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) for injection, for subcutaneous use
Initial U.S. Approval: 2012

----------INDICATIONS AND USAGE----------

GATTEX® 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 ----------

Important Administration Information

Within 6 months prior to initiating treatment with GATTEX:

- Perform a colonoscopy (or alternate imaging) of the entire colon with removal of polyps. (2.1, 2.4, 5.1)
- Obtain baseline laboratory assessments (bilirubin, alkaline phosphatase, lipase and amylase). (2.1, 2.4, 5.3)

Dosage and Administration

- For subcutaneous use only. (2.2)
- The recommended dosage of GATTEX is 0.05 mg/kg once daily by subcutaneous injection. (2.2)
- Alternate sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms. (2.2)

Dosage Adjustment for Renal Impairment

- For patients with moderate and severe renal impairment and end-stage regnal disease (creatinine clearance less than 60 mL/min) the recommended dosage is 0.025 mg/kg once daily. (2.3)

Discontinuation

- When treatment is discontinued, monitor for fluid and electrolyte imbalances. (2.5, 5.4)

Preparation

- See full prescribing information for instructions on reconstitution. (2.6)

---------- DOSAGE FORMS AND STRENGTHS ----------

For injection: 5 mg teduglutide in a single-dose vial supplied with 0.5 mL Sterile Water for Injection in a prefilled syringe. (3)

----------CONTRAINDICATIONS----------

None (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Acceleration of Neoplastic Growth: Colonoscopy is recommended after 1 year of treatment and with subsequent colonoscopies 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 benefit-risk considerations. (5.1)
- Intestinal Obstruction: In patients who develop intestinal or stomal obstruction, temporarily discontinue GATTEX pending further clinical evaluation and management. (5.2)
- Biliary and Pancreatic Disease: Obtain bilirubin, alkaline phosphatase, lipase, amylase every 6 months. If clinically meaningful changes are seen, further evaluation is recommended including imaging, and reassess continued GATTEX treatment. (5.3)
- Fluid Overload, Including Congestive Heart Failure: If fluid overload occurs, adjust parenteral support, and reassess continued GATTEX treatment. (5.4)
- Potential for Increased Absorption of Oral Medications: Monitor patients on concomitant oral medications (e.g., benzodiazepines) for adverse reactions related to the concomitant drug; dosage reduction of the other drug may be required. (5.5, 7.1)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (≥10%) are: abdominal pain, nausea, upper respiratory tract infection, abdominal distension, injection site reaction, vomiting, fluid overload, and hypersensitivity. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Shire-NPS Pharmaceuticals, Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GATTEX® is indicated for the treatment of adult patients with Short Bowel Syndrome (SBS) who are dependent on parenteral support.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Information

Within 6 months prior to starting treatment with GATTEX:

- Perform a colonoscopy (or alternate imaging) of the entire colon with removal of polyps *[see Warnings and Precautions (5.1)]*.
- Obtain baseline laboratory assessments (bilirubin, alkaline phosphatase, lipase and amylase) *[see Warnings and Precautions (5.3)]*.

2.2 Recommended Dosage and Administration

GATTEX is for subcutaneous injection only. Not for intravenous or intramuscular administration.

The recommended dosage of GATTEX is 0.05 mg/kg once daily administered by subcutaneous injection.

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.

Alternation of sites for subcutaneous injection is recommended, and can include the thighs, arms, and the quadrants of the abdomen.

2.3 Dosage Adjustment for Renal Impairment

The recommended dosage in patients with moderate and severe renal impairment and end-stage renal disease (creatinine clearance less than 60 mL/min) is 0.025 mg/kg once daily *[see Use in Specific Populations (8.6)]*.

2.4 Monitoring to Assess Safety

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.

Laboratory assessments are recommended every 6 months. If any clinically meaningful elevation is seen, further diagnostic workup is recommended as clinically indicated (i.e., imaging of the biliary tract, liver, or pancreas) *[see Warnings and Precautions (5.1), (5.3)]*.

2.5 Discontinuation of Treatment

Discontinuation of treatment with GATTEX may result in fluid and electrolyte imbalance. Monitor fluid and electrolyte status in patients who discontinue GATTEX treatment *[see Warnings and Precautions (5.4)]*.

2.6 Preparation Instructions

- Reconstitute each vial of GATTEX by slowly injecting the 0.5 mL of preservative-free Sterile Water for Injection provided in the prefilled syringe. A 10 mg/mL sterile solution is obtained after reconstitution.
- Allow the vial containing GATTEX and water to stand for approximately 30 seconds and then gently roll the vial between the 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.
- Inspect the reconstituted GATTEX solution for particulate matter and discoloration prior to administration. GATTEX is a clear, colorless to light straw-colored solution. If there is any discoloration or particulates, discard the solution.
- Administer within 3 hours after reconstitution. Discard any unused portion.
- Do not shake or freeze the reconstituted solution.
- For single use only.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 5 mg teduglutide as a white lyophilized powder for reconstitution in a single-dose vial supplied with 0.5 mL Sterile Water for Injection in a prefilled syringe and 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 *[see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1)]*. 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 who develop active gastrointestinal malignancy (GI tract, hepatobiliary, pancreatic) while on GATTEX, discontinue GATTEX treatment. In patients who develop active non-gastrointestinal malignancy while on GATTEX, the clinical decision to continue GATTEX should be made based on benefit-risk considerations.

Colorectal Polyps

Colorectal polyps were identified during the clinical trials *[see Adverse Reactions (6.1)]*. Within 6 months prior to starting treatment with GATTEX, perform colonoscopy of the entire colon with removal of polyps *[see Dosage and Administration (2.1)]*. A follow-up colonoscopy (or alternate imaging) is recommended at the end of 1 year of GATTEX. Perform subsequent colonoscopies every 5 years or more often as needed. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. If colorectal cancer is diagnosed, discontinue GATTEX therapy.

Small Bowel Neoplasia

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

5.2 Intestinal Obstruction

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

5.3 Biliary and Pancreatic Disease

Gallbladder and Biliary Tract Disease

Cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies *[see Adverse Reactions (6.1)]* and postmarketing. For identification of the onset or worsening of gallbladder/biliary disease, obtain 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 reassess the need for continued GATTEX treatment.

Pancreatic Disease

Pancreatitis has been reported in clinical studies *[see Adverse Reactions (6.1)]*. For identification of onset or worsening of pancreatic disease, obtain laboratory assessments 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 reassess the need for continued GATTEX treatment.

5.4 Fluid Imbalance and Fluid Overload

Fluid Overload

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

Fluid and Electrolyte Imbalance

Discontinuation of treatment with GATTEX may also result in fluid and electrolyte imbalance. Monitor fluid and electrolyte status in patients who discontinue treatment with GATTEX *[see Dosage and Administration (2.5)]*.

5.5 Increased Absorption of Concomitant Oral Medication

In the placebo-controlled trials, an analysis of episodes of cognition and attention disturbances was performed for patients on benzodiazepines. One patient receiving prazepam concomitantly with GATTEX 0.05 mg/kg once daily experienced a dramatic deterioration in mental status progressing to coma during the first week of GATTEX therapy. The patient was admitted to the ICU and the prazepam blood concentration was >300 mcg/L. GATTEX and prazepam were discontinued, and coma resolved 5 days later.

Monitor patients receiving concomitant oral drugs requiring titration or with a narrow therapeutic index, for adverse reactions due to potential increased absorption of the concomitant drug. The concomitant drug may require a reduction in dosage *[see Drug Interactions (7.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Acceleration of Neoplastic Growth *[see Warnings and Precautions (5.1)]*
- Intestinal Obstruction *[see Warnings and Precautions (5.2)]*
- Biliary and Pancreatic Disease *[see Warnings and Precautions (5.3)]*
- Fluid Imbalance and Fluid Overload *[see Warnings and Precautions (5.4)]*

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.

The rates of adverse reactions in 136 adult patients 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.

Table 1: Common Adverse Reactions* in Adult Patients with SBS in Placebo-Controlled Trials: Studies 1 and 3

Adverse Reaction	Placebo (N=59) (%)	GATTEX 0.05 mg/kg Once Daily (N=77) (%)
Abdominal pain[1]	22	30
Nausea	20	23
Upper respiratory tract infection[2]	12	21
Abdominal distension	2	20
Injection site reaction[3]	12	13
Vomiting	10	12
Fluid Overload[4]	7	12
Hypersensitivity[5]	7	10
Flatulence	7	9
Decreased appetite	3	7
Influenza[6]	2	7
Skin hemorrhage[7]	2	5
Cough	0	5
Sleep disturbances[8]	0	5

* Reported at a rate of at least 5% in the GATTEX group, and greater than the placebo group.
[1] Includes: Abdominal pain, upper abdominal pain, lower abdominal pain
[2] Includes: Upper respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, laryngitis, rhinitis, viral upper respiratory tract infection
[3] Includes: Injection site hematoma, injection site erythema, injection site pain, injection site swelling, injection site hemorrhage, injection site discoloration, injection site reaction, injection site rash
[4] Includes: Fluid overload, peripheral edema, edema, generalized edema, fluid retention and jugular vein distension
[5] Includes Erythema, rash, dermatitis allergic, pruritus, rash macular, drug eruption, eyelid edema, flushing
[6] Includes: Influenza, influenza-like illness
[7] Includes: Hematoma, abdominal wall hematoma, post procedural hematoma, umbilical hematoma, blood blister
[8] Includes: Insomnia (3 patients) and hypersomnia (1 patient)

Adverse Reactions in the Subset of Patients with a Stoma

Among the 53 patients with a stoma in the placebo-controlled studies (Study 1 and Study 3), the percentage of patients with gastrointestinal stoma complication was 42% (13/31) for patients receiving GATTEX 0.05 mg/kg/day and 14% (3/22) for patients receiving placebo.

Less Common Adverse Reactions

Adverse Reactions of Special Interest

Malignancy

Three patients were diagnosed with malignancy in the SBS clinical trials, all of whom were male and had received GATTEX 0.05 mg/kg/day in Study 2. One 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. Two 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 *[see Warnings and Precautions (5.1)]*.

Intestinal Polyps

In the clinical trials, 14 patients with SBS were diagnosed with polyps of the GI tract after initiation of study treatment. In the SBS placebo-controlled studies, 1/59 (2%) of patients on placebo and

1/109 (1%) of patients 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 12 polyp cases occurred in the extension studies – 2 colorectal villous adenomas (onset at 6 and 7 months in GATTEX 0.1 mg/kg/day (twice the recommended dose) and 0.05 mg/kg/day dose groups, respectively), 2 hyperplastic polyps (onset 6 months in GATTEX 0.1 mg/kg/day dose group and 24 months in GATTEX 0.05 mg/kg/day dose group), 4 colorectal tubular adenomas (onset between 24 and 29 months in GATTEX 0.05 mg/kg/day dose group), 1 serrated adenoma (onset at 24 months in GATTEX 0.05 mg/kg/day dose group), 1 colorectal polyp biopsy not done (onset at 24 months in GATTEX 0.05 mg/kg/day dose group), 1 rectal inflammatory polyp (onset at 10 months in the GATTEX 0.05 mg/kg/day dose group, and 1 small duodenal polyp (onset at 3 months in GATTEX 0.05 mg/kg/day dose group) *[see Warnings and Precautions (5.1)]*.

Gastrointestinal Obstruction

Overall, 12 patients with SBS experienced one or more episodes of intestinal obstruction/stenosis: 6 in SBS placebo-controlled studies and 6 in the extension studies. The 6 patients in the placebo-controlled trials were all on GATTEX: 3/77 (4%) on GATTEX 0.05 mg/kg/day and 3/32 (9%) on GATTEX 0.1 mg/kg/day (twice the recommended dose). No cases of intestinal obstruction occurred in the placebo group. Onset ranged from 1 day to 6 months. In the extension studies, 6 additional patients (all on GATTEX 0.05 mg/kg/day) were diagnosed with intestinal obstruction/stenosis with onsets ranging from 6 days to 19 months. Two of the 6 patients from the placebo-controlled trials experienced recurrence of obstruction in the extension studies. Of all 8 patients with an episode of intestinal obstruction/stenosis in these extension studies, 2 patients required endoscopic dilation and 1 required surgical intervention) *[see Warnings and Precautions (5.2)]*.

Gallbladder, Biliary and Pancreatic Disease

For gallbladder and biliary disease in the placebo-controlled studies, 3 patients with SBS were diagnosed with cholecystitis, all of whom had a prior history of gallbladder disease and were in the GATTEX 0.05 mg/kg/day dose group. No cases were reported in the placebo group. One of these 3 cases had gallbladder perforation and underwent cholecystectomy the next day. The remaining 2 cases underwent elective cholecystectomy at a later date. In the extension studies, 4 patients had an episode of acute cholecystitis; 3 patients had new-onset cholelithiasis; and 1 patient experienced cholestasis secondary to an obstructed biliary stent. For pancreatic disease in the placebo-controlled studies, 1 patient (GATTEX 0.05 mg/kg/day dose group) had a pancreatic pseudocyst diagnosed after 4 months of GATTEX. In the extension studies, 1 patient was diagnosed with chronic pancreatitis; and 1 patient was diagnosed with acute pancreatitis) *[see Warnings and Precautions (5.3)]*.

Fluid Overload

In the placebo-controlled trials, peripheral edema was reported in 2/59 (3%) of patients on placebo and 8/77 (10%) patients on GATTEX; fluid overload was reported in 1/77 (1%) patient in the GATTEX group; no cases of fluid overload were seen in the placebo arm. There were 2 cases of congestive heart failure (CHF, 3%) in the GATTEX arm, 1 of which 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 *[see Warnings and Precautions (5.4)]*.

Other Less Common Adverse Reactions
Reported in less than 5% of patients treated with GATTEX:

Gastrointestinal disorders: Colonic stenosis, Pancreatic duct stenosis, Small intestinal stenosis
Respiratory, thoracic and mediastinal disorders: Dyspnea

6.2 Immunogenicity

As with all peptides, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to teduglutide in the

studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Based on integrated data from two trials in adults with SBS (a 6-month randomized placebo-controlled trial, followed by a 24-month open-label trial), the development of anti-teduglutide antibodies in patients who received subcutaneous administration of 0.05 mg/kg GATTEX once daily was 3% (2/60) at Month 3, 17% (13/77) at Month 6, 24% (16/67) at Month 12, 33% (11/33) at Month 24, and 48% (14/29) at Month 30. Anti-teduglutide antibodies were cross-reactive to native glucagon-like peptide (GLP-2) in 5 of the 6 patients (83%) who had anti-teduglutide antibodies and were tested for cross-reactivity. In the same two trials, a total of 36 patients were tested for neutralizing antibodies: one patient developed borderline positive neutralizing antibody responses at month 24 of the extension trial. The antibody formation has not been associated with clinically relevant safety findings, reduced efficacy or changed pharmacokinetics of GATTEX.

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. Altered mental status has been observed in patients taking GATTEX and benzodiazepines in clinical trials *[see Warnings and Precautions (5.5)]*.

Monitor patients on concomitant oral drugs requiring titration or with a narrow therapeutic index for adverse reactions related to the concomitant drug while on GATTEX. The concomitant drug may require a reduction in dosage.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports with GATTEX use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Pregnant women with short bowel syndrome are at risk for malnutrition, which is associated with adverse maternal and fetal outcomes *(see Clinical Considerations)*. In animal reproduction studies, no effects on embryo-fetal development were observed with the subcutaneous administration of teduglutide to pregnant rats and rabbits during organogenesis at exposures up to 686 times the clinical exposure at the recommended human dose (based on AUC) (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnant women with short bowel syndrome are at risk for malnutrition. Severe malnutrition in pregnant women is associated with preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations and perinatal mortality.

Data

Animal Data

Reproduction studies have been performed in pregnant rats at subcutaneous doses of teduglutide up to 50 mg/kg/day (resulting in exposures of about 686 times the clinical exposure (AUC) at the recommended daily human dose of 0.05 mg/kg) and in pregnant rabbits at subcutaneous doses up to 50 mg/kg/day (resulting in exposures of about 657 times the clinical exposure (AUC) at the recommended daily human dose of 0.05 mg/kg) during the period of organogenesis. These studies did not reveal any evidence of impaired fertility or harm to the fetus due to teduglutide. In a pre- and postnatal development study in rats (gestation day 7 to lactation day 20), teduglutide did not show any significant adverse effects on pre- and postnatal development at doses up to 50 mg/kg/day (about 161 times the recommended daily human dose of 0.05 mg/kg, based on body surface area [BSA]).

8.2 Lactation

Risk Summary

There is no information regarding the presence of GATTEX in human milk, the effects of GATTEX on the breastfed infant, or the effects of GATTEX on milk production. Teduglutide is present in the milk of lactating rats (*see Data*). Systemic exposure of teduglutide to a breastfed infant is expected to be low. However, because of the potential for serious adverse reactions in a breastfed infant, including tumorigenicity *[see Nonclinical Toxicology (13.1)]*, advise patients that breastfeeding is not recommended during treatment with GATTEX.

Data

In a milk excretion study in the rat, a single subcutaneous dose of 25 mg/kg of teduglutide (81 times the recommended daily human dose of 0.05 mg/kg based on BSA) was administered to lactating female rats at Day 12 postpartum. The maximum concentration of teduglutide in the milk corresponded to 0.9% and 2.9% of the plasma concentration at 1.5 and 4 hours after dosing, respectively.

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 134 patients that were treated with GATTEX at the recommended dose of 0.05 mg/kg/day in the SBS safety and efficacy studies, 19 patients were 65 years or older while 5 patients were 75 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients, 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

In subjects with moderate to severe renal impairment or end-stage renal disease (ESRD) (creatinine clearance <60 mL/min), the exposure to teduglutide increased with the degree of renal impairment *[see Clinical Pharmacology (12.3)]*. Reduce the dose of GATTEX by half in these patients *[see Dosage and Administration (2.3)]*.

8.7 Hepatic Impairment

GATTEX has not been studied in patients with severe hepatic impairment (Child-Pugh grade C). No dosage adjustment is recommended for patients with mild and moderate hepatic impairment (Child-Pugh grade A and B) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

The maximum dose of GATTEX studied during clinical development was 80 mg/day for 8 days. No unexpected systemic adverse reactions were seen. In the event of overdose, the patient should be carefully monitored by the medical professional.

11 DESCRIPTION

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

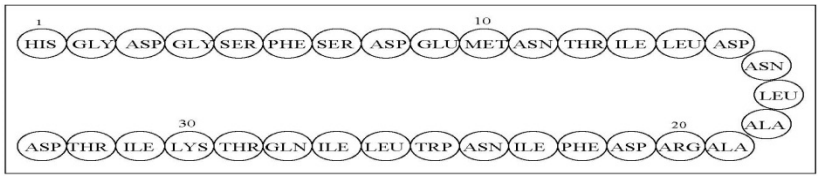


Figure 1: Structural formula of teduglutide

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

Each single-dose vial of GATTEX contains 5 mg of teduglutide as a white lyophilized powder for reconstitution and administration by subcutaneous injection. In addition to the active pharmaceutical ingredient (teduglutide), each vial of GATTEX contains 3.434 mg dibasic sodium phosphate heptahydrate, 3.88 mg L-histidine, 15 mg mannitol, and 0.644 mg monobasic sodium phosphate monohydrate 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

Intestinal Fluid Absorption

The ability of GATTEX to improve intestinal absorption was studied in 17 adult subjects with Short Bowel Syndrome (N=2-3 per dose group) using daily doses of 0.03, 0.1, 0.15 mg/kg (doses ranging from 0.6 to 3 times the recommended dose) 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 to 1000 mL/day, and increased villus height and crypt depth of the intestinal mucosa.

Cardiac Electrophysiology

At a dose 5 times the recommended dose, GATTEX did not prolong the QT 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 to 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 at steady state (AUC_{tau}) was 0.15 μg•hr/mL. No accumulation of teduglutide was observed following repeated subcutaneous administrations.

The C_{max} and AUC of teduglutide was dose proportional over the dose range of 0.05 to 0.4 mg/kg (up to 8 times the recommended dose of GATTEX).

Distribution

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

Elimination

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.

Excretion

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.

Use in Specific Populations

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.

Male and Female Patients

No clinically relevant gender differences were observed.

Patients with Renal Impairment

In subjects with moderate to severe renal impairment or end stage renal disease (ESRD) (creatinine clearance <60 mL/min), the C_{max} and $AUC_{0\text{-}inf}$ of teduglutide increased with the degree of renal impairment following a single subcutaneous dose of 10 mg GATTEX. Teduglutide exposure increased by a factor of 1.6, 1.4, and 2.1 (C_{max}) and 1.5, 1.7, and 2.6 ($AUC_{0\text{-}inf}$) in subjects with moderate, severe renal impairment and ESRD, respectively, compared to healthy subjects *[see Dosage and Administration (2.3), Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

Subjects with moderate hepatic impairment (Child-Pugh Class B) had an approximately 10 to 15% lower teduglutide C_{max} and AUC compared to healthy matched control subjects after a single subcutaneous dose of 20 mg GATTEX. This reduction in teduglutide exposure is not thought to be clinically meaningful. GATTEX was not studied in subjects with severe hepatic impairment (Child-Pugh Class C).

Drug Interaction Studies

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic potential of GATTEX was assessed in 2-year subcutaneous carcinogenicity studies in rats and mice. In a 2-year carcinogenicity study in Wistar Han rats at subcutaneous doses of 3, 10, and 35 mg/kg/day (resulting in exposures of about 15, 41, and 199 times the exposures achieved at the recommended daily human dose of 0.05 mg/kg, respectively, on an AUC basis), teduglutide caused statistically significant increases in the incidences of adenomas in the bile duct and jejunum of male rats. In a 2-year carcinogenicity study in Crl:CD1(ICR) mice at subcutaneous doses of 1, 3.5, and 12.5 mg/kg/day (resulting in exposures of about 32, 66, and 244 times the exposures achieved at the recommended daily human dose of 0.05 mg/kg, respectively, on an AUC basis), teduglutide caused a significant increase in papillary adenomas in the gall bladder; it also caused adenocarcinomas in the jejunum in male mice at the high dose of 12.5 mg/kg/day.

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 161 times the recommended daily human dose of 0.05 mg/kg based on BSA) 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 (CL0600-020, NCT00798967)

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 patients. Optimization was followed by a 4-week to 8-week period of fluid stabilization. Patients 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 patient 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 patients was 50 years. Mean duration of PN/I.V. dependency prior to enrollment was 6 years (range 1 to 26 years). The most common reasons for intestinal resection leading to SBS were vascular disease (34%, 29/85), Crohn's Disease (21%, 18/85), and "other" (21%, 18/85). Stoma was present in 45% (38/85) of patients, and the most common type was jejunostomy/ileostomy (82%, 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 44% (37/85) patients. 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. Sixty-three percent (27/43) of GATTEX-treated patients versus 30% (13/43) of placebo-treated patients 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 patients (from pre-treatment baseline of 12.9 Liters) versus 2.3 Liters for placebo-treated patients (from pre-treatment baseline of 13.2 Liters/week) (p<0.001).

Twenty-one patients on GATTEX (54%) versus 9 on placebo (23%) 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.

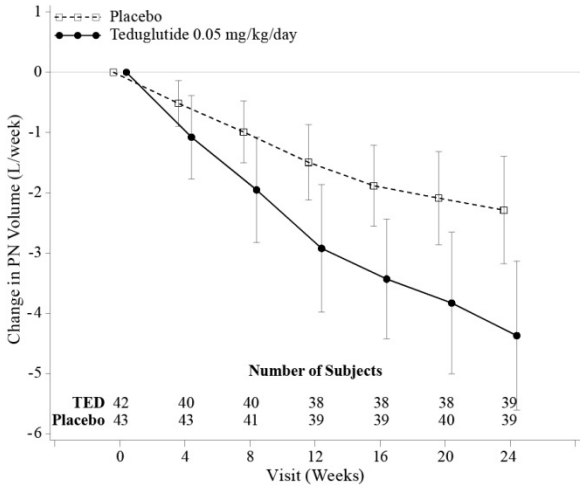


Figure 2: Change (±95% CI) in PN/I.V. volume (L/week)

Study 2 (CL0600-021, NCT00930644)

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

30 months exposure

Thirty GATTEX patients completed a total duration of 30 months (Study 1 followed by Study 2 treatment). Of these, 28 patients (93%) achieved a 20% or greater reduction of parenteral support. Of responders in Study 1 who had completed 2 additional years of continuous treatment with GATTEX, 96% (21/22) sustained their response to GATTEX. The mean reduction in PN/I.V. (n=30) was 7.55 L/week (a 66% reduction from baseline). Ten patients were weaned off their PN/I.V. support while on GATTEX treatment for 30 months. Patients were maintained on GATTEX even if no longer requiring PN/I.V. support. These 10 patients had required PN/I.V. support for 1.2 to 15.5 years, and prior to GATTEX had required between 3.5 L/week and 13.4 L/week of PN/I.V. support. At the end of study, 21 (70%), 18 (60%) and 18 (60%) of the 30 completers achieved a reduction of 1, 2, or 3 days per week in PN/I.V. support, respectively.

24 months exposure

Of the 39 placebo-treated patients from Study 1 entering Study 2, 29 completed 24 months of treatment with GATTEX. The mean reduction in PN/I.V. was 3.11 L/week (an additional 28.3% reduction) from the start of Study 2. Sixteen (55%) of the 29 completers achieved a 20% or greater reduction of parenteral support. At the end of the study, 14 (48%), 7 (24%) and 5 (17%) achieved a reduction of 1, 2, or 3 days per week in PN/I.V. support, respectively. Two patients were weaned off their PN/I.V. support while on GATTEX. Of the 12 patients entering Study 2 directly, 6 completed 24 months of treatment with GATTEX. Similar effects were seen. One of the six patients was weaned off their PN/I.V. support while on GATTEX.

14.2 Study 3 (Placebo-controlled) and Study 4 (Blinded Uncontrolled Extension of Study 3)

Study 3 (CL0600-004, NCT00081458)

Study 3 was a randomized, double-blind, placebo-controlled, three parallel-group, multinational study 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. After a period of optimization and stabilization similar to Study 1, patients were randomized to receive 24 weeks of one of the following treatment regimens: GATTEX 0.05 mg/kg/day (n=35), GATTEX 0.1 mg/kg/day (twice the recommended dose) (n=33), or placebo (n=16). GATTEX 0.1 mg/kg/day is not a recommended dosage *[see Dosage and Administration (2.2)]*. 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 0.1 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 patients on GATTEX 0.05 mg/kg/day responded versus 6% on placebo. Patients on GATTEX in both dose groups experienced a 2.5 L/week reduction in parenteral support requirements versus 0.9 L/week for placebo at 24 weeks. Two patients in the GATTEX 0.05 mg/kg/day dose group were weaned off parenteral support by Week 24.

Study 4 (CL0600-005, NCT00172185)

Study 4 was a blinded, uncontrolled extension of Study 3, in which 65 patients 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 patients. 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 patients 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 patient from Study 3 was weaned off parenteral support.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

GATTEX (teduglutide) for injection is supplied in a sterile, single-dose 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-dose vials of drug (NDC 68875-0101-1)

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

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

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

One-vial kit (NDC 68875-0103-1):
- One single-dose 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.

Storage and Handling

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

Instruction for the Pharmacist:

Prior to Dispensing: Store at 2°C to 8°C (36°F to 46°F) for **Cartons of Drug Vials** and the **One-vial kits**. Do not freeze.

Dispensing Instructions: Dispense with a 90-day “use by” dating and specify “Store at room temperature up to 25°C (77°F). Do not freeze.” Dispense Medication Guide to each patient.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Acceleration of Neoplastic Growth

Advise patients that they will need to undergo clinical examinations and repeated colonoscopies (or alternate imaging) during treatment with GATTEX to monitor for the development of polyps and/or neoplasia of the GI tract *[see Warnings and Precautions (5.1)]*.

Intestinal Obstruction

Advise patients to immediately contact their healthcare provider if they experience any symptoms suggestive of intestinal or stomal obstruction *[see Warnings and Precautions (5.2)]*.

Biliary and Pancreatic Disease

Advise patients that laboratory assessments will be done periodically while on GATTEX to monitor for the onset or worsening of gallbladder, biliary and pancreatic disease, and to report immediately to their healthcare provider if they develop symptoms suggestive of cholecystitis, cholangitis, cholelithiasis or pancreatic disease *[see Warnings and Precautions (5.3)]*.

Fluid Overload

Advise patients to immediately contact their healthcare provider if they develop fluid overload or symptoms of congestive heart failure while on GATTEX *[see Warnings and Precautions (5.4)]*.

Fluid Imbalance

Advise patients of the risk of fluid and electrolyte imbalance with discontinuation of GATTEX, and to contact their healthcare provider if they develop symptoms suggestive of electrolyte imbalances *[see Warnings and Precautions (5.4)]*.

Increased Absorption of Concomitant Oral Medication

Instruct patients to report to their healthcare provider 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)]*.

Lactation

Advise women that breastfeeding is not recommended during treatment with GATTEX *[see Use in Specific Populations (8.2)]*.

GATTEX® is a registered trademark of Shire-NPS Pharmaceuticals, Inc.

GATTEX® is covered by US Patent Nos. 5,789,379, 7,056,886, 7,847,061, and 9,060,992.

Manufactured for:
Shire-NPS Pharmaceuticals, Inc.
300 Shire Way
Lexington, MA 02421
USA

For information about GATTEX contact:
Shire-NPS Pharmaceuticals, Inc.
300 Shire Way
Lexington, MA 02421
USA
1-800-828-2088
www.GATTEX.com

MEDICATION GUIDE
GATTEX® (Ga'-tex)
(teduglutide)
for injection, for subcutaneous use

Read this Medication Guide carefully before you start taking GATTEX and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your 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 increased 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 provider 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 right away if you have any of these symptoms of a bowel or stomal 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 a 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
- chills
- fever
- a change in your stools
- nausea
- vomiting
- 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 using GATTEX, tell your healthcare provider about all your medical conditions, including 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.
- 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. Talk to your healthcare provider about the best way to feed your baby while using GATTEX. Breastfeeding is not recommended during treatment with GATTEX.

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 (medicines taken by

mouth) 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 dose vial). The powder must be mixed with Sterile Water for Injection (a diluent) provided in a prefilled 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.**
- **Do not stop taking GATTEX without consulting your healthcare provider.**
- **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
- nausea
- cold or flu symptoms
- skin reaction where the injection was given
- vomiting
- swelling of the hands or feet
- allergic reactions

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.

What are the ingredients in GATTEX?

Active ingredient: teduglutide

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

Manufactured for:
Shire-NPS Pharmaceuticals, Inc.
300 Shire Way
Lexington, MA 02421
USA

For more information, go to www.GATTEX.com or call 1-800-828-2088.

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 12/2018

Instructions for Use
GATTEX®(Ga'-tex)
(teduglutide)
for injection, for subcutaneous use

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.

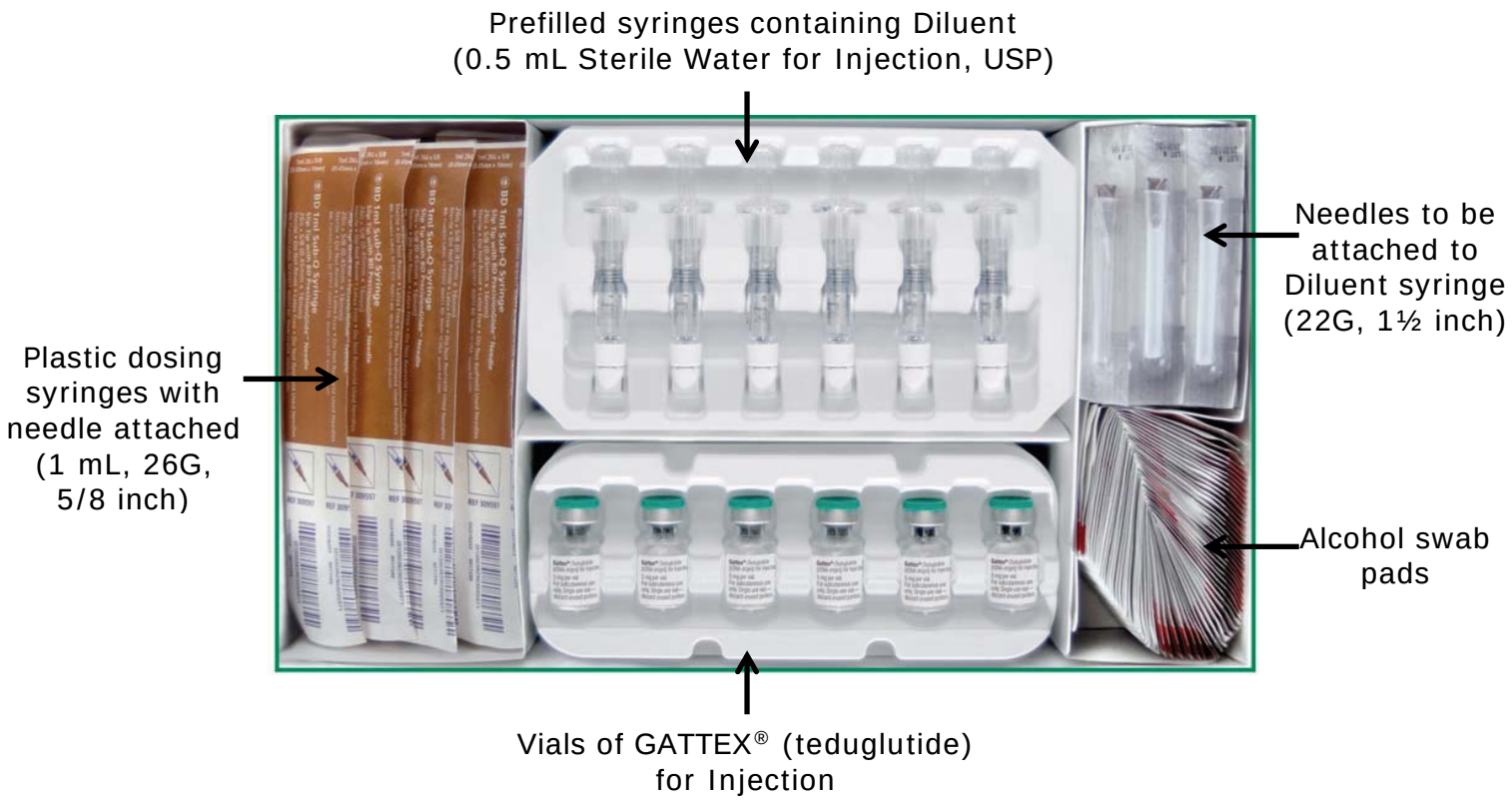
If you cannot give yourself the injection:

- 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 1 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
- 22G, 1½ inch needle
- Plastic dosing syringe with needle attached
- A sharps disposal container. See **"Step 7: Dispose of needles and syringes."** (not included in the GATTEX kit)

  You may also need an adhesive bandage (not included in your GATTEX kit).

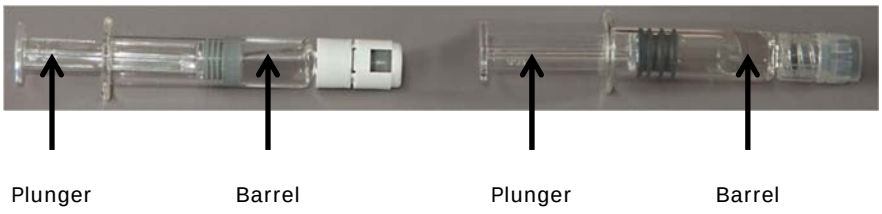
Step 1: Prepare the injection.

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

Figure B1



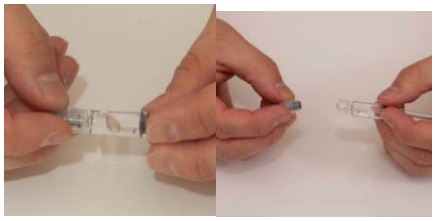
- Hold the Diluent syringe by the barrel.

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

Figure J 

Step 4: Check the mixed GATTEX.

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

Step 5: Draw up your dose of GATTEX.

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

Figure K 

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

Figure L 

- Carefully pull back on the plunger to the line that matches the dose prescribed by your healthcare provider.
- Use 1 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 1 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 Figure R and Figure S)**

Figure R

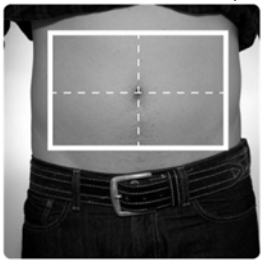
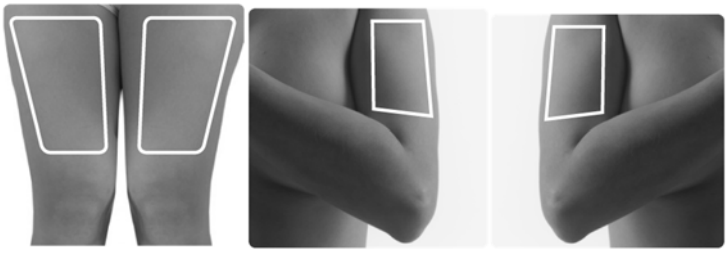


Figure S

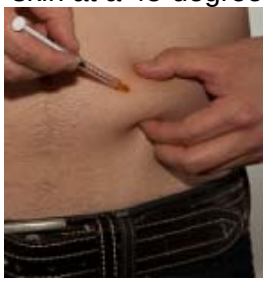


- Clean the skin where you plan to give the injection with a new alcohol swab pad. Do not touch this area again before giving the injection.
- Use 1 hand to gently pinch up a fold of skin around the injection site (**See Figure T**).

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 1 hand while you slowly push down the plunger until the syringe is empty (**See Figure V**).

Figure V

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

Step 7: Dispose of syringes and needles.

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

If you have any questions, talk to your healthcare provider or pharmacist.

How should I store GATTEX?

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

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

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Shire-NPS Pharmaceuticals, Inc.
300 Shire Way
Lexington, MA 02421
USA
1-800-828-2088

Revised: 12/2018