Drug Monograph

Drug/Drug Class:	**Xermelo® (telotristat ethyl) tablet/ Carcinoid Syndrome Diarrhea**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Xermelo® is available in a tablet containing 250 mg telotristat ethyl. Manufacturer: Lexicon Pharmaceuticals, Inc., The Woodlands, TX 77381
Summary of Findings:	The efficacy of Xermelo® was established in a randomized, placebo-controlled clinical trial in adults with metastatic neuroendocrine tumors and carcinoid syndrome diarrhea who were receiving an SSA for at least the previous 3 months. Treatment with Xermelo® reduced the frequency of daily bowel movements (BMs) by 1.7 compared with 0.9 in the placebo group. Also, 44% of patients taking Xermelo® had a reduction of at least 30% in BM frequency over at least 50% of the 12-week period compared to only 20% of patients taking placebo.
Status Recommendation:	☐ Prior Authorization (PA) Required ☒ Open Access ☐ Clinical Edit ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☐ Preferred Agent ☐ Appropriate Indications ☒ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [3]

Chronic diarrhea is present in up to 80% of patients with carcinoid syndrome. There are many causes of chronic diarrhea; however, certain characteristics may help associate this symptom with carcinoid syndrome and aid in a differential diagnosis. The stools in diarrhea associated with carcinoid syndrome are watery and result from intestinal hypermotility and hypersecretion. The increase in gut motility in patients with carcinoid syndrome is likely to be caused by serotonin, which is released by certain types of neuroendocrine tumors and stimulates small bowel and colonic secretions and motility.

Dosage Form(s) [1]

Xermelo® is available in a tablet containing 250 mg telotristat ethyl.

Manufacturer [1]

Lexicon Pharmaceuticals, Inc., The Woodlands, TX 77381

Indication(s) [1]

Xermelo® is indicated for the treatment of carcinoid syndrome diarrhea in adults, in combination with somatostatin analog (SSA) therapy, when SSA therapy alone is inadequate.

Clinical Efficacy [1,2] (mechanism of action/pharmacology, comparative efficacy)

Telotristat ethyl and its active metabolite, telotristat, inhibit tryptophan hydroxylase which reduces production of peripheral serotonin. Serotonin mediates secretion, motility, inflammation, and sensation in the gastrointestinal tract, and is overproduced in carcinoid syndrome. The potency of telotristat is 29 times higher than telotristat ethyl.

Pharmacokinetics:

	Xermelo®
Protein Binding	> 99%
Metabolism	Hydrolysis via carboxylesterases to active metabolite, telotristat
Excretion	Feces, 92.8% Urine, < 0.4%
Half-Life	Telotristat ethyl, 0.6 hours Telotristat, 5 hours

Carcinoid Syndrome Diarrhea

Treatment with Xermelo® improved the frequency of daily bowel movements compared with placebo in patietns with carcinoid syndrome diarrhea.

STUDY DESIGN	Randomized, double-blind, placebo-controlled, international, 12-week, phase 3 clinical trial (N=135).
INCLUSION CRITERIA	Adults with metastatic neuroendocrine tumors, a history of carcinoid syndrome, an average of at least 4 BMs per day, and receiving a stable dose of an SSA for a least the previous 3 months.
EXCLUSION CRITERIA	Patients with severe diarrhea, evidence of enteric infection, history of short bowel, or poor performance status.
TREATMENT REGIMEN	Patients were randomized to receive Xermelo® 250 mg orally 3 times/day, 500 mg 3 times/day, or placebo for 12 weeks. All patients maintained background SSA therapy and were allowed unlimited rescue use of short-acting octreotide or antidiarrheal agents.
RESULTS	The mean reduction in daily BMs at 12 weeks from a mean baseline of 5.1 to 6.2 BMs/day was greater (1.7 vs 0.9) with Xermelo® 250 mg three times daily (n=45) compared with placebo (n=45). 44% of patients taking Xermelo® had a reduction of at least 30% in BM frequency over at least 50% of the 12 week periods compared to only 20% of patients taking placebo. The Xermelo® 500 mg three times daily regimen did not provide any additional benefit over 250 mg three times daily, but did increase the frequency of adverse events.
SAFETY	The overall incidence of adverse events was similar across treatment groups.

Contraindications (1)

- None

Warnings and Precautions (1)

- Constipation, sometimes serious and requiring hospitalization, has been reported and may lead to intestinal perforation and obstruction; monitoring recommended and discontinue use if severe constipation or severe, persistent or worsening abdominal pain occurs.

Adverse Effects [1]

Most common, ≥ 5%	Xermelo® (telotristat ethyl) (n=45)	Placebo (n=45)
Nausea	13%	11%
Headache	11%	4%
Gamma-glutamyl-transferase increased	9%	0%
Depression	9%	7%
Peripheral edema	7%	2%
Flatulence	7%	2%
Decreased appetite	7%	4%
Pyrexia	7%	4%

Drug Interactions [1]

- CYP3A4 substrates: Midazolam
- Octreotide, short-acting

Dosage and Administration [1]

The FDA recommended dose is 250 mg three times daily with food.

Cost

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH*
Telotristat ethyl	Xermelo	Lexicon	250 mg tablets	1 tablet three times daily	$5,532.30

* Wholesale Acquisition Cost

Conclusion

Xermelo® is the first tryptophan hydroxylase inhibitor and the first oral treatment option approved for carcinoid syndrome diarrhea in combination with an SSA in patients with inadequate response to SSA therapy. It received fast track designation, priority review, and orphan drug designation for the treatment of rare diseases by the US Food and Drug Administration. Telotristat ethyl is converted to the active metabolite telotristat, and inhibits the production of serotonin in the gastrointestinal tract. In clinical trials, Xermelo® reduced the frequency of daily BMs and improved the response rate when compared to placebo.

Recommendation

MO HealthNet Division recommends Open Access status for this product.

References

1) Product Information: Xermelo™, telotristat ethyl tablets. Lexicon Pharmaceuticals, Inc, The Woodlands, TX, 02/2017
2) Kulke MH, Horsch D, Caplin ME et al: Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. J Clin Oncol 2017; 35(1): 14-23.
3) Carcinoid Syndrome. Retrieved 8/16/2017 from http://www.neuroendocrinetumor.com/health-care-professional/carcinoid-syndrome.jsp

Prepared by: Luke Boehmer PharmD
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