Description:

Xermelo (telotristat ethyl) is a tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

Carcinoid syndrome is a term applied to a group of symptoms that occur with a type of cancer called carcinoid tumor. Most individuals with carcinoid syndrome will have metastatic disease at the time of diagnosis. Carcinoid tumors originate from neuroendocrine cells that are found throughout the body which are capable of producing various peptides. Although carcinoid tumors are commonly found in the gastrointestinal tract, they can also be found in the lungs, pancreas, thymus, kidney, ovaries and elsewhere. While the tumors can originate from any location in the body, they have been traditionally described on the basis of embryonic divisions of the gut: foregut, midgut, and hindgut. Foregut includes the thymus, respiratory tract, ovaries, stomach, pancreas, and duodenum. The midgut includes the jejunum, ileum, appendix, cecum, Meckel's diverticulum, and ascending colon. The hindgut includes the colon and rectum. Five growth patterns are observed with carcinoid tumors: insular, trabecular, glandular, undifferentiated (usually designated A through D or I through IV), and mixed.
Carcinoid syndrome is caused by a carcinoid tumor that secretes serotonin and other hormones into the bloodstream, causing a variety of signs and symptoms. The signs and symptoms of carcinoid syndrome depend on which substance the carcinoid tumor secretes. Hormones secreted by carcinoid tumors and functional pancreatic neuroendocrine tumors include, adrenocorticotropic hormone (ACTH), bombesin, calcitonin, catecholamines, chromogranin-A and C, gastrin, glucagon, growth hormone, growth hormone-releasing hormone, histamine, 5-hydroxytryptophan (5-HTP), insulin, kallikrein, neuron-specific enolase, neurotensin, pancreatic polypeptide, prostaglandins, serotonin, somatostatin, synaptophysin, substance P, tachykinins, vasoactive intestinal peptide (VIP), and various growth factors such as transforming growth factor (TGF-), platelet-derived growth factor (PDGF), and beta-fibroblast growth factor.

Clinical signs and symptoms of carcinoid syndrome include facial skin flushing and flushing of the upper chest that may also feel hot and change color, ranging from pink to purple. The flushing episodes may last from a few minutes to a few hours. Flushing may occur for no obvious reason, although it can be triggered by stress, exercise or drinking alcohol. Facial skin lesions appear as purple spiderlike veins on the nose and upper lip. There is frequent watery diarrheal stools sometimes accompanied by abdominal cramps. Diarrhea may be seen in up to 78% of individuals and can be severe and debilitating with as many as 30 episodes of loose stools per day in some. An individual will also have difficulty breathing or asthma-like signs and symptoms, with wheezing and shortness of breath that may occur at the same time as skin flushing. A rapid heartbeat is seen and in later stages carcinoid syndrome may damage heart valves resulting in tricuspid regurgitation or pulmonary stenosis in approximately 50% of individuals.

The most common endocrine cell found in the gastrointestinal tract is the enterochromaffin-like (ECL) cell which synthesize and secrete histamine, serotonin and other compounds.

Neuroendocrine tumors (NET) are neoplasms that arise from cells of the endocrine (hormonal) and nervous systems. They commonly occur in the intestine, where they are often called carcinoid tumors, but they are also found in the pancreas, lung and the rest of the body. There are two main types of NET: those which arise from the gastrointestinal tract (GIT) and those that arise from the pancreas. The term "carcinoid" has often been applied to both, although sometimes it is restrictively applied to NET of GIT origin, or to those tumors which secrete functional hormones or polypeptides associated with clinical symptoms. About 2/3 of gastroenteropancreatic NET are carcinoid tumors and about 1/3 are pancreatic neuroendocrine tumors.

VIPomas are rare functioning neuroendocrine tumors that secrete vasoactive peptide (VIP). Other substances, such as prostaglandin E2, may occasionally be secreted by these tumors. VIP is a polypeptide that binds to high affinity receptors on intestinal epithelial cells, leading to activation of cellular adenyate cyclase and cyclic adenosine monophosphate (cAMP) production. This results in net fluid and electrolyte secretion into the gastrointestinal lumen, resulting in secretory diarrhea and hypokalemia. Other biologic actions of VIP include vasodilation, inhibition of gastric acid secretion, bone resorption, and enhanced glycogenolysis as well as laboratory findings of hypochlorhydria, hypercalcemia, and hyperglycemia seen in patients with VIPomas. The majority of VIPomas arise within the pancreas, and are classified as functioning pancreatic neuroendocrine (islet cell) tumors. In adults, VIPomas are intrapancreatic in over 95 percent of cases. However, other VIP-secreting tumors have been reported, including lung cancer, colorectal cancer, ganglioneuroblastoma, pheochromocytoma, hepatoma, and adrenal tumors.

Xermelo (telotristat ethyl) is a tryptophan hydroxylase inhibitor. The enzyme tryptophan hydroxylase is involved in the first and rate limiting step in serotonin biosynthesis. Serotonin plays a role in mediating secretion, motility, inflammation, and sensation of the gastrointestinal tract, and it is over-produced in patients with carcinoid
syndrome. Through inhibition of tryptophan hydroxylase, telotristat reduces the production of peripheral serotonin, and the frequency of carcinoid syndrome diarrhea.

The package label for Xermelo (telotristat ethyl) describes a randomized trial using of Xermelo 500 mg three times daily that did not demonstrate additional treatment benefit on the primary endpoint and had a greater incidence of severe adverse reactions than Xermelo 250 mg three times daily. Therefore, Xermelo (telotristat ethyl) 500 mg three times daily is not recommended.

Definitions:

Somatostatin analogs:
- Somatuline depot (lanreotide)
  - Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) unresectable, well or moderately differentiated, locally advanced or metastatic, to improve progression-free survival.

Octreotide acetate – generic, Sandostatin, & Sandostatin depot
- Carcinoid tumors:
  - Solution: Symptomatic treatment of patients with metastatic carcinoid tumors where it suppresses or inhibits the severe diarrhea and flushing episodes associated with the disease.
  - Suspension: Long-term treatment of severe diarrhea and flushing episodes associated with metastatic carcinoid tumors.

Vasoactive intestinal peptide tumors (VIPomas):
- Solution: Treatment of the profuse watery diarrhea associated with VIP-secreting tumors.

Gastroenteropancreatic neuroendocrine tumors (metastatic) – off-label, rated “A” by F&C
- Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form to support the off-label use. Data from a randomized, placebo-controlled, phase 3 study support the use of octreotide LAR in the management of well-differentiated metastatic midgut neuroendocrine tumors. Clinical experience also suggests the utility of octreotide in managing gastroenteropancreatic neuroendocrine tumors.

5-hydroxyindolacetic acid (5-HIAA) testing:
- Reference range:
  - 24 hour urine: 2-7 mg or 10.5-36.6 µmol
  - Urine spot: 0-14 mg/g creatinine
  - Plasma: 0-22 np/mL

Chromogranin A (CgA) blood test:
- Reference range: Serum
  - Less than 36.4 ng/mL (conventional units)
  - Less than 36.4 µg/L (system international)
XERMELO™ (telotristat ethyl) oral tablet (cont.)

Serotonin (5-HT) blood test:
Reference range:
   101-283 ng/mL

Drug related events:
Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual's outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or permanent change, impairment, damage or disruption in the individuals' body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm.

If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record
Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

This Pharmacy Coverage Guideline does not apply to FEP or other states’ Blues Plans.

Information about medications that require precertification is available at [www.azblue.com/pharmacy](http://www.azblue.com/pharmacy).

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Xermelo (telotristat ethyl) requires completion of the specific request form in its entirety. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to [Pharmacyprecert@azblue.com](mailto:Pharmacyprecert@azblue.com). Incomplete forms will be returned.

- **Initial therapy**: FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Xermelo (telotristat ethyl) is considered *medically necessary* when ALL of the following criteria are met:
  1. Individual is 18 years of age or older
  2. Medical record documentation of a confirmed diagnosis of carcinoid syndrome diarrhea on somatostatin analog (SSA) therapy that is inadequately controlled by SSA therapy **and**
     - Somatostatin analog will be continued
  3. **ALL** of the following baseline tests have been completed before initiation of treatment:
     - Measurement of 24-hour urinary excretion of 5-hydroxyendolacetic acid (5-HIAA), a product of the breakdown of serotonin
     - Serum chromogranin-A or serum serotonin
     - Somatostatin receptor scintigraphy
  4. Absence of **ALL** of the following exclusions:
     - End-stage renal disease (ESRD) patients who require dialysis
     - Moderate or severe hepatic impairment (defined as total bilirubin > 1.5 times the upper limit of normal and any value for AST)
**Continuation of coverage (renewal request):** Xermelo (telotristat ethyl) is considered **medically necessary** with documentation of **ALL** of the following:

1. The individual has benefited from therapy but remains at high risk
2. The condition has not progressed or worsened while on therapy
3. Individual has not developed any contraindications or other exclusions to its continued use

**Xermelo (telotristat ethyl) for all other indications not previously listed is considered **experimental or investigational** based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:

- Allergies and other allergic conditions
- Diarrhea from other causes
- Irritable bowel syndrome with diarrhea
- Flushing syndrome
- Flushing from any other cause
- Short gut syndrome
- Gastrointestinal malabsorption
- Zollinger-Ellison syndrome
- Cushings syndrome
- Hyperthyroidism
- Mastocytosis
- Pheochromocytoma
- Crohn’s disease
- Drug induced diarrhea

**Resources:**


**XERMELO™ (telotristat ethyl) oral tablet (cont.)**

FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>Xermelo (telotristat ethyl) is a tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.</td>
<td>The recommended dosage of Xermelo (telotristat ethyl) in adult patients is 250 mg three times daily for patients whose diarrhea is inadequately controlled by SSA therapy.</td>
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<td></td>
<td>When short-acting octreotide is used in combination with Xermelo (telotristat ethyl), administer short-acting octreotide at least 30 minutes after administering Xermelo (telotristat ethyl).</td>
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<tr>
<td></td>
<td>Discontinue Xermelo (telotristat ethyl) if severe constipation develops.</td>
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