**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**

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## 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

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