Clinical Policy Title:	telotristat ethyl
Policy Number:	RxA.305
Drug(s) Applied:	Xermelo®
Original Policy Date:	02/07/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
telotristat ethyl (Xermelo®)	Carcinoid syndrome diarrhea	250 mg orally three times daily	750 mg/day

Dosage Forms

- Tablet: 250 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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 contraindicated or clinically significant adverse effects are experienced;
3. Xermelo® is prescribed in combination with an SSA, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 750 mg per day.

Approval duration

Commercial: 6 months

Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
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 contraindicated or clinically significant adverse effects are experienced;
5. If request is for a dose increase, new dose does not exceed 750 mg per day.

Approval duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
5-HIAA: 5-hydroxyindoleacetic acid
FDA: Food and Drug Administration
SSA: somatostatin analog

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
Sandostatin®, octreotide (Sandostatin® LAR Depot)	Severe diarrhea or flushing associated with carcinoid syndrome: Sandostatin 100-600 mcg/day subcutaneous in 2-4 divided doses for 2 weeks, followed by Sandostatin LAR 20 mg intramuscular 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
Somatuline® Depot	Gastroenteropancreatic neuroendocrine tumors: 120 mg subcutaneous every 4 weeks	120 mg/4 weeks

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

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- 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® 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
- Constipation: Xermelo® reduces bowel movement frequency; monitor patients for constipation and/or severe persistent or worsening abdominal pain. Discontinue Xermelo® if severe constipation or abdominal pain develops.

References

1. Xermelo® Prescribing Information. The Woodlands, TX: Lexicon Pharmaceuticals, Inc; March 2017. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f11c21f8-f725-445e-b38e-1e4c5b05bcc6. Accessed July 12, 2021.
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. Available at: https://pubmed.ncbi.nlm.nih.gov/27918724/ https://pubmed.ncbi.nlm.nih.gov/27918724/. Accessed July 12, 2021.
3. National Comprehensive Cancer Network. Neuroendocrine Tumors Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed July 07, 2021.
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. Available at: https://pubmed.ncbi.nlm.nih.gov/23591432/. Accessed July 07, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Drug(s) Applied was updated 3. Line of Business Policy Applies to was updated. 4. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 5. Commercial approval duration and Medicaid approval duration updated. 6. References were updated	06/30/2020	09/14/2020

Policy was reviewed: 1. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 2. Continued Therapy Approval Criteria II.A.1 was rephrased to "Member is currently receiving medication that has been authorized by RxAdvance...". 3. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance..". 4. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 5. Appendix D was updated to include “Constipation: Xermelo® reduces bowel movement frequency; monitor patients…”. 6. References were reviewed and updated.	7/12/2021	9/14/2021