

## Positive Quality Intervention: Telotristat Ethyl for the Management of Carcinoid Syndrome Diarrhea

### Description:

Treatment options for patients with carcinoid syndrome diarrhea that is refractory to somatostatin analog (SSA) therapy are limited. A first in class oral tryptophan hydroxylase inhibitor, telotristat ethyl (Xermelo), was approved in February for 2017 for use in combination with SSA therapy in adults with carcinoid syndrome diarrhea inadequately controlled by SSA.

### Background:

Carcinoid tumors are well-differentiated neuroendocrine tumors that typically originate in the digestive track or lungs. These tumors may secrete as many as 40 different bioactive products, with the most pronounced being serotonin, histamine, tachykinins, kallikrein and prostaglandins. Carcinoid syndrome diarrhea is thought to be caused by the overproduction and release of serotonin by the carcinoid tumor, resulting in stimulation of intestinal secretions as well as motility and inhibition of intestinal absorption.

TELESTAR was a phase III placebo-controlled trial that demonstrated a significant decrease in bowel movement frequency with the addition of telotristat ethyl to SSA therapy in patients with uncontrolled carcinoid syndrome with a manageable adverse event profile. Bowel movement (BM) frequency decreased by approximately two movements a day, and a responder analysis identified that more than 40% of patients receiving telotristat ethyl had a  $\geq 30\%$  decrease in BM frequency compared with 20% of patient receiving placebo. The most common treatment-related adverse events reported in TELESTAR in patients receiving telotristat ethyl 250mg were nausea (13.3%), headache (11.1%), increased gamma-glutamyl-transferase (8.9%), depression (6.7%), peripheral edema (7%), flatulence (6.7%), decreased appetite (6.7%) and pyrexia (6.7%).

Clinicians should be aware of this oral option for carcinoid tumor patients who exhibit diarrhea symptoms that continue to be refractory to SSA therapy.

### PQI Process:

Upon receipt of a new prescription for telotristat ethyl:

- Verify initial dosage is 250mg orally three times a day
- Ensure adult patient with the diagnosis of carcinoid syndrome is:
  - Currently receiving a long-acting SSA at a stable-dose (3 months of treatment at the same dose)

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- Depot octreotide
- Long-acting lanreotide
- Suffering from inadequately controlled diarrhea
- Dosages >30mg for depot octreotide and >120mg for long-acting lanreotide may not be reimbursed by insurance companies as this is above the Food and Drug Administration (FDA)-approved dosages. Additionally, administering at an interval of <4 weeks is also outside of the prescribing guidelines and may cause reimbursement issues.
- Provide patients with refractory carcinoid symptoms (either during the dose escalation phase of the long-acting SSA or while waiting to receive telotristat ethyl) with a rescue short-acting octreotide prescription, if not already receiving, as well as an antidiarrheal. Initial dosing of short-acting octreotide is typically 100mcg subcutaneously three times a day. This dose may be titrated up to 600mcg per day.
- Telotristat ethyl can be administered concomitantly with antidiarrheals and/or short-acting octreotide, but the injection must be given at a minimum 30 minutes after the telotristat ethyl as octreotide may decrease the serum concentration of the medication.
- Consider screening for depression using an approved depression test questionnaire. Although preclinical trials with telotristat ethyl did not demonstrate significant central nervous system penetration, at higher doses (e.g., 500mg three times daily vs 250mg three times daily) an increase in depression-related adverse events were reported (placebo = 6.7% vs telotristat ethyl 500mg TID = 15.6%). Further examination of this adverse event is being explored in a phase III trial.

#### **Patient Centered Activities:**

- Educate patients receiving telotristat ethyl:
  - Response times
    - Response times vary, but they may need to allow the full 12 weeks of therapy to respond to the treatment
  - Bowel Habits
    - Monitor their BM closely and if they begin to experience constipation make their healthcare team aware
    - Report any severe or persistent bowel pain as intestinal perforation and bowel obstruction was observed in TELESTAR
  - Nausea
    - Report so that an anti-nausea medication can be prescribed
    - Important to remember that many anti-nausea medications can cause constipation, so counsel patients to monitor closely

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- Administration
  - Take with food (meals preferred over a snack)
  - If used in combination with short-acting octreotide must inject the octreotide at least 30 minutes after the telotristat ethyl
- Financial Assistance
  - LexCares (<http://www.lexiconcares.com>)
    - Medicare, Medicaid or uninsured patients can work with LexCare Specialty Pharmacies (Biologics, Inc. or Diplomat Specialty Pharmacy) to identify patient assistance programs
    - Co-pay assistance cards for commercial insurance patients

#### References:

1. Kulke MH, Horsch D, Caplin ME et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2016; 35: 14-23.
2. Xermelo (telotristat ethyl) [package insert]. The Woodlands, TX: Lexicon Pharmaceuticals Inc. 2017.
3. Modlin IM, Kidd M, Latich I et al. Current status of gastrointestinal carcinoids. *Gastroenterology*. 2005; 128(6): 1717-51.
4. Kvolts LK. Metastatic carcinoid tumors and the malignant carcinoid syndrome. *Ann N Y Acad Sci*. 1994; 733: 464-70.

#### Supplemental Information:

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