GATTEX® (teduglutide) REMS Prescriber Education Slide Deck

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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 Prescriber Education Slide Deck is required by the FDA as part of the GATTEX REMS.

US-TED-1140v1.0 10/22

Gattex® (teduglutide) for injection

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Indication

- GATTEX® (teduglutide) for injection is indicated for the treatment of adults and pediatric patients 1 year of age and older 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

- Safety risks with GATTEX
  - Possible acceleration of neoplastic growth
  - Enhanced growth of colorectal polyps
  - Intestinal 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

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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 cannot be excluded that GATTEX promotes growth of existing neoplasms in the GI tract.
- 3 adult patients on GATTEX were reported to have neoplasms:*
  - 2 cases of lung cancer with extensive smoking history
  - 1 case of GI metastatic adenocarcinoma (unknown origin) following abdominal radiation for Hodgkin's disease
- No GATTEX-treated pediatric patients were reported to have neoplasms in the pediatric clinical studies.**

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

* As of 24 January 2013; ** As of 24 July 2018

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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.
- 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 risk-benefit considerations.
- Based on tumor findings in the rat and mouse carcinogenicity studies, 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.

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Enhanced Growth of Colorectal Polyps

- GATTEX's mechanism of action and nonclinical data are consistent with a potential to enhance growth of polyps.
- In the adult clinical studies, 14 patients with SBS were diagnosed with polyps of the GI tract after initiation of study treatment.
  - 2 patients in the SBS-placebo-controlled studies: 2 colorectal villous adenomas
    - 1 patient (1/59; 2%) on placebo with an inflammatory stomal polyp after 3 months
    - 1 patient (1/109; 1%) on GATTEX 0.05 mg/kg/day with a hyperplastic sigmoidal polyp after 5 months
  - 12 GATTEX-treated patients (12/173; 6.9%) in the extension studies:*
    - 2 colorectal villous adenomas
    - 2 hyperplastic polyps
    - 4 colorectal tubular adenoma
    - 1 serrated adenoma
    - 1 rectal inflammatory polyp
    - 1 colorectal polyp biopsy not done
    - 1 small duodenal polyp
- In the pediatric clinical studies (up to 69 weeks of exposure) there was one case of cecal polyp that was not biopsied and was not seen on repeat colonoscopy.**

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Enhanced Growth of Colorectal Polyps
GATTEX Label – Warnings and Precautions

Colorectal Polyps in adults

- 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.

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Enhanced Growth of Colorectal Polyps
GATTEX Label – Warnings and Precautions

Colorectal Polyps in children and adolescents

- Fecal occult blood testing prior to initiating treatment with GATTEX should be done.
- Colonoscopy/sigmoidoscopy is required if there is unexplained blood in the stool.
- Subsequent fecal occult blood testing annually in children and adolescents should be performed while they are receiving GATTEX.
- Colonoscopy/sigmoidoscopy is recommended for all children and adolescents after 1 year of treatment, every 5 years thereafter while on continuous treatment with GATTEX, and if they have new or unexplained gastrointestinal bleeding.

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Intestinal Obstruction

- 12 adult patients were reported to have one or more episodes of serious intestinal obstruction/stenosis events*
  - 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
    - 2/6 patients had recurrence of intestinal obstruction in the extension studies
  - 6 additional patients in the extension studies (all on GATTEX, 0.05 mg/kg/day)
    - Onset 6 days to 19 months
  - Of all 8 patients with an episode of intestinal obstruction/stenosis in the extension studies, 2 patients required endoscopic dilatation and 1 required surgical intervention

* As of 24 January 2013; ** Note that as per the GATTEX Prescribing Information, the recommended dosage of GATTEX for both adult and pediatric patients is 0.05 mg/kg/day

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Intestinal Obstruction

- 1 pediatric patient was reported to have a serious reaction of obstruction that was assessed as related to teduglutide in the pediatric clinical studies.**
  - GATTEX was temporarily withheld, the obstruction resolved without additional intervention, and there was no recurrence once GATTEX was restarted.

** As of 24 July 2018

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Intestinal Obstruction
GATTEX Label – Warnings and Precautions

Intestinal Obstruction

- Intestinal obstruction has been reported in clinical studies and postmarketing.
- 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.

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Gallbladder and Biliary Tract Disease

- 13/173 (7.5%) of GATTEX-treated adult patients were reported to have biliary events, including cholecystitis and gallstones/sludge in pooled Phase III SBS studies*
  - 5 adult patients had a history of biliary disease
  - None of these events resulted in study withdrawal
- No GATTEX-treated pediatric patients were reported to have biliary events related to teduglutide in the pediatric clinical studies.**

* As of 24 January 2013; **As of 24 July 2018

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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 and postmarketing.
- Patients should undergo laboratory assessment of bilirubin and alkaline phosphatase within 6 months prior to starting GATTEX.
- Subsequent laboratory assessments are recommended at least every 6 months while on GATTEX. If clinically meaningful changes are seen, further evaluation including imaging of the gallbladder and/or biliary tract is recommended. Reassess the need for continued GATTEX treatment.

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Pancreatic Disease

- 3/173 (1.7%) of GATTEX-treated adult patients were reported to have pancreatitis in pooled Phase III SBS studies.*
  - All 3 patients had a history of pancreatitis
  - None of these events resulted in study withdrawal
- No GATTEX-treated patients were reported to have pancreatic adverse events related to teduglutide in the pediatric clinical studies.**

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Pancreatic Disease
GATTEX Label – Warnings and Precautions

Pancreatic Disease

- Pancreatitis has been reported in adult clinical studies.
- Patients should undergo laboratory assessment of lipase and amylase within 6 months prior to starting GATTEX.
- Subsequent laboratory assessments are recommended at least every 6 months while on GATTEX; if clinically meaningful changes are seen, further evaluation such as imaging of the pancreas is recommended; reassess the need for continued GATTEX treatment.

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Post-marketing Data Source: Intestinal Obstruction, Biliary and Pancreatic Disease

- All post marketing data are reviewed on an ongoing basis. No new safety findings have been uncovered regarding intestinal obstruction, biliary or pancreatic disease.
- As of 30 August 2018, estimated cumulative worldwide patient exposure to teduglutide was 4,740 patient-years.

Risk	Number of Cumulative Post-Marketing Cases*
Intestinal Obstruction	314
Gallbladder and Biliary Tract Disease	122
Pancreatic Disease	431

*Post -marketing data are reported on a voluntary basis from a population of uncertain size, and it is not always possible to obtain reliable estimate of AE frequency, or to establish a causal relationship of AEs to drug exposure.
Sources: spontaneous cases, solicited cases, cases from Registry TED-R13-002

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Fluid Overload

- 23/173 (13.3%) of adult patients treated with GATTEX were reported to have fluid overload in pooled Phase III SBS studies.*
- Fluid overload should be considered when administering GATTEX in patients with underlying heart disease.
- No GATTEX-treated patients were reported to have serious events of fluid overload in the pediatric clinical studies.** There was 1 patient who had a non-serious related adverse event of peripheral edema in the 0.025 mg/kg/day group.†

* As of 24 January 2013; **As of 24 July 2018

† Note that as per the GATTEX Prescribing Information, the recommended dosage of GATTEX for both adult and pediatric patients is 0.05 mg/kg/day

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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.

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PN/IV Volume Adjustment in Adults

To minimize the risk of fluid overload, the following adjustment algorithm is recommended.

48-Hour Urine Output**	PN/IV* Action
• <1.0 L/day or target based on stabilized urine output	• Increase PN/IV* by ≥10% (week 2) or to previous level
• ≥1.0 L/day but < baseline	• If patient is dehydrated or inadequately nourished, increase PN/IV* • If not dehydrated maintain PN/IV*
• 0% to <10% increase over baseline	• Maintain PN/IV*
• ≥10% increase over baseline	• Reduce PN/IV* by ≥10% of stabilized baseline level up to a clinically appropriate amount (maximum of 30%)

* PN/IV=parenteral nutrition and/or intravenous fluids

** Baseline urine output is volume obtained during stabilization period before treatment is initiated

†Data presented are based on the STEPS clinical trial and are not contained within the Gattex label

Jeppesen PB, et al. Gastroenterology. 2012;143:1473-81

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PN/IV Volume Adjustment in Children and Adolescents

To minimize the risk of fluid overload or dehydration, the following nutritional support adjustment algorithm is suggested:

- Clinic visits every 1-2 weeks during the first 6 weeks of treatment
- Evaluate hydration status at every clinic visit, which may include:
  - Weight trajectory
  - Urine sodium (target > 20 meq/L)
  - Urine output (target 25-50 ml/kg/day)
  - Physical exam findings of hydration status
- Adjust PN/IV volume in increments/decrements of 10%-30% to avoid fluid overload or dehydration
- At every clinic visit, evaluate growth trajectory, enteral intake, and severity of diarrhea
- If growth trajectory is adequate and diarrhea is manageable, consider reducing PN calories and increasing enteral nutrition

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Increased Absorption of Concomitant Oral Medications

- 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 medications requiring titration or that have a narrow therapeutic index

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Increased Absorption of Concomitant Oral Medication GATTEX Label – Warnings and Precautions

Risks resulting from increased absorption of concomitant oral medications

- Altered mental status in association with GATTEX has been observed in patients on benzodiazepines in adult clinical studies.
- Patients on concomitant oral medications (e.g., benzodiazepines, phenothiazines) requiring titration or with a narrow therapeutic index may require a reduction in dosage of the concomitant drug while on GATTEX.

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