A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. The GATTEX Prescriber Education Slide Deck is required by the FDA as part of the GATTEX REMS Program.
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Indication

- 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.
- Teduglutide is a recombinant analog of GLP-2
Overview

Important Adverse Reactions of Special Interest

- Possible safety risks with GATTEX
  - Possible acceleration of neoplastic growth and enhanced growth of colorectal polyps
  - Gastrointestinal obstruction
  - Gallbladder, biliary tract and pancreatic disease
  - Increased absorption of fluids leading to fluid overload in patients with cardiovascular disease
  - Increased absorption of oral medications with narrow therapeutic index
Possible Acceleration of Neoplastic Growth

- GLP-2 receptors are localized mainly in the GI tract\(^1\)
- GATTEX promotes growth of intestinal epithelial cells in the GI tract
- It can not be excluded that GATTEX promotes growth of existing neoplasms in the GI tract
- 3 patients on GATTEX were reported with neoplasms*:  
  – 2 cases of lung cancer with smoking history  
  – 1 case of GI metastatic adenocarcinoma (unknown origin) following abdominal radiation for Hodgkin’s disease

* As of January 24, 2013
Possible Acceleration of Neoplastic Growth

Based on the pharmacologic activity and findings in animals, GATTEX has the potential to cause hyperplastic changes including neoplasia.

Based on benign tumor findings in the rat carcinogenicity study, patients should be monitored clinically for small bowel neoplasia. If a benign neoplasm is found, it should be removed. In case of small bowel cancer, GATTEX therapy should be discontinued.

In patients with active gastrointestinal malignancy (GI tract, hepatobiliary, pancreatic), GATTEX therapy should be discontinued.

In patients with active non-gastrointestinal malignancy, the clinical decision to continue GATTEX should be made based on risk-benefit considerations.

In patients at increased risk for malignancy, the clinical decision to use GATTEX should be considered only if the benefits outweigh the risks.
11/173 (6.4%) GATTEX-treated patients developed GI polyps in pooled Phase III SBS studies*
- 2 villous adenomas
- 3 hyperplastic
- 3 tubular adenomas
- 1 serrated adenomas
- 1 inflammatory
- 1 biopsy not done

GATTEX mechanism of action and nonclinical data are consistent with a potential to enhance growth of polyps

* As of January 24, 2013
Colorectal Polyps

- 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.
12 patients experienced one or more episodes of intestinal obstruction/stenosis*

- 6 in SBS placebo-controlled studies
  - 3/77 (3.9%) on GATTEX, 0.05 mg/kg/day
  - 3/32 (9.4%) on GATTEX, 0.10 mg/kg/day
  - None in placebo-group
  - Onset 1 day to 6 months
- 6 in the extension studies (all on GATTEX, 0.05 mg/kg/day)
  - Onset 6 days to 19 months
  - Of all of these patients, 2 patients required endoscopic dilatation; and one required surgical intervention

* As of January 24, 2013
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.
13/173 (7.5%) of GATTEX-treated patients reported biliary events, including cholecystitis and gallstones/sludge in pooled Phase III SBS studies* 
- 5 patients had a history of biliary disease 
- None of these events resulted in study withdrawal

* As of January 24, 2013
Gallbladder and Biliary Tract Disease

GATTEX Label – Warnings and Precautions

Gallbladder and Biliary Tract Disease

- Cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies.
- Patients must undergo initial (within 6 months prior) laboratory assessment of bilirubin and alkaline phosphatase.
- Subsequent laboratory assessments are recommended every 6 months; if a clinically meaningful elevation is seen imaging of the biliary tract is recommended to identify possible obstruction.
Pancreatic Disease

- 3/173 (1.7%) of GATTEX-treated patients developed pancreatitis in pooled Phase III SBS studies*
  - All 3 patients had a history of pancreatitis
  - None of these events resulted in study withdrawal

* As of January 24, 2013
Pancreatic Disease

GATTEX Label – Warnings and Precautions

Pancreatic Disease

– Pancreatidis has been reported in clinical studies.
– Patients must undergo initial (within 6 months prior) laboratory assessment of lipase and amylase.
– Subsequent laboratory assessments are recommended every 6 months; if a clinically meaningful elevation is seen imaging of the pancreas is recommended to identify possible obstruction.
Fluid Overload

- 23/173 (13.3%) of patients treated with GATTEX reported fluid overload in pooled Phase III SBS studies*

- Fluid overload should be considered when administering GATTEX in patients with underlying heart disease

* As of January 24, 2013
Cardiovascular Disease

- Due to increased intestinal fluid absorption, patients with cardiovascular disease, such as cardiac insufficiency and hypertension, should be monitored with regard to fluid overload, especially during initiation of therapy.
- Parenteral nutrition/intravenous (PN/IV) fluid volume should be reassessed relative to signs of fluid overload.
- In case of a significant deterioration of the cardiovascular disease, the need for continued GATTEX treatment should be reassessed.
PN/IV Volume Adjustment

- In order to reduce risk for fluid overload the following PN/IV volume adjustment algorithm is suggested
  - Determine pre-treatment urine output (ideally 1 to 2 L/day)
  - Determine urine output 2 to 4 weeks after starting treatment
  - Reduce weekly PN/IV volume by 10% to 30% if urine output increased at least 10% compared with pre-treatment volume
  - Evaluate if the patient tolerated the PN/IV reduction 1 to 2 weeks later
  - Continue monitoring urine output on a regular basis and adjust PN/IV volume accordingly with the goal of reducing or achieving complete independence from PN/IV support and maintaining clinical nutrition status
Based on the pharmacodynamic effect of GATTEX, there is a potential for increased absorption of concomitant oral medications.

Considerations should be given for dosage adjustment of concomitant oral medication requiring titration or that have a narrow therapeutic index.
Increased Absorption of Concomitant Oral Medication
GATTEX Label – Warnings and Precautions

Risks Resulting from 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.