GATTEX® (Teduglutide [rDNA origin]) for Injection REMS Program: Prescriber Education

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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

GLP-2, glucagon-like peptide-2

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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

1. Munroe DG et al. Proc Natl Acad Sci. 1999; 96:1569-1573.

* As of January 24, 2013

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Possible Acceleration of Neoplastic Growth GATTEX Label – Warnings and Precautions

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.

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Possible Enhanced Growth of Colorectal Polyps

- 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

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Possible Enhanced Growth of Colorectal Polyps GATTEX Label – Warnings and Precautions

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.

Gastrointestinal Obstruction

- 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

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Gastrointestinal Obstruction
GATTEX Label – Warnings and Precautions

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.

Gallbladder and Biliary Tract Disease

- 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

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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.

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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

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Pancreatic Disease
GATTEX Label – Warnings and Precautions

Pancreatic Disease

- Pancreatitis 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

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Fluid Overload
GATTEX Label – Warnings and Precautions

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

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Increased Absorption of Concomitant Oral Medication

- 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.