DR.012.A	Gattex® (teduglutide)	Health Partners Plans

Title: Gattex® (teduglutide)
Policy #: DR.012.A
Type: Medical
Sub-Type: Drug

Original Implementation Date: 12/1/2021
Version [A] Effective Date: 12/1/2021
Last reviewed: 10/20/2021
30-day Notification Published: 11/1/2021

TABLE OF CONTENTS

PRODUCT VARIATIONS

This policy only applies to Health Partners Plans (HPP) Medicaid and CHIP product lines.

POLICY STATEMENT

Health Partners Plans (HPP) considers Gattex® medically necessary for the treatment of short bowel syndrome in adults and pediatric patients ≥1 year of age who are dependent on parenteral support and meet the prior authorization criteria listed in this policy.

OFF-LABELED USE

Authorization for off-labeled use of medication will be evaluated on an individual basis. Review of an off-labeled request by the Medical Staff will be predicated on the appropriateness of treatment and full consideration of medical necessity.

PRIOR AUTHORIZATION

1. Is the medication prescribed by or in consultation with a gastroenterologist or a colorectal surgeon? *If YES, go to 2. If NO, refer to Medical Director.*

2. Does the patient have a documented diagnosis of short bowel syndrome? *If YES, go to 3. If NO, refer to Medical Director.*

3. Is the patient currently receiving parenteral nutrition and/or intravenous fluids for at least 12 months 3 or more days per week despite optimized dietary modifications and use of the following medications (a and b):

    a. An antimotility agent (e.g. loperamide, diphenoxylate with atropine, opioids);
    b. An antisecretory agent (e.g. histamine-2 receptor blockers, proton pump inhibitors, octreotide).
    If YES, go to 4. If NO, refer to Medical Director.

4. Does the patient have active gastrointestinal malignancy? *If YES, refer to Medical Director. If NO, go to 5.*

5. Does the patient have biliary and/or pancreatic disease? *If YES, refer to Medical Director. If NO, go to 6.*

6. If 18 years or older, is there documentation of colonoscopy to rule out polyps within the last 6 months?
    If YES, go to 7. If NO, refer to Medical Director.

7. Is the prescription within the FDA-labeled dose of 0.05 mg/kg/day? *If YES, approve for 6 months.*
    If NO, refer to Medical Director.

HPP considers Gattex® 5 mg (teduglutide) **experimental and investigational** for all other indications including the following (not an all-inclusive list):

- Chemotherapy-induced enteritis
- Gastrointestinal mucositis (including chemotherapy-induced mucositis)
- Gastrointestinal stromal tumors
- Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
- Intestinal anastomotic healing
- Necrotizing enterocolitis
- Post-operative ileus
- Short Bowel Syndrome and chronic diarrhea without parenteral support
- Radiation-induced enteritis
- Radiation-induced intestinal injury
- Routine use following small bowel transplantation

RATIONALE: To ensure appropriate utilization.

RENEWAL CRITERIA

1. Is the medication prescribed by or in consultation with a gastroenterologist or a colorectal surgeon?
    If YES, go to 2. If NO, refer to Medical Director.
2. Is there documentation of reduction in parenteral support by at least 20% as a result of Gattex® treatment and no treatment-related adverse events (medical records must be included)?
    If YES, approve 12 months. If NO, refer to Medical Director.

DOSAGE AND ADMINISTRATION

Short bowel syndrome: SubQ: 0.05 mg/kg once daily

Pediatric: Children and adolescents weighing ≥10 kg: SubQ: 0.05 mg/kg/dose once daily

RISK FACTORS/SIDE EFFECTS

Contraindications: There are no contraindications listed in the US manufacturer's labeling

Warnings/precautions:

Colorectal polyps: Short bowel syndrome: Development of colorectal polyps has occurred. In adults, perform a baseline colonoscopy of the entire colon with polyp removal ≤6 months prior to initiation of therapy. Follow-up colonoscopy (or alternative imaging) should be performed at 1 year and at least every 5 years, thereafter. In children and adolescents, perform fecal occult blood testing at baseline and annually; if unexplained blood detected, perform colonoscopy/sigmoidoscopy. Additionally, perform colonoscopy/sigmoidoscopy after 1 year, every 5 years thereafter during therapy, or for new or unexplained GI bleeding. Discontinue teduglutide in patients who develop colorectal cancer.

Fluid overload: Increased fluid absorption and subsequent fluid overload/congestive heart failure has been reported; consider modification of parenteral support in patients who develop fluid overload, especially in patients with underlying cardiovascular disease.

Gallbladder/biliary tract disease: Cholecystitis, cholangitis, and cholelithiasis have been reported; monitor serum bilirubin and alkaline phosphatase ≤6 month prior to initiation of therapy and at least every 6 months for duration of therapy.

Intestinal obstruction: Temporarily discontinue treatment in patients that develop intestinal or stomal obstruction; teduglutide may be resumed (if clinically indicated) once the obstruction is resolved.

Malignancy: Teduglutide may increase the risk of hyperplastic changes, including neoplasia. In patients at increased risk for malignancy, consider treatment only if benefits outweigh the risks. Discontinue treatment in patients with active gastrointestinal malignancy (GI tract, hepatobiliary, pancreatic); evaluate risk versus benefit in patients with active non-GI malignancy. Monitor for small bowel neoplasia; remove any benign neoplasm. Discontinue in patients who develop small bowel cancer.

Pancreatitis: Pancreatitis has been reported; monitor serum lipase and amylase ≤6 months prior to initiation of therapy and at least every 6 months for duration of therapy.

MONITORING

Screen for colorectal polyps-within 1 year before start of therapy and every 5 years thereafter

LFT(serum bilirubin and alkaline phosphatase) within 6 months before the start of therapy and every 6 months thereafter

Amylase, Lipase within 6 months before the start and every 6 months thereafter

BACKGROUND

Short bowel syndrome (SBS) is a malabsorptive state that typically occurs following extensive resection of the small intestine. Clinical disease is only weakly correlated with the amount of intestine that is resected because of the highly variable length of the human small bowel and the remarkable ability of the bowel to compensate for bowel resection. Therefore, the best definition of SBS is a functional definition, implying a significant amount of malabsorption of both macronutrients and micronutrients. Intestinal failure describes the state when an individual's gastrointestinal function is inadequate to maintain his or her nutrient and hydration status without intravenous or enteral supplementation.

Functionally, intestinal failure may be classified by duration, as type I (acute), type II (prolonged acute), or type III (chronic).

SBS is the most common cause of chronic intestinal failure (approximately 60 percent of the cases in adults). SBS in adults usually results from surgical resection of the small intestine for Crohn disease, trauma, malignancy, radiation, or mesenteric ischemia. In addition, SBS caused by postoperative vascular and obstructive catastrophes requiring massive intestinal resection seems to be increasing in incidence. Advances in the treatment of Crohn disease may lead to a reduction in SBS; however, these improvements do not yet appear to have led to a reduction in the number of patients requiring home parenteral nutrition (PN). In infants and small children, necrotizing enterocolitis and congenital intestinal anomalies, such as mid-gut volvulus, atresias, or gastroschisis, are the most common causes of SBS. (John K DiBaise, MD). Patients with SBS are at risk for several complications. These complications may result from the underlying disease, altered bowel anatomy and physiology, or its treatment, including the need for parenteral nutrition and the use of a central venous catheter. Acute complications that can occur at any time include watery diarrhea, electrolyte disturbances, and catheter-related complications.

On December 21, 2012, the Food and Drug Administration (FDA) approved teduglutide (Gattex®) for the treatment of adults with SBS who need additional nutrition from intravenous feeding (parenteral nutrition). Teduglutide is a human recombinant analog of glucagon-like peptide 2 (GLP-2) and is designed to restore intestinal structural and functional integrity by promoting growth of the intestinal mucosa as well as increasing intestinal and portal blood flow and reducing gastric emptying and secretion. These effects lead to greater surface area in the gut and slower transit time which allow for greater nutrient absorption. It is injected subcutaneously once daily (0.05 mg/kg of body weight) to improve intestinal absorption of fluids and nutrients, reducing the frequency and volume of PN.

On May 17, 2019 the U.S. Food and Drug Administration (FDA) extended the indication of Gattex® (teduglutide) for injection to pediatric patients 1 year of age and older with Short Bowel Syndrome (SBS) who need additional nutrition or fluids from intravenous (IV) feeding (parenteral support).

CLINICAL TRIAL EVIDENCE

Available evidence has demonstrated a desirable benefit-to-risk profile in regard to its safety and effectiveness; enhanced absorption has been shown in clinical trials by a reduction in PN/intravenous fluids requirements in patients with SBS treated with teduglutide (Vipperla and O'Keefe, 2011; Norholk et al, 2012).

In a 24-week placebo-controlled study, Jeppesen et al (2011) evaluated the ability of teduglutide to reduce parenteral support in patients with SBS with intestinal failure (SBS-IF). A total of 83 patients were randomized to receive subcutaneous teduglutide 0.10 mg/kg/day (n = 32), 0.05 mg/kg/day (n = 35) or placebo (n = 16) once daily. Subjects

were adults with SBS who were dependent on PN/intravenous support for at least 12 months and required PN at least 3 times per week. Parenteral fluids were reduced at 4-week intervals if intestinal fluid absorption (48-hr urine volumes) increased greater than or equal to 10 %. Responders were subjects who demonstrated reductions of greater than or equal to 20 % in parenteral volumes from baseline at weeks 20 and 24. The results were tested according to a step-down procedure starting with the 0.10 mg/kg/day dose. Teduglutide in a dose of 0.10 mg/kg/day did not have a statistically significant effect compared with placebo (8/32 versus 1/16, p = 0.16), while teduglutide in a dose of 0.05 mg/kg/day had a significant effect (16/35, p = 0.007). Three teduglutide-treated patients were completely weaned off parenteral support. Serious adverse events were distributed similarly between active treatment groups and placebo. Villus height, plasma citrulline concentration (a biomarker of mucosal mass) and lean body mass were significantly increased with teduglutide compared with placebo. The authors concluded that teduglutide was safe, well-tolerated, intestine-trophic and suggested pro-absorptive effects facilitating reductions in parenteral support in patients with SBS-IF.

In a prospective study, Jeppesen et al (2012) examined if teduglutide reduces parenteral support in patients with SBS-IF. These investigators performed a 24-week study of patients with SBS-IF who were given subcutaneous teduglutide (0.05 mg/kg/day; n = 43) or placebo (n = 43) once-daily. Subjects were adults with SBS who were dependent on PN/intravenous support for at least 12 months and required PN at least 3 times per week. Parenteral support was reduced if 48-hr urine volumes exceeded baseline values by greater than or equal to 10 %. The primary efficacy end point was number of responders (patients with greater than 20 % reduction in parenteral support volume from baseline at weeks 20 and 24). There were significantly more responders in the teduglutide group (27/43 [63 %]) than the placebo group (13/43 [30 %]; p = 0.002). At week 24, the mean reduction in parenteral support volume in the teduglutide group was 4.4 +/- 3.8 L/week (baseline 12.9 +/- 7.8 L/week) compared with 2.3 +/- 2.7 L/week (baseline 13.2 +/- 7.4 L/week) in the placebo group (p < 0.001). The percentage of patients with a 1-day or more reduction in the weekly need for parenteral support was greater in the teduglutide group (21/39 [54 %]) than in the placebo group (9/39 [23 %]; p = 0.005). The distribution of treatment-emergent adverse events that led to study discontinuation was similar between patients given teduglutide (n = 2) and placebo (n = 3). The authors concluded that 24 weeks of teduglutide treatment was generally well-tolerated in patients with SBS-IF. Treatment with teduglutide reduced volumes and numbers of days of parenteral support for patients with SBS-IF.

O'Keefe et al (2013) examined the 12-month tolerability and effectiveness of teduglutide to reduce PN dependency. Patients who received teduglutide (0.05 or 0.10 mg/kg/day) for 24 weeks in a randomized controlled trial were eligible for a 28-week double-blind extension study; 52 patients were given 52 weeks of the same doses of teduglutide. These researchers investigated the safety, tolerability and clinical effectiveness (defined as a clinically meaningful = 20 % reduction in weekly PN volume from baseline) at week 52. The most common adverse events reported included abdominal pain (25 %), headache (35 %), and nausea (31 %); 7 patients withdrew because of adverse events (gastro-intestinal disorders in 4). Both groups had progressive reduction in PN. At week 52, 68 % of the 0.05 mg/kg/day and 52 % of the 0.10 mg/kg/day dose group had a greater than 20 % reduction in PN, with a reduction of = 1 day of PN dependency in 68 % and 37 %, respectively. Four patients achieved complete independence from PN. The authors concluded that for patients with SBS-IF, the effectiveness of teduglutide was maintained over 52 weeks, and the safety profile was sufficient for it to be considered for long-term use.

Pediatric Short Bowel Syndrome

The expanded approval in pediatric patients was based on a 24-week pediatric study (Study 5,TED-C14-006, NCT02682381) which demonstrated teduglutide helped reduce the volume of daily parenteral support required and time spent administering parenteral support. Some children even achieved complete freedom from parenteral support

(Shire-NPS Pharmaceuticals, Inc., a Takeda company, 2019). Fifty- nine pediatric patients with SBS aged 1 year through 17 years chose whether to receive teduglutide or standard of care (SOC). The teduglutide group was subsequently randomized in a double-blind manner to 0.025 mg/kg/day (n=24) or 0.05 mg/kg/day (n=26), while 9 patients enrolled in the SOC arm. The recommended dosage of teduglutide is 0.05 mg/kg/day. Patients treated with 0.05 mg/kg had a mean age of 6 years at baseline. The most common reasons for intestinal resection leading to SBS were gastroschisis (54%, 14/26), midgut volvulus (23%, 6/26), and necrotizing enterocolitis (12%, 3/26). Stoma was present in 19% (5/26) of patients, and the most common type was jejunostomy (80%, 4/5). The mean length of remaining small intestine was 47 (±28) cm (range: 9 to 120 cm). In the 25 patients who had remaining colon, the colon was in continuity in 22 patients. At baseline, the mean parenteral support volume was 60 (±29) mL/kg/day (range: 24 to 133 mL/kg/day) [8 (±4) L/week (range: 3 to 19 L/week)] and mean parenteral support infusion time was 7 (±1) days/week (range: 5 to 7 days/week) and 11 (±3) hours/day (range: 7 to 20 hours/day).

Randomization to the teduglutide dose groups was stratified by age. At the end of the 24-week study, 69% of patients (18/26) who took teduglutide 0.05 mg/kg each day reduced parenteral support volume by 20% or more. Based on patient-diary data, patients who received teduglutide 0.05 mg/kg/day experienced a 42% mean reduction in parenteral support volume (mL/kg/day) from baseline (-23 mL/kg/day from baseline). At week 24, 38% of patients (10/26) were able to reduce parenteral support infusion by at least 1 day per week. Patients reduced their parenteral support infusion time by 3 hours per day on average compared to baseline. In addition, during this study 3 out of 26 (12%) children who received teduglutide 0.05 mg/kg/day completely weaned off parenteral support.

Study 6 (SHP633-304, NCT02954458) was a prospective, open-label, long-term extension study of pediatric patients who completed Study 5. In the extension study, patients received additional treatment with teduglutide 0.05 mg/kg subcutaneously once daily if they deteriorated or stopped improving after discontinuation of prior teduglutide treatment. Of the 15 patients who initially responded in Study 5 and enrolled in Study 6, 13 patients (87%) required additional treatment with teduglutide. Efficacy results at the end of the first 24-week treatment period in Study 6 (total treatment for a mean of 40 weeks) were similar to those achieved at the end of 24 weeks treatment in Study 5. One additional patient treated with 0.05 mg/kg in Study 5 eventually achieved enteral autonomy during follow-up in Study 6.

Teduglutide has a demonstrated safety profile that is similar overall in pediatric and adult patients.

The most common side effects of teduglutide identified in clinical trials were abdominal distension, abdominal pain, headaches, injection site reactions, nausea, and upper respiratory tract infection. Patients treated with teduglutide have a potential increased risk of developing biliary tract disease, cancer and polyps in the intestine, gallbladder disease, obstructions in the intestine, and pancreatic disease.

To ensure that the benefits of teduglutide outweigh the potential risks, the drug is being approved with a Risk Evaluation and Mitigation Strategy, consisting of a communication plan and training for prescribers.

To study teduglutide's long-term safety, the FDA is requiring a post-market study of SBS patients treated with the drug in a routine clinical setting to further evaluate the drug's potential increased risk to cause colorectal cancer and other conditions. Patients in this study will be followed for at least 10 years.

CODING

NOTE: The Current Procedural Terminology (CPT®) codes and Healthcare Common Procedure Coding System (HCPCS) codes listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service is covered and is not a guarantee of payment. Other policies and coverage guidelines may apply. When reporting services, providers/facilities should code to the highest level of specificity using the code that was in effect on the date the service was rendered. This list may not be all inclusive.

CPT Code	Description
N/A	

CPT® is a registered trademark of the American Medical Association.

HCPCS Code	Description
	There is no specific HCPCS Code for Teduglutide (Gattex®)
J3490	Unclassified drugs
J3590	Unclassified biologics

ICD-10 code	Description
K91.2	Postsurgical malabsorption, not elsewhere classified [short bowel syndrome]

POLICY HISTORY

This section provides a high-level summary of changes to the policy since the previous version.

Summary	Version	Version Effective Date
This is a new drug policy.	A	12/1/2021

REFERENCES

1. Product Information. Gattex®. 2021.
2. UpToDate. Accessed 2021. (John K DiBaise, MD).
3. Buchman AL, Katz S, Fang JC, et al; Teduglutide Study Group. Teduglutide, a novel mucosally active analog of glucagon-like peptide-2 (GLP-2) for the treatment of moderate to severe Crohn's disease. Inflamm Bowel Dis. 2010;16(6):962-973.
4. Carter BA, Cohran VC, Cole CR, et al. Outcomes from a 12-week, open-label, multicenter clinical trial of teduglutide in pediatric short bowel syndrome. J Pediatr. 2017;181:102-111.
5. Jeppesen PB, Gilroy R, Pertkiewicz M, et al. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011;60(7):902-914.

6. Tee CT, Wallis K, Gabe SM. Emerging treatment options for short bowel syndrome: Potential role of teduglutide. Clin Exp Gastroenterol. 2011;4:189-196.
7. Jeppesen PB, Pertkiewicz M, Messing B, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology. 2012;143(6):1473-1481.
8. Schwartz LK, O'Keefe SJD, Fujioka K, et al. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. *Clin Transl Gastroenerol*. 2016; 7:e142.
9. Seidner DL, Schwartz LK, Winkler MF, et al. Increased intestinal absorption in the era of teduglutide and Its impact on management strategies in patients With short bowel syndrome-associated intestinal failure. JPEN J Parenter Enteral Nutr. 2013;37(2):201-211.
10. Shire-NPS Pharmaceuticals, Inc. Gattex® (teduglutide) for injection, for subcutaneous use. Prescribing Information. Lexington, MA: Shire-NPS Pharmaceuticals, Inc.; June 2019.
11. U.S. Food and Drug Administration (FDA). Gattex® (teduglutide) for injection, for subcutaneous use. Prescribing Information. Reference ID: 4434570. Rockville, MD: FDA; revised May 2019.
12. U.S. Food and Drug Administration (FDA). FDA approves Gattex® to treat short bowel syndrome. Press Release. Silver Spring, MD: FDA; December 21, 2012. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333171.htm.
13. Vipperla K, O'Keefe SJ. Teduglutide for the treatment of short bowel syndrome. Expert Rev Gastroenterol Hepatol. 2011;5(6):665-678.
14. Wismann P, Pedersen SL, Hansen G, et al. Novel GLP-1/GLP-2 co-agonists display marked effects on gut volume and improves glycemic control in mice. Physiol Behav. 2018;192:72-81.
15. Yazbeck R. Teduglutide, a glucagon-like peptide-2 analog for the treatment of gastrointestinal diseases, including short bowel syndrome. Curr Opin Mol Ther. 2010;12(6):798-809.