Xermelo (telotristat ethyl)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

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

POLICY

Xermelo (telotristat ethyl) is considered **not covered** for all indications, including the treatment of carcinoid syndrome diarrhea, due to insufficient evidence to demonstrate clinical efficacy.

CLINICAL RATIONALE

In patients with carcinoid syndrome, an over-production of serotonin by the neuroendocrine tumors is believed to cause diarrhea. Xermelo is an inhibitor of tryptophan hydroxylase, the enzyme responsible for the synthesis of serotonin. Serotonin is metabolized to urinary 5-hydroxyindoleacetic acid (u5-HIAA). This metabolite is often elevated in patients with carcinoid syndrome and u5-HIAA has been used to assess response to Xermelo in clinical trials.

A phase III trial examined the safety and efficacy of Xermelo. The primary endpoint was the mean reduction of daily BMs from baseline. A ≥30% reduction for ≥50% of the study duration was considered statistically significant. Secondary endpoints included adverse events and u5-HIAA change from baseline. The 12 week

study included 135 patients already established on therapy with somatostatin analogs (SSA). Baseline daily BM frequency ranged from 3.5-13.00. Patients were randomized to receive Xermelo 250 mg, Xermelo 500 mg, or placebo three times a day, in addition to their SSA dose. At the conclusion of the study, there was a statistically significant difference in the primary outcome when comparing treatment with Xermelo to placebo. The mean reductions compared to placebo for the 250 and 500 mg doses, respectively, were -0.81 and -0.69 BMs. There was a greater incidence of nausea and depression, as well as dose-related increases in hepatic enzymes in the group treated with Xermelo 500 mg compared to placebo. Results from this study found a statistical difference in efficacy between the treatment and placebo, but failed to find a clinically significant difference. An average reduction of less than one BM daily does not demonstrate an optimal clinical response.

A phase III companion study was also completed to include patients excluded from the first study. These patients had a baseline average of <4 BMs/day but had other carcinoid syndrome manifestations including elevated u5-HIAA, flushing, watery stools, nausea, and abdominal pain. Patients were randomized to receive Xermelo 250 mg, Xermelo 500mg, or placebo three times daily. The study included 76 patients, with 67 receiving concurrent SSA therapy. The primary outcomes included treatment-emergent adverse events (TEAEs) and percent change in baseline of U5-HIAA levels after 12 weeks. Change in daily BM frequency was included as a secondary endpoint. A statistically significant reduction in u5-HIAA was observed in both treatment groups compared with placebo. Statistically significant differences were also observed in the reduction of daily BMs. The 250 mg group saw a difference of -0.45 and the 500 mg group a difference of -0.54 from placebo. The safety analysis found a similar incidence of TEAEs between treatment and placebo groups. While this study found statistical significance in reduction of u5-HIAA in the treatment groups, this finding did not translate to a clinically significant response, failing to reduce the frequency of daily BMs by even one on average.

In summary, clinical trials have failed to demonstrate a clinically meaningful benefit for patients with carcinoid syndrome diarrhea.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

REFERENCES

- AdisInsight. Available with subscription at http://adisinsight.springer.com/. Accessed 2017 April.
- Food and Drug Administration. Drugs@FDA. URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. Available from Internet. Accessed 2017a March.
- Food and Drug Administration. FDA approves Xermelo for carcinoid syndrome diarrhea. 2017b February 28. URL: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm544035.htm. Available from Internet. Accessed 2017 March.
- Kulke MH, Hörsch D, Caplin ME et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2016; 35:14-23.
- Medi-Span® Master Drug Data Base v2.5 (MDDB®), 13 April 2017, Clinical Drug Information, LLC.

- National Cancer Institute. Gastrointestinal carcinoid tumors treatment (PDQ®). National Institutes of Health. 2015 July. URL: https://www.cancer.gov/types/gi-carcinoid-tumors/hp/gi-carcinoid-treatment-pdq. Available from Internet. Accessed 2017 March.
- RxPipeline. Available with subscription at https://client.caremark.com/wps/portal/client. Accessed 2017 April.
- Xermelo prescribing information. The Woodlands, TX: Lexicon Pharmaceuticals, Inc.; 2017 February.
- Pavel M, Gross DJ, Benavent M, et al. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. Endocr Relat Cancer. 2018;25(3):309-322.
- Shah MH, Goldner WS, Benson AB et al. NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. 2020;2. Accessed September 10, 2020.
- Strosberg J, Joish VN, Giacalone S et al. TELEPRO: Patient-Reported Carcinoid Syndrome Symptom Improvement Following Initiation of Telotristat Ethyl in the Real World. *Oncologist.* 2019;24(11):1446-1452. Accessed September 10, 2020.

POLICY HISTORY

Policy #: 05.02.43
Original Effective Date: July 18, 2017
Reviewed: October 2022
Revised: July 18, 2017
Current Effective Date: July 18, 2017