BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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XERMELO™ (telotristat ethyl)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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.

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.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **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. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Initial therapy:** Xermelo (telotristat ethyl) is considered ***medically necessary*** when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Endocrinologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of carcinoid syndrome diarrhea that is inadequately controlled by somatostatin analog (SSA) therapy

  4. Documented failure (after at least 3-months use), contraindication per FDA label, intolerance to **ONE** of the following somatostatin analog (SSA) therapy:
     a. Generic octreotide injection
     b. Sandostatin LAR Depot (octreotide)
     c. Somatuline Depot (lanreotide)

  5. Continues to have 4 or more diarrhea bowel movements per day

  6. Somatostatin analog (SSA) therapy will be use simultaneously with Xermelo (telotristat)

  7. **ALL** of the following baseline tests have been completed before initiation of treatment:
     a. Measurement of 24-hour urinary excretion of 5-hydroxyindolacetic acid (5-HIAA), a product of the breakdown of serotonin
     b. Serum chromogranin-A or serum serotonin

  8. Individual does not have moderate or severe hepatic impairment (Child-Pugh Class B or C)

  Initial approval duration: 6 months

- **Continuation of coverage (renewal request):** Xermelo (telotristat ethyl) is considered ***medically necessary*** with documentation of **ALL** of the following:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Endocrinologist

  2. Individual's condition responded while on therapy
     a. Response is defined as:
        i. Reduction in whole blood serotonin levels or reduction in urinary 5-hydroxyindolacetic acid (u5-HIAA) levels
        ii. Reduced number of daily bowel movements by at least 20% or improvement in stool consistency

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3. Individual has been adherent with the medication and somatostatin analog

4. Individual has not developed any significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Severe persistent constipation
        ii. Worsening abdominal pain

5. Individual does not have moderate or severe hepatic impairment (Child-Pugh Class B or C)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

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 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, pancreastatin, 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.

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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 adenylate 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.

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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.
Suspension: Long-term treatment of profuse watery diarrhea associated with VIP-secreting tumor.

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)

Serotonin (5-HT) blood test:

Reference range:
101-283 ng/mL

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Characteristics of gastroenteropancreatic neuroendocrine tumors:

	Foregut	Midgut	Hindgut
Localization	Stomach, duodenum, bronchus, thymus	Jejunum, ileum, appendix, ascending colon	Transverse, descending, and sigmoid colon, rectum, genitourinary
Secretory products	5-hydroxytryptophan, histamine, multiple polypeptides	Serotonin prostaglandins, polypeptides	Variable
Carcinoid syndrome	Rare, and atypical when it happens	Classic	Rare

Resources:

Xermelo (telotristat ethyl) product information, revised by Lexicon Pharmaceuticals, Inc. 10-2020. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 04, 2022.

Strosberg JR. Diagnosis of carcinoid syndrome and tumor localization. In: UpToDate, Tanabe KK, Whitcomb DC, Savarese DMF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated April 20, 2022. Accessed May 04, 2022.

Strosberg JR. Clinical features of carcinoid syndrome. In: UpToDate, Tanabe KK, Whitcomb DC, Savarese DMF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated November 16, 2021. Accessed May 04, 2022.

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National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Neuroendocrine and Adrenal Tumors Version 4.2021 – Updated December 14, 2021. Available at https://www.nccn.org. Accessed May 04, 2022.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.