CENTENE Corporation

Clinical Policy: Telotristat Ethyl (Xermelo)

Reference Number: CP.PHAR.337
Effective Date: 06.01.17
Last Review Date: 05.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Telotristat ethyl (Xermelo®) is a tryptophan hydroxylase inhibitor.

FDA Approved Indication(s)

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

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Xermelo is **medically necessary** when the following criteria are met:

I. **Initial Approval Criteria**
   A. **Carcinoid Syndrome Diarrhea** (must meet all)**:**
      1. Diagnosis of carcinoid syndrome diarrhea;
      2. Failure of a one month trial of an SSA (e.g., octreotide, lanreotide)* at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated;
         **Prior authorization may be required for SSA therapy*
      3. Xermelo is prescribed in combination with an SSA, unless clinically significant adverse effects are experienced or all are contraindicated;
      4. For Xermelo requests, member must use telotristat ethyl, if available, unless contraindicated or clinically significant adverse effects are experienced;
      5. Dose does not exceed both of the following (a and b):
         a. 750 mg per day;
         b. 3 tablets per day.

      Approval duration: 6 months

   B. **Other diagnoses/indications** (must meet 1 or 2)**:**
      1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
         a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Carcinoid Syndrome Diarrhea (must meet all):

1. Member meets one of the following (a or b):
   - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B)*;
2. Member is responding positively to therapy (*see Appendix D for examples*);
3. Member continues to have diarrhea;
4. Xermelo is prescribed in combination with an SSA, unless clinically significant adverse effects are experienced or all are contraindicated;
5. For Xermelo requests, member must use telotristat ethyl, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. If request is for a dose increase, new dose does not exceed both of the following (a and b):
   - a. 750 mg per day;
   - b. 3 tablets per day.

Approval duration: 12 months

B. Other diagnoses/indications (1 or 2):

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents;

B. Other symptoms of carcinoid syndrome (e.g., flushing, abdominal pain, venous telangiectasia, bronchospasm, cardiac valvular lesions).

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

5-HIAA: 5-hydroxyindoleacetic acid
FDA: Food and Drug Administration
SSA: somatostatin analog

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
octreotide (Sandostatin®, Sandostatin® LAR Depot)	Severe diarrhea or flushing associated with carcinoid syndrome: Sandostatin 100-600 mcg/day SC in 2-4 divided doses for 2 weeks, followed by Sandostatin LAR 20 mg IM every 4 weeks for 2 months; at 2 months, can reduce (10 mg) or increase (30 mg) dose as needed	Sandostatin: 600 mcg/day Sandostatin LAR: 30 mg/4 weeks
lanreotide (Somatuline® Depot)	Gastroenteropancreatic neuroendrocrine tumors: 120 mg SC every 4 weeks	120 mg/4 weeks

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): history of hypersensitivity to telotristat
- Boxed warning(s): none reported

Appendix D: Management of Carcinoid Syndrome

- SSA therapy is the standard of care for carcinoid syndrome. While SSAs are highly effective, tachyphylaxis is a well-known occurrence. The duration of response to SSA therapy varies; some patients lose effectiveness within months of treatment initiation while others are able to retain control for years. Examples of inadequate response to SSA therapy include reduction of bowel movement by less than 3 or by less than 25%, or 4 or more bowel movements per day.
- Interferon alfa has historically been used to manage carcinoid syndrome as a second-line therapy in patients who are refractory to SSA therapy. It relieves symptoms such as diarrhea and flushing in 40-50% of patients, but its use is largely limited by side effects such as fatigue, depression, myelosuppression, flu-like symptoms, weight loss, and alteration of thyroid function.
- In Xermelo's phase 3 trial TELESTAR, a reduction in bowel movement frequency was observed as early as 1-3 weeks of starting therapy and persisted for the remaining 9 weeks of the study. A 36-week open-label extension is currently ongoing to assess if response is sustained.
- Examples of positive response to therapy may include, but are not limited to:
  - Reduction in bowel movement frequency
  - Reduction in urinary 5-HIAA levels

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Carcinoid syndrome diarrhea	250 mg PO TID	750 mg/day

VI. Product Availability

Tablet: 250 mg

VII. References

1. Xermelo Prescribing Information. Deerfiled, IL: TerSera Therapeutics LLC; September 2022. Available at: www.xermelo.com. Accessed January 29, 2025.
2. Kulke MH, Horsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2016; 25(1): 14-23.
3. National Comprehensive Cancer Network. Neuroendocrine and Adrenal Tumors Version 4.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed January 29, 2025.
4. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. North American Neuroendocrine Tumor Society (NANETS) guidelines: consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas.* 2013; 42: 557-577.
5. Del Rivero J, Mailman J, Rabow MW, et al. Practical considerations when providing palliative care to patients with neuroendocrine tumors in the context of routine disease management or hospice care. *Endocr Relat Cancer*. 2023 Jun 21;30(7):e220226. doi: 10.1530/ERC-22-0226.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2021 annual review: no significant changes; references for HIM line of business off-label use revised from HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	02.04.21	05.21
2Q 2022 annual review: no significant changes; references reviewed and updated.	02.14.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.21.22	
2Q 2023 annual review: no significant changes; added redirection to generic telotristat for brand Xermelo requests; updated Appendix C to include contraindication per PI; references reviewed and updated.	01.24.23	05.23
2Q 2024 annual review: no significant changes; added asterisk stating prior authorization may be required for SSA therapy; references reviewed and updated.	02.09.24	05.24
2Q 2025 annual review: no significant changes; updated Appendix B to show generic octreotide is available and lanreotide is available unbranded; references reviewed and updated.	01.29.25	05.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory

requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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