soon as possible as to the expected submission date of these revised and new materials.

Proposed REMS

See the attached **REMS Document** (with track changes) that incorporates some of the comments below:

(b) (4)

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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/

CAROLYN L YANCEY
11/20/2012
GATTEX REMS Interim Comments Review (Set 1)

CLAUDIA B MANZO
11/20/2012
concur