



## Positive Quality Intervention: Telotristat Ethyl (Xermelo®) for the Management of Carcinoid Syndrome Diarrhea

**Description:** This PQI will review appropriate patient identification and management techniques to ensure optimal benefit from telotristat ethyl therapy.

**Background:** A first in class oral tryptophan hydroxylase inhibitor, telotristat ethyl, is approved for use in combination with somatostatin analogues (SSA) therapy in adults with carcinoid syndrome diarrhea inadequately controlled by SSA. 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. 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:** Consider EMR review of all patients with neuroendocrine tumors and assess adequate control of diarrhea; upon receipt of a new prescription for telotristat ethyl

- Verify initial dosage is 250 mg 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)
    - Depot octreotide
    - Long-acting lanreotide
  - Suffering from inadequately controlled diarrhea
- Dosages >30 mg for depot octreotide and >120 mg for long-acting lanreotide may not be reimbursed by insurance as this is above the approved dosages; 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 with a rescue short-acting octreotide prescription and an antidiarrheal
  - Initial dosing of short-acting octreotide is typically 100 mcg subcutaneously three times a day (may be titrated up to 600 mcg/day); injection must be given at a minimum 30 minutes after the telotristat ethyl as octreotide may decrease the serum concentration
- Consider screening for depression using an approved depression test questionnaire; at higher doses an increase in depression-related adverse events were reported (placebo = 6.7% vs telotristat ethyl 500 mg TID = 15.6%)

### Patient-Centered Activities:

- Educate patients receiving telotristat ethyl
  - Response times vary, allow the full 12 weeks of therapy to respond to the treatment
  - Monitor bowel habits closely and if patient begins to experience constipation make their healthcare team aware
    - Report any severe or persistent bowel pain as intestinal perforation and bowel obstruction was observed in clinical trials

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- Most common adverse reactions ( $\geq 5\%$ ) include nausea, headache, increased gammaglutamyl-transferase, depression, flatulence, decreased appetite, peripheral edema, and pyrexia
  - Report nausea so that an anti-nausea medication can be prescribed
    - Many anti-nausea medications can cause constipation; counsel patients to monitor
- 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
- Patient Assistance: [NCODA Financial Assistance Tool](#)

## References:

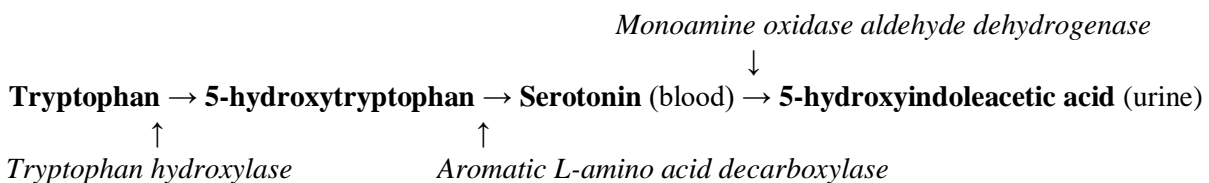
1. Kulke MH, Horsch D, Caplin ME et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. J Clin Oncol. 2016; 35: 14-23.
2. [Xermelo® \(telotristat ethyl\) \[package insert\]](#).
3. Modlin IM, Kidd M, Latich I et al. Current status of gastrointestinal carcinoids.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

## Supplemental Information:

### Background on Carcinoid Syndrome Diarrhea:

Carcinoid syndrome is most commonly associated with metastatic tumors of the jejunum, ileum and cecum, most commonly in the setting of liver metastases, as the liver is responsible for inactivating the bioactive products secreted by the tumor into the bloodstream. These tumors secrete substances like serotonin which is then metabolized to 5-hydroxyindoleacetic acid (5-HIAA) and excreted in the urine. Patients suffering from carcinoid syndrome are known to have modified metabolism of tryptophan. In healthy individuals only about 1% of tryptophan is converted to serotonin, but in patients suffering from carcinoid syndrome up to 70% of tryptophan can be converted to serotonin. Serotonin however does not cause flushing in carcinoid syndrome; this symptom is thought to be due to other bioactive products released by the tumor. Figure 1 outlines the metabolism of tryptophan and serotonin.

Figure 1: Tryptophan and Serotonin Metabolism



### Clinical Trial Experience:

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 250 mg 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%).