Clinical Policy: Telotristat Ethyl (Xermelo)

Reference Number: PA.CP.PHAR.337
Effective Date: 01/2018
Last Review Date: 04/2025

Description
Telotristat ethyl (Xermelo™) is a tryptophan hydroxylase inhibitor.

FDA approved indication
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 (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of PA Health & Wellness® 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. Dose does not exceed 750 mg (3 tablets) per day.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to PA.CP.PMN.53

II. Continued Therapy

A. Carcinoid Syndrome Diarrhea (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit or member has previously met initial approval criteria; or the Continuity of Care policy (PA.PHARM.01) applies;
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. If request is for a dose increase, new dose does not exceed 750 mg (3 tablets) per day.

Approval duration: 12 months

B. Other diagnoses/indications (1 or 2)**:**
1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to PA.CP.PMN.53.

III. 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 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

IV. Dosage and Administration

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

V. Product Availability

Tablet: 250 mg

VI. References

1. Xermelo Prescribing Information. Deerfield, 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 Tumors and Adrenal 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
2Q 2018 annual review: references reviewed and updated.	02/2018
2Q 2019 annual review: references reviewed and updated.	04/2019
2Q 2020 annual review: references reviewed and updated.	04/2020
2Q 2021 annual review: no significant changes; references reviewed and updated.	04/2021
2Q 2022 annual review: references reviewed and updated.	04/2022
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.	04/2023

Reviews, Revisions, and Approvals	Date
2Q 2024 annual review: no significant changes; added asterisk stating prior authorization may be required for SSA therapy; references reviewed and updated.	04/2024
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.	04/2025