CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memorandum

Date	February 28, 2017
From	Julie Beitz, MD
Subject	Office Director Decisional Memorandum
NDA #	208794
Applicant Name	Lexicon Pharmaceuticals, Inc.
Date of Submission	March 30, 2016
PDUFA Goal Date	February 28, 2017
Proprietary Name / Established (USAN) Name	Xermelo (telotristat ethyl)
Dosage Forms / Strengths	Tablets 250 mg
Proposed Indication	Treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy
Recommended Action:	Approval

Materials Reviewed/Consulted OND Action Package, including reviews from:	**Discipline Reviewers**
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DGIEP = Division of Gastroenterology and Inborn Errors Products
DPMH = Division of Pediatrics and Maternal Health
OCP = Office of Clinical Pharmacology
OND = Office of New Drugs
DMEPA = Division of Medication Error Prevention and Analysis
OB = Office of Biostatistics
OSE = Office of Surveillance and Epidemiology

1. Benefit-Risk Summary and Assessment

Xermelo (telotristat ethyl), a tryptophan hydroxylase inhibitor, has been evaluated for the treatment of carcinoid syndrome diarrhea (CSD) in adults with well-differentiated neuroendocrine tumors (NETs), a relatively rare heterogeneous group of tumors that arise from cells of the neuroendocrine system in the pancreas and gut. Approximately 5% of patients with NETs develop carcinoid syndrome (CS); of these, 75% will develop diarrhea. Complications of uncontrolled diarrhea include weight loss, malnutrition, dehydration, and electrolyte imbalance; when severe, life-threatening malabsorption may result. Octreotide acetate, a somatostatin analog available in immediate release and depot formulations, is approved in the U.S. for the treatment of severe CSD, however, clinical response may decline due to tachyphylaxis or to an increase in tumor burden. There are no approved alternative therapies for CSD for patients who are inadequately controlled by somatostatin analog (SSA) therapy.

I concur with the recommendation of the Division of Gastroenterology and Inborn Errors Products, to approve Xermelo (telotristat ethyl) for the treatment of CSD in combination with SSA therapy in adults inadequately controlled by SSA therapy. The recommended dose regimen is 250 mg taken orally three times daily with food. Although a regimen of 500 mg taken three times daily was also studied, the applicant will not market this regimen.[1] The safety and effectiveness of Xermelo (telotristat ethyl) in patients less than 18 years of age have not been established.

An FDA Advisory Committee Meeting was not held to discuss this application because the application did not raise significant safety or efficacy issues that were unexpected for a drug in this class.

Data submitted in the NDA supported the efficacy and safety of Xermelo (telotristat ethyl). In a randomized controlled clinical trial involving 90 patients with NETs and CSD despite the use of a somatostatin analog, there were significantly greater reductions with Xermelo treatment relative to placebo in the mean number of bowel movements/day averaged over a 12-week double-blind period. There were also significantly greater reductions in u5-HIAA excretion over 24 hours with Xermelo treatment relative to placebo at week 12. There were no significant differences between treatment groups in the occurrence of other symptoms of CS, such as flushing or abdominal pain.

In patients with NETs and CSD, Xermelo treatment was generally well tolerated. Treatment-emergent adverse events commonly reported with

[1] In clinical trials of Xermelo (telotristat ethyl), the 250 mg and 500 mg three times daily dose regimens were similarly effective. However, patients treated with the higher dose reported a slightly higher incidence of gastrointestinal adverse reactions, including nausea, vomiting and upper abdominal pain.

Xermelo use included nausea, headache, elevations in gamma-glutamyl transferase, and depression. Severe constipation was reported rarely in patients receiving higher than the recommended dose of Xermelo.

The safety concerns identified with use of Xermelo (telotristat ethyl) in patients with NETs and CSD can be adequately managed by professional labeling and routine pharmacovigilance in the postmarket setting. A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Xermelo (telotristat ethyl) to ensure that the benefits of the drug outweigh the risks. It is likely that practitioners who will prescribe Xermelo will be aware of the typical clinical course in patients with NETs, including the signs and symptoms of carcinoid syndrome, the complications of uncontrolled diarrhea, and the attendant risks of available treatments for CSD.

The results of postmarketing studies will inform product labeling regarding Xermelo's carcinogenicity potential, the effects of moderate and severe hepatic impairment and of concomitant use of gastric acid inhibitors on the pharmacokinetics of Xermelo, and Xermelo's drug interaction potential.

Dimension	Evidence, Uncertainties and Conclusions
Analysis of Condition	Carcinoid syndrome (CS) occurs when well-differentiated NETs secrete large amounts of serotonin, tachykinins, and other vasoactive mediators into the systemic circulation. Classically, the signs and symptoms associated with CS include diarrhea, cutaneous flushing, and wheezing. Complications of uncontrolled diarrhea include weight loss, malnutrition, dehydration, and electrolyte imbalance; when severe, life-threatening malabsorption may result. Liver metastases may cause symptoms related to tumor bulk and capsular invasion. Other clinical features include mesenteric fibrosis and ischemia, and cardiac valvulopathy. The median survival for patients with NETs is approximately 31-75 months; the most frequent cause of death is liver failure due to liver metastases. The estimated U.S. prevalence of NETs from SEER data is 103,312 cases; the prevalence for CS is 5,166 cases, and 3,874 cases for CS with diarrhea. ***Comment.*** Xermelo (telotristat ethyl) is being developed for patients with CSD who are inadequately controlled by SSA therapy, so the prevalence of the target population in the U.S. is likely to be lower than 3,874 cases.

Dimension	Evidence, Uncertainties and Conclusions
	Effective treatment of CSD may reduce the complications of uncontrolled diarrhea which can lead to deterioration in overall health and adversely affect the ability of NET patients to tolerate their cancer treatments. The availability of Xermelo (telotristat ethyl) would offer an FDA-approved, alternative treatment for adults with CSD who are inadequately controlled by SSA therapy.
Current Treatment Options	Treatment for patients with NETs is highly individualized. Surgery can be curative in patients with limited disease. Cytoreductive surgery is also performed for palliation in patients with advanced disease. For liver metastases, hepatic resection or hepatic artery embolization using gelatin sponge particles, microspheres, or cytotoxic agents may be performed.[2] Somatostatin analogs are the mainstay of CS treatment. Octreotide acetate, available in immediate release and depot formulations, is approved in the U.S. for the treatment of severe diarrhea and flushing episodes associated with CS. Octreotide exerts pharmacologic actions similar to the natural hormone, somatostatin. Somatostatin, via somatostatin receptor subtype 2, inhibits secretion of a variety of vasoactive mediators from neuroendocrine cells. In patients with functioning NETs, octreotide controls CS signs and symptoms, and reduces excretion of urinary 5-hydroxyindoleacetic acid (u5-HIAA), the major metabolite of serotonin. In a head-to-head comparison, patients treated with Sandostatin Injection and Sandostatin LAR Depot experienced comparable levels of diarrhea control (i.e., approximately 2-2.5 stools/day).[3] Clinical response to somatostatin analogs may decline due to tachyphylaxis or to an increase in tumor burden. When clinical response to a long-acting somatostatin analog declines, it is common practice to continue therapy while initiating additional treatments, including anti-diarrheal agents and supplemental doses of short-acting somatostatin analogs. (b) (4) Other than octreotide, there are currently no alternative therapies approved for the treatment of CSD.[4]

[2] Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Della Fave G, Kaltsas GA, Krenning EP, Moss SF, Nilsson O, Rindi G, Salazar R, Ruszniewski P, Sundin A. Gastroenteropancreatic neuroendocrine tumors. *Lancet Oncol* 2008; 9:61-72.

[3] *See* Professional Prescribing Information for Sandostatin LAR Depot

[4] Lanreotide, another somatostatin analog, was approved in the U.S. in 2007 for the treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors to improve progression-free survival. Efficacy was evaluated in patients with nonfunctioning tumors and no hormone-related symptoms.

Dimension	Evidence, Uncertainties and Conclusions
	In contrast to somatostatin analogs, Xermelo (telotristat ethyl) and its active metabolite (telotristat) inhibit L-tryptophan hydroxylase which catalyzes the rate limiting step in serotonin biosynthesis. Serotonin plays a critical role in regulating several major physiological processes of the gastrointestinal tract, including secretion, motility, inflammation, and sensation, and is over-secreted in patients with CS. Through inhibition of tryptophan hydroxylase, Xermelo reduces the production of serotonin. Telotristat ethyl was designed not to cross the blood–brain barrier, and nonclinical studies suggest that the drug acts primarily peripherally, with little, if any, activity observed in the central nervous system.[5] ***Comment.*** Although octreotide formulations are commercially available in the U.S., there are no approved alternative therapies for the treatment of CSD. Xermelo (telotristat ethyl) would be the first tryptophan hydroxylase inhibitor approved for this use. Currently available somatostatin analogs are administered by subcutaneous injection. Xermelo is an oral formulation, which may facilitate compliance with treatment.
Benefit	The efficacy of Xermelo (telotristat ethyl) was established in a randomized, double-blind, placebo-controlled clinical trial involving 90 patients with well-differentiated NETs and CSD. **Study LX1606.1-301-CS (Study 301).** A total of 90 patients were randomized 1:1 to receive Xermelo 250 mg tid or placebo tid for 12 weeks. The double-blind period was followed by a 36-week extension period in which patients received open-label treatment with Xermelo 500 mg tid. Participants were required to have 4-12 daily bowel movements despite the use of stable doses of long-acting somatostatin analogs for at least 3 months. Patients were allowed to use rescue medications, including anti-diarrheals and short-acting somatostatin analogs. The mean age was 63 years (range 37 to 83 years), 50% were male, and 90% were Caucasian. • **Primary Efficacy Endpoint.** Clinical efficacy of Xermelo was assessed as the change from baseline in the mean number of bowel movements/day averaged over 12 weeks. The baseline mean number of daily bowel movements ranged from 5.2 to

[5] Kulke MH, O'Dorisio T, Phan A, Bergsland E, Law L, Banks P, Freiman J, Frazier K, Jackson J, Yao JC, Kvols L, Lapuerta P, Zambrowicz B, Fleming D, Sands A. Telotristat etiprate, a novel serotonin synthesis inhibitor, in patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide. *Endocrine-Related Cancer* 2014; 21(5) 705-714.

Dimension	Evidence, Uncertainties and Conclusions
	6.1 across treatment groups (with a median of 5.1-5.5 bowel movements/day). There were significantly greater reductions with Xermelo treatment relative to placebo in the mean number of bowel movements/day averaged over the 12-week double-blind period: -.06 for placebo vs. -1.4 for Xermelo 250 mg tid. To provide additional context for these changes, the proportion of patients who experienced a reduction of 2 bowel movements/day was considered; 33% of patients on Xermelo vs. 4% on placebo experienced this magnitude reduction. In Xermelo-treated patients, a difference in weekly reductions in bowel movement frequency relative to placebo was observed as early as 1-3 weeks, and persisted for the next 9 weeks of the 12 week placebo-controlled period. • **Other Endpoints.** Compared to placebo, u5-HIAA excretion over 24 hours decreased in Xermelo-treated patients at weeks 6 and 12. There were no significant differences between treatment groups in the occurrence of other symptoms of CS, such as flushing or abdominal pain. **Other Considerations.** • Exposure to telotristat ethyl and its metabolite, telotristat, increases following administration with a high-fat meal. • Telotristat ethyl has pH-dependent solubility, i.e., its solubility decreases as the pH increases. Patients taking gastric acid inhibitors such as proton pump inhibitors may experience lower Xermelo absorption and reduced efficacy. • Concomitant use of short-acting octreotide decreases the systemic exposure of telotristat ethyl and its active metabolite. Short-acting octreotide should be administered at least 30 minutes after administration of Xermelo. • Following administration of multiple doses of telotristat ethyl, the systemic exposure of concomitant midazolam (a CYP3A4 substrate) decreases. Suboptimal efficacy should be monitored for, and consideration given to increasing the dose of CYP3A4 substrates administered concomitantly with Xermelo. ***Comments.*** The efficacy of Xermelo (telotristat ethyl) has been established in a randomized controlled clinical trial involving patients with NETs and CSD. The assumption that diarrhea in CS patients is mediated by serotonin and that a decrease in serotonin production would result in improvement in diarrhea has been borne out by the submitted clinical trial of Xermelo. The effectiveness of Xermelo (telotristat ethyl) in patients less than 18 years of age has not been established. Assuming that control of diarrhea on octreotide is expected to be approximately 2-2.5 stools/day, then Study 301 enrolled patients who were not well controlled on their somatostatin analog.

Dimension	Evidence, Uncertainties and Conclusions
	Xermelo-induced reduction in u5-HIAA excretion is expected given the pharmacologic action of the drug. However, not all study participants had elevated u5-HIAA levels at baseline, and patients with normal u5-HIAA at baseline showed improvements in clinical parameters similar to those seen in patients with elevated u5-HIAA. Variations in diet and inconsistencies in 24-hour urine collections can affect u5-HIAA levels. Concomitant use of somatostatin analogs would decrease serotonin secretion, resulting in decreased systemic 5-HIAA levels. Therefore, u5-HIAA levels may be an imperfect predictor of serotonin-mediated diarrhea in patients who are already receiving treatment with somatostatin analogs. There were no significant differences between treatment groups in the occurrence of flushing episodes. This result was not necessarily unexpected since the etiology of carcinoid flushing episodes is believed to be multifactorial.[6] In addition, flushing was not a prerequisite for study entry, and there were patients that did not report flushing at baseline. Thus, the clinical trial may have lacked sufficient power to show substantial changes in flushing episodes with treatment. In theory, sustained reductions in circulating serotonin levels may provide important long-term clinical benefits in CS patients that could include reduction in the risk of CS-related cardiac valvulopathy. Further studies are needed to examine the potential long-term benefits of treatment with Xermelo (telotristat ethyl).
Risk	In Study 301, a randomized controlled clinical trial in patients with well-differentiated NETs and CSD, 45 patients received Xermelo 250 mg and 45 received placebo three times daily. All patients were also receiving treatment with a somatostatin analog, 43% were taking concomitant anti-diarrheal medications, 39% were taking pancreatic enzymes, and 29% were taking opioid analgesics during the 12-week placebo-controlled period of the trial. **Treatment-Emergent Adverse Events.** During the 12-week double-blind, placebo-controlled period of Study 301, the most frequent treatment-emergent adverse events (TEAEs) were: nausea (in 13% and 11% of patients treated with Xermelo 250 mg and placebo, respectively); headache (in 11% and 4% of patients treated with Xermelo 250 mg and placebo, respectively) elevations of gamma-glutamyl-transferase (in 9% and 0% of patients treated with Xermelo 250 mg and placebo, respectively); and depression (in 9% and 7% of patients treated with Xermelo 250 mg and placebo, respectively).

[6] Balks HJ, Conlon JM, Creutzfeldt W, Stockmann F. Effect of a long-acting somatostatin analog (octreotide) on circulating tachykinins and the pentagastrin-induced carcinoid flush. *Eur J Pharmacol* 1989; 36:133-137.

Dimension	Evidence, Uncertainties and Conclusions
	Eight patients experienced TEAEs leading to study drug discontinuation: 5 on placebo and 3 on Xermelo 250 mg. Abdominal pain was the only TEAE that led to discontinuation of study drug in more than 1 patient in any treatment group. The overall incidence of TEAEs leading to study drug discontinuation was similar across treatment groups. During the 36-week open-label extension period of Study 301, the occurrence of overall TEAEs and TEAEs leading to discontinuation of study drug was generally similar to that observed in the double-blind, placebo-controlled period. ***Comment.*** In patients with NETs and CSD, Xermelo treatment was generally well tolerated. The treatment-emergent adverse events commonly reported were mild or moderate in intensity, and did not limit treatment. **Hepatic Enzyme Elevations.** Elevations in hepatic enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and gamma-glutamyl transferase [GGT]) were observed more frequently with Xermelo than placebo treatment during the 12-week double-blind, placebo-controlled period of Study 301. A comprehensive review of hepatic enzyme elevations and potential liver injury events found that treatment with Xermelo did not lead to clinically significant outcomes or drug-induced liver injury. There was a single report of a patient treated with a higher than recommended dose of Xermelo (i.e., 500 mg tid) that met biochemical criteria for Hy's Law. The enzyme abnormalities were attributed to a radiofrequency ablation that resulted in liver necrosis with necrotic debris lodged in the bile duct. The patient improved following ERCP; Xermelo treatment was continued. ***Comment.*** Assessment of the contribution of Xermelo to hepatic enzyme elevations in patients with NETs and CSD is challenging. Progression of liver metastases and liver injury caused by interventions such as radiofrequency ablation can lead to hepatic enzyme elevations. Of note, population pharmacokinetic analysis has shown that mild hepatic impairment does not affect the pharmacokinetics of Xermelo. The applicant will be required to assess the effect of moderate and severe hepatic impairment on the pharmacokinetics of Xermelo.

Dimension	Evidence, Uncertainties and Conclusions
	Constipation. Among patients treated with Xermelo 250 mg tid, constipation was reported less frequently during the first 12 weeks of treatment among patients with greater than 4 bowel movements per day at baseline (4%, Study 301) as compared to patients enrolled in a separate trial with less than 4 bowel movements per day at baseline (16%)[7]. Six reports of constipation were characterized as serious, including two deaths. One patient who received Xermelo 250 mg tid in the double-blind period and switched to 500 mg tid in the open-label extension period was hospitalized with constipation, nausea, vomiting and renal failure, and later developed ileal perforation, peritonitis, and multi-organ failure. Another patient who received Xermelo 500 mg tid developed bouts of severe abdominal pain, intestinal perforation, peritonitis, and multi-organ failure. ***Comment.*** Small intestinal carcinoids can cause intestinal fibrosis and stenosis, as well as ileus and obstruction. There is no direct evidence that Xermelo treatment causes intestinal obstruction or perforation. Because Xermelo reduces bowel movement frequency and has been associated with the development of constipation, patients should be monitored for severe constipation or severe persistent or worsening abdominal pain, and treatment should be discontinued if these develop. **Other Considerations.** There are no human data with Xermelo use in pregnant women to inform a drug-associated risk. There are no data on the presence of telotristat ethyl in human or animal milk, the effects on the breast-fed infant, or the effects on milk production. The safety of Xermelo (telotristat ethyl) in patients less than 18 years of age has not been established. No differences in safety or effectiveness were noted for patients 65 years and over compared with younger patients.
Risk Management	**Labeling.** Product labeling will include a Warning regarding the risk of constipation observed in patients treated with Xermelo (telotristat ethyl).

[7] In the NDA, results from a second randomized, double-blind, placebo-controlled clinical trial in patients with well-differentiated NETs and CSD, Study LX1606.1-303-CS (Study 303) were also provided. In contrast to Study 301, participants in Study 303 were not required to have at least 4 bowel movements per day at baseline. The baseline mean number of daily bowel movements ranged from 2.2 to 2.5 across treatment groups (with a median of 2.2 bowel movements/day). In this trial, 25 patients were randomized to receive Xermelo 250 mg tid and 26 to placebo tid for 12 weeks, followed by open-label treatment with Xermelo 500 mg tid.

Dimension	Evidence, Uncertainties and Conclusions

	Risk Mitigation. A Risk Evaluation and Mitigation Strategy (REMS) will not be required for Xermelo (telotristat ethyl).
	
	Postmarketing Required Studies.
	
	Pediatric Research Equity Act (PREA)
	Xermelo (telotristat ethyl) has orphan product designation and is not subject to PREA provisions.
	
	Food and Drug Administration Amendments Act (FDAAA)
	The applicant will be required to conduct:
	• A 2-year rat carcinogenicity study to identify an unexpected risk of carcinogenicity with long-term exposure to Xermelo (telotristat ethyl). This study is ongoing.
	• A pharmacokinetic study in patients with moderate and hepatic impairment. A study assessing the effects of mild and moderate hepatic impairment on the pharmacokinetics of Xermelo has been completed; the final report is pending. A new study that assesses the effect of severe hepatic impairment will be needed. Results from these studies will inform labeling and support dose adjustment for patients with moderate and severe hepatic impairment, as needed. Currently available data do not support a dose adjustment for patients with mild hepatic impairment.
	• *In vitro* drug interaction studies to evaluate whether telotristat ethyl or its metabolites, telotristat and LP-951757:
	  ○ inhibit activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6;
	  ○ inhibit one or more of the following transporters: BCRP, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3); or
	  ○ induce the activity of CYP1A2, CYP2B6, and UGT.
	These studies will further evaluate the drug interaction potential of Xermelo given its anticipated chronic use and the likelihood that Xermelo users may be administered concomitant potentially interacting medications.
	
	Postmarketing Commitment.
	The applicant has agreed to conduct:
	• (b) (4) drug interaction study (b) (4) to evaluate the effects of (b) (4) on the pharmacokinetics of telotristat ethyl, (b) (4) Xermelo. Telotristat ethyl has pH-dependent solubility, i.e., its solubility decreases as the pH increases. Patients taking gastric acid inhibitors (b) (4) may experience lower Xermelo absorption and reduced efficacy. This study will inform

Dimension	Evidence, Uncertainties and Conclusions
	labeling regarding the effect of concomitant use (b) (4) on Xermelo pharmacokinetics. (b) (4) ***Comment.*** The safety concerns identified with clinical use of Xermelo (telotristat ethyl) can be adequately managed by professional labeling and routine pharmacovigilance in the postmarket setting. A REMS will not be required for Xermelo (telotristat ethyl) to ensure that the benefits of the drug outweigh the risks. It is likely that practitioners who will prescribe Xermelo will be aware of the typical clinical course in patients with NETs, including the signs and symptoms of carcinoid syndrome, the complications of uncontrolled diarrhea, and the attendant risks of available treatments for CSD. The results of postmarketing studies will inform product labeling regarding Xermelo's carcinogenicity potential, the effects of moderate and severe hepatic impairment and of concomitant use of gastric acid inhibitors on the pharmacokinetics of Xermelo, and Xermelo's drug interaction potential.

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/s/

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02/28/2017