CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

BRAND NAME
Xermelo™

GENERIC NAME
Telotristat ethyl

MANUFACTURER
Lexicon Pharmaceuticals

DATE OF APPROVAL
February 28, 2017

PRODUCT LAUNCH DATE
March 1, 2017

REVIEW TYPE

☒ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☐ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastic, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Reviews for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

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.

OFF-LABEL USES
None identified

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CLINICAL EFFICACY

The safety and efficacy of telotristat ethyl were demonstrated in TELESTAR, a 12-week double-blind, placebo-controlled, randomized, multicenter, phase 3 trial. Adult patients (N=135) with well-differentiated metastatic neuroendocrine tumors and carcinoid syndrome diarrhea inadequately controlled by SSA therapy were randomized in 1:1:1 ratio to receive telotristat ethyl 250 mg, telotristat ethyl 500 mg, or placebo. All doses were given orally three times per day. At baseline, patients had between 4 to 12 daily bowel movements (BM) and were on stable doses of SSA therapy for at least 3 months. Throughout the trial, patients were required to continue their baseline SSA regimen and were allowed to use rescue medication (short-acting octreotide) or antidiarrheals (e.g., loperamide) for symptomatic relief.

The primary endpoint was mean reduction from baseline in daily BMs averaged over 12 weeks. Responders were defined as patients experiencing ≥ 30% reduction in BM frequency relative to baseline for at least half of the trial period. Key secondary endpoints included change from baseline in urinary 5-hydroxyindoleacetic acid (u5-HIAA) at week 12, the number of daily flushing episodes, and abdominal pain severity averaged over 12 weeks. Assessments of all primary and secondary endpoints, except for u5-HIAA, were self-reported in daily electronic diaries. Of note, the telotristat ethyl 500 mg dose did not demonstrate additional treatment benefit on the primary endpoint and had a greater incidence of adverse reactions than the 250 mg dose. Therefore, the following results discussion is focused only on the FDA approved dose of 250 mg.

At week 12, treatment with telotristat 250 mg resulted in statistically significant reductions in BMs compared to placebo. The mean reduction in daily BM frequency was -1.43 for patients receiving telotristat ethyl 250 mg and -0.62 for patients receiving placebo (treatment difference of -0.81, $p<0.001$). In addition, 44% of telotristat ethyl 250 mg patients were considered responders compared to only 20% of placebo patients (OR: 3.49, 95% CI: 1.33-9.16). Further, patients receiving telotristat 250 mg had statistically significant reduction in u5-HIAA compared to placebo patients. Levels in telotristat ethyl 250 mg patients decreased by an average of 40.1 mg/24 hours while levels in placebo patients increased by an average of 11.5 mg/24 hours (treatment difference per Hodges-Lehmann estimator of -30.1 mg/24 hours, $p<0.001$). Changes in daily flushing episodes and abdominal pain severity were not statistically significant.

A total of 4 telotristat ethyl 250 mg arm, 8 telotristat ethyl 500 mg arm, and 7 placebo arm patients withdrew from the study for various reasons (e.g., adverse events, death, physician decision, withdrawal of consent). No patients were lost to follow up.

At the conclusion of the 12 week period, all patients were offered treatment with telotristat ethyl 500 mg (with downward dose adjustment as needed for intolerability) in a 36-week open-label extension (OLE). Although the OLE is ongoing, follow-up thus far has revealed no new safety concerns and suggests sustained BM response to treatment.

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CONTRAINDICATIONS
None

BLACK BOX WARNINGS
None

DRUG INTERACTIONS
Concomitant use of Xermelo may decrease the efficacy of drugs that are CYP3A4 substrates (e.g., midazolam) by decreasing their systemic exposure. Monitor for suboptimal efficacy, and consider increasing the dose for concomitant CYP3A4 substrates if necessary.

Concurrent administration of short-acting octreotide with Xermelo significantly decreased the systemic exposure of telotristat ethyl and telotristat, the active metabolite. If treatment with short-acting octreotide is needed in combination with Xermelo, administer short-acting octreotide at least 30 minutes after administration of Xermelo.

ADVERSE REACTIONS
The most common adverse reactions (incidence ≥ 5%) are nausea, headache, increased gamma-glutamyl-transferase (GGT), depression, flatulence, decreased appetite, peripheral edema, and pyrexia.

In addition, Xermelo reduces bowel movement frequency. Monitor patients for constipation and/or severe persistent or worsening abdominal pain. If severe constipation or abdominal pain develops, discontinue Xermelo.

DOSAGE AND ADMINISTRATION
The recommended dosage of Xermelo is 250 mg three times daily taken with food.

PRODUCT AVAILABILITY
Tablets: 250 mg

THERAPEUTIC ALTERNATIVES

DRUG NAME	USAGE REGIMEN (route of admin/frequency of use)	COMMENTS
Octreotide (**Sandostatin**, Sandostatin LAR Depot)	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	• Standard of care for carcinoid syndrome • Tachyphylaxis is a well-known occurrence- duration of response varies from months to years
Lanreotide (Somatuline Depot)	120 mg SC every 4 weeks	

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Loperamide (Imodium)	4 mg orally initially, followed by 2 mg orally after each unformed stool (maximum: 16 mg/day)	• Used off-label for symptomatic treatment of diarrhea; does not affect the underlying pathophysiology • If symptoms are not improved after 10 days at maximum daily doses, improvement is not likely to occur with further therapy
Interferon alfa (Intron A)	3-5 million units (mU) subcutaneously (SC) 3-5 times/week (maximum: literature suggests up to 9 mU 7 times/week may be used)	• Used off-label as second-line after SSA therapy for carcinoid syndrome control • Limited by side effects (e.g., fatigue, depression, myelosuppression, flu-like symptoms, weight loss, alteration of thyroid function)
Peg-interferon alfa (Pegasys, Pegintron, Sylatron)	80-150 mcg/week SC	• Similar to interferon alfa, but may be better tolerated • Very limited data compared to interferon alfa

Boldface indicates generic availability

Utilization Management Recommendation

- There is significant potential for inappropriate use and utilization management should be considered for the following reason(s):

  i) To ensure appropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcome:
  - Xermelo is indicated as an add-on therapy to a somatostatin analog (SSA) in patients who have had inadequate response to an appropriate trial of first-line SSA therapy
  - Xermelo is not indicated to treat other symptoms (e.g., flushing) associated with carcinoid syndrome. It has demonstrated efficacy only for reducing carcinoid syndrome diarrhea

  ii) Recommended utilization management tool(s): (check all that apply)
  (1) ☒ Prior authorization
  (2) ☐ Quantity limits
  (3) ☐ Provider newsletter
  (4) ☐ Hard block (plan exclusion)
  (5) ☐ Messaging

(6) ☐ Electronic step therapy
(7) ☐ Clinical Program

Product Comparison

- Xermelo was not scored because it is the only FDA-approved second-line therapeutic option for carcinoid syndrome diarrhea.
- It is clinically appropriate to require a trial of a somatostatin analog (e.g., octreotide, lanreotide) prior to Xermelo.
- It is not clinically appropriate to require a trial of antidiarrheals such as loperamide prior to Xermelo. Antidiarrheals are used symptomatically while Xermelo is intended for chronic use to target the underlying pathophysiology.
- It is not clinically appropriate to require a trial of interferon alfa prior to Xermelo. Although both interferon alfa and Xermelo have demonstrated efficacy in carcinoid syndrome, interferon alfa's studies (retrospective series) were not designed to specifically evaluate diarrhea control, so a direct comparison of efficacy is not feasible. Further, interferon alfa has significant safety concerns compared to Xermelo.

REFERENCES

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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.
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