CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203441Orig1s000

LABELING

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

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

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

----------DOSAGE AND ADMINISTRATION----------
- The recommended once daily dose of GATTEX is 0.05 mg/kg (2.1)
- Administer by subcutaneous injection; alternate sites between 1 of the 4 quadrants of the abdomen, or into alternating thighs or alternating arms. (2.1)
- For subcutaneous injection only. (2.1)
- For single-use only. Use within 3 hours after reconstitution, discard any unused portion. (2.5)

----------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 A maximum of 0.38 mL of reconstituted solution which contains 3.8 mg of teduglutide can then be withdrawn from the vial.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

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

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

2.2 Monitoring to Assess Safety

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

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

2.3 Dosage Modifications in Renal Impairment

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

2.4 Discontinuation of Treatment

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

2.5 Preparation for Administration

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

3 DOSAGE FORMS AND STRENGTHS

For Injection: Each single-use glass vial contains a dose of 5 mg teduglutide as a lyophilized powder that upon reconstitution with the 0.5 mL Sterile Water for Injection provided in the prefilled syringe delivers a maximum of 0.38 mL of the reconstituted sterile solution which contains 3.8 mg of teduglutide.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acceleration of Neoplastic Growth

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

Colorectal Polyps

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

Small Bowel Neoplasia

Based on 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,

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

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