CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203441Orig1s000

<u>LABELING</u>

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)

----------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 A maximum of 0.38 mL of reconstituted solution which contains 3.8 mg of teduglutide can then be withdrawn from the vial.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)
- 50% dosage reduction recommended in patients with moderate to severe renal impairment (2.3) (8.6) (12.3)

----------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: 12/2012

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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 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. *[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, 566 subjects were exposed to at least one dose of GATTEX (190 patient-years of exposure; mean duration of exposure was 17 weeks). Of the 566 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 patients treated with GATTEX across all clinical studies (n = 566) were: abdominal pain (30.0%); injection site reactions (22.4%); nausea (18.2%); headaches (15.9%); abdominal distension (13.8%); upper respiratory tract infection (11.8%).

The rates of adverse reactions in subjects with SBS participating in two 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% (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, 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 extension 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.

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. In a randomized, double-blind, placebo-controlled, parallel-group, multi-national, multi-center, clinical trial (Study 1) in adults with SBS, the incidence of anti-GATTEX antibody was 0% (0/16) at Week 12 and 18% (6/34) at Week 24 in subjects who received subcutaneous administration of 0.05 mg/kg GATTEX once daily. The anti-GATTEX antibodies were cross-reactive to native glucagon-like peptide (GLP-2) in five of the six subjects (83%) who had anti-GATTEX antibodies. In the extension study (Study 2), the immunogenicity incidence rate increased over time to 27% (14/51) at 12 months and 38% (13/34) at 18 months. Anti-GATTEX antibodies appear to have no impact on short term (up to 1.5 years) efficacy and safety although the long-term impact is unknown.

A total of 40 subjects were tested for neutralizing antibodies – 20 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).

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.

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

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 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 566 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 name 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:

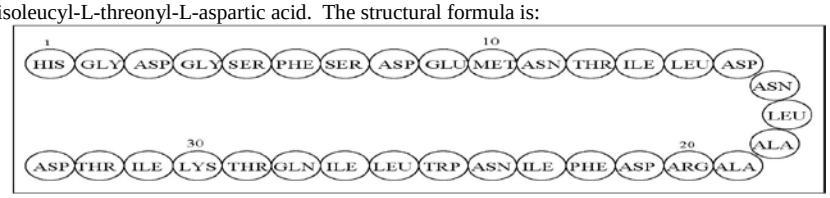

Figure 1: Structural formula of teduglutide

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

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.

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.

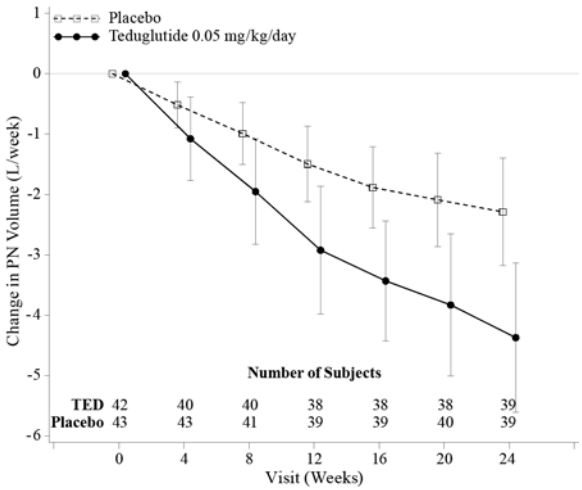

Figure 2: Change (±95% CI) in PN/I.V. volume (L/week)

Study 2. Study 2 is an ongoing two-year open-label extension of Study 1 in which 88 subjects receive GATTEX 0.05 mg/kg/day. Ninety-seven percent (76/78) of subjects from Study 1 elected to enroll in Study 2. An additional 12 subjects entered Study 2, who had been optimized and stabilized but not randomized in Study 1 because of closed enrollment. Of responders in Study 1 who entered Study 2, 100% (25/25) sustained their response to GATTEX after one year of continuous treatment. A 20% or greater reduction of parenteral support was achieved in 72% (31/43) of subjects after an additional 28 weeks of continuous GATTEX treatment. The mean reduction of weekly PN/I.V. volume was 5.2 L/week after one year of continuous GATTEX treatment. Six subjects in Study 2 were weaned off their PN/I.V. support while on GATTEX. Subjects were maintained on GATTEX even if no longer requiring PN/I.V. support. These 6 subjects had required PN/I.V. support for 3 to 18 years, and prior to GATTEX had required between 4 L/week and 13 L/week of PN/I.V. support.

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 (NDC 68875-0101-3):

- 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 68875-0101-3):

- 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 68875-0101-4):

- 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 and 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 may 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.

GATTEX® is a registered trademark of NPS Pharmaceuticals

GATTEX is covered by US Patent Nos. 5,789,379, 7,056,886 and 7,847,061

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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.
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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.

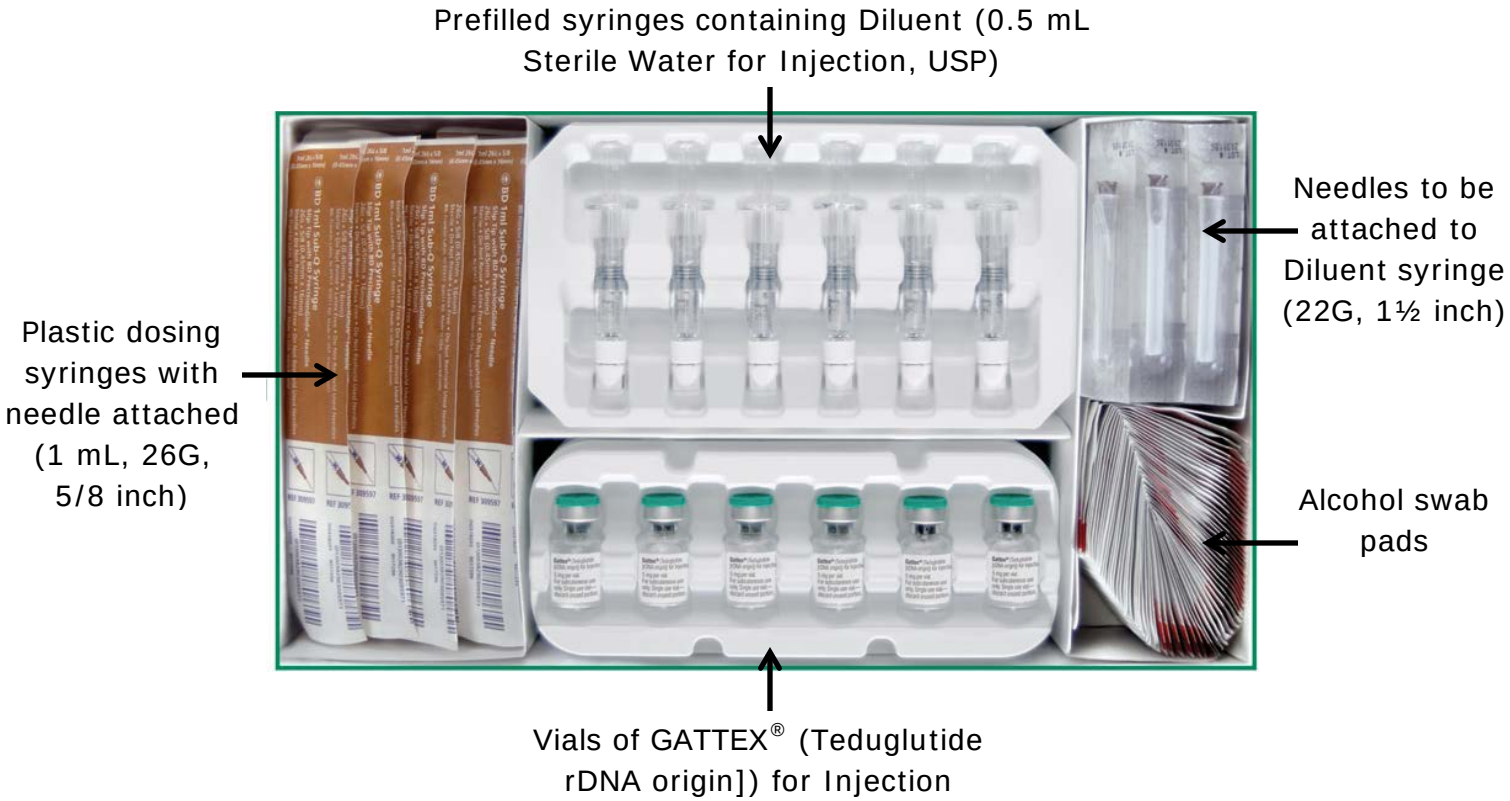
If you cannot give yourself the injection:

- 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."**

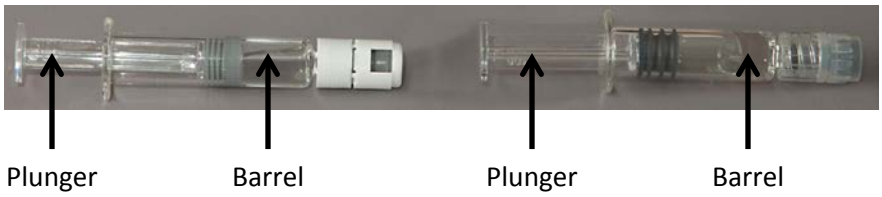
Step 1: Prepare the injection.

- 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 1 ½ 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.

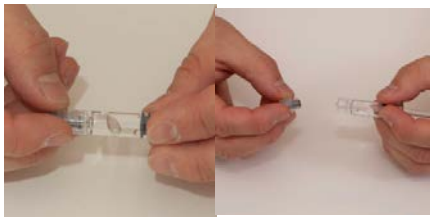


Figure B3

- 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.

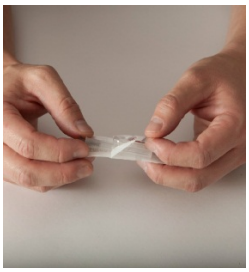


Figure C

- 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.

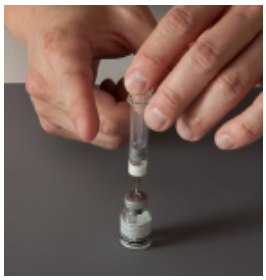


Figure I

- 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.

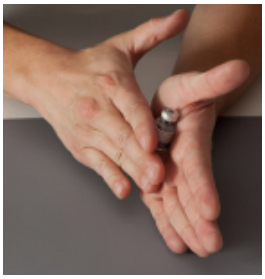


Figure J

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 of 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, S, and T)**

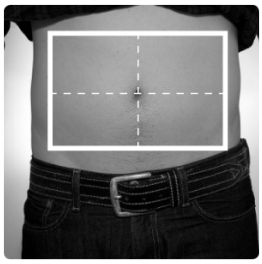


Figure R

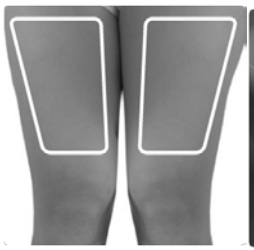


Figure S

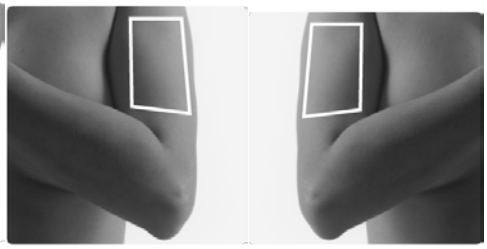


Figure T

- 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.

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/s/

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12/21/2012