CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
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Reviewer Name	Laura Zendel, PharmD, Division of Risk Management (DRISK)
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Review Completion Date	January 17, 2017
Subject	To determine if a REMS is necessary for telotristat ethyl
Established Name	telotristat ethyl
(Proposed) Trade Name	Xermelo
Applicant	Lexicon Pharmaceuticals, Inc.
Therapeutic Class	L-tryptophan hydroxylase inhibitor
Formulation(s)	Oral tablets
Proposed Dosing Regimen	(b) (4)

Table of Contents

Executive Summary

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Xermelo (telotristat ethyl) is necessary to ensure the benefits of this product outweigh its risks. Lexicon Pharmaceuticals, Inc. submitted a New Drug Application (NDA 208794) for telotristat ethyl with the proposed indication for treatment of diarrhea associated with carcinoid syndrome (CS) in patients with diarrhea inadequately controlled by a somatostatin analogue. The risks associated with the use of telotristat ethyl are gastrointestinal (GI) adverse events (nausea, vomiting and constipation), hepatic enzyme abnormalities, and depression; however, it is unclear if they are due to drug effect or the underlying disease state. All patients in the trial had metastatic cancer at baseline. Patients with CS with metastatic neuroendocrine tumor (NET) with commonly develop tumors in the GI tract and the liver. Depression was also commonly reported in patients in the clinical trials at baseline. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Gastroenterology and Inborne Errors Products (DGEIP) agree that a REMS is not needed to ensure the benefits of telotristat ethyl outweigh its risks. Telotristat ethyl will treat a small target population diagnosed with metastatic cancer. In general, healthcare providers who treat CS are specialists and are familiar with the risk of GI symptoms as well as management of abnormal liver function which may be due to the underlying disease condition with common tumor locations in the GI tract and the liver and these providers are aware of the importance of patient monitoring.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) telotristat ethyl is necessary to ensure the benefits of this product outweigh its risks. Lexicon Pharmaceuticals, Inc. submitted a New Drug Application (NDA 208794) for telotristat ethyl with the proposed indication for treatment of diarrhea associated with carcinoid syndrome (CS) in patients with diarrhea inadequately controlled by a somatostatin analogue (SSA). This application is under review in the Division of Gastroenterology and Inborn Errors Products (DGEIP). The applicant did not submit a proposed REMS or risk management plan with this application

2 Background

2.1 Product Information

Telotristat ethyl, a new molecular entity, is a tryptophan hydroxylase (TPH) inhibitor proposed for the (b) (4) treatment of diarrhea in patients with carcinoid syndrome (CS) not adequately controlled with long acting SSAs. Telotristat ethyl is the ethyl ester-drug of telotristat, the active moiety. TPH is the rate limiting enzyme involved in the production of serotonin. As an inhibitor of TPH, telotristat takes a novel approach to reduce serotonin levels due to CS. At clinically relevant doses, telotristat ethyl and its active metabolite do not cross the blood brain barrier (BBB) to minimize potential central nervous system (CNS) effects.

The proposed dosing regimen for telotristat ethyl is 250 mg by mouth three times per day (TID) with food (b) (4)

Telotristat ethyl is proposed to be available as 250 mg tablets. Telotristat ethyl is in a new medication class.

Telotristat ethyl was granted fast track and orphan drug designation for management of symptoms of CS associated with carcinoid tumor in patients who no longer respond to standard therapy due to the significant impact symptoms have on activities of daily living (ADLs), lack of other approved therapies, and small target population.

Telotristat ethyl is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for telotristat ethyl relevant to this review:

- 05/19/2008: Telotristat ethyl received Fast Track designation for the treatment of gastrointestinal symptoms associated with CS in patients who no longer respond to standard care with Octreotide.
- 03/09/2012: Telotristat ethyl received orphan product designation for the treatment of CS.
- 03/30/2016: The Agency received NDA submission for telotristat ethyl (NDA 208794) for the (b) (4) treatment of CS in patients with metastatic neuroendocrine tumor (NET) who are receiving SSA therapy. The submission did not include a proposed REMS or risk management plan.
- 07/20/2016: A Mid-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, a REMS was not needed for telotristat ethyl at this time.
- 09/02/2016: The Agency issued a major amendment to the application due to the volume of information provided in the response to requests for information dated August 12 and 17 2016
- 12/8/2016: A Late-Cycle meeting was held between the Agency and the Applicant. The Agency informed the Applicant that based on benefit-risk analysis, the lowest effective dose is recommended, (b) (4) Based on the currently available data, a REMS was not needed for telotristat ethyl at this time.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition[1-9]

Well differentiated neuroendocrine tumor (NET), formerly known as carcinoid tumor, is a rare tumor type that arises from cells of the neuroendocrine system which are found throughout the body and may secrete hormones and vasoactive substances such as serotonin, bradykinin, histamine, and

prostaglandins.[1] Common sites of origin include the gastrointestinal (GI) tract, pancreas and lung.[2] Carcinoid Syndrome (CS) develops when serotonin and other vasoactive substances produced by NETs gain access to systemic circulation.[3] When the NET occurs in the GI tract, vasoactive substances enter portal circulation and undergo metabolism in the liver. NETs originating in the GI tract often do not produce symptoms until later stages of the disease due to liver metastases rendering the liver unable to metabolize the excess vasoactive substances and thus allowing these substances to enter systemic circulation. NET originating elsewhere may have symptoms at earlier stages of the disease since vasoactive substances may have direct access to systemic circulation. Symptoms of CS include flushing, severe diarrhea, abdominal pain, wheezing, and valvular heart disease. Serotonin-secreting NETs are suspected based on signs and symptoms, but diagnosis is confirmed by demonstrating increased urinary excretion of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA).[4]

Diarrhea associated with CS can be severe and persistent. Multiple causes of diarrhea associated with CS include increased GI motility due to excess serotonin secretion, tumor-related partial small bowel obstruction, short gut syndrome due to tumor resection, intestinal ischemia, and GI malabsorption.[5] Diarrhea can have a direct impact on ADLs contributing to emotional disorders, social isolation and poor quality of life. Uncontrolled diarrhea can lead to malabsorption, weight loss, malnutrition, dehydration, electrolyte imbalance, and death if severe.

Median survival in CS is estimated at approximately 31-75 months from the time of diagnosis of metastatic disease with liver failure being the most frequent cause of death due to hepatic replacement by tumor.[6] Poor prognostic factors include age, sex, histological type, location of origin, tumor stage, and the presence 5-HIAA in the urine. The occurrence of carcinoid heart disease is directly related to circulating levels of serotonin and 5-HIAA as shown by urinary 5-HIAA levels nearly 4-fold higher in patients with carcinoid heart disease than in patients with CS without carcinoid heart disease.[7]

Prevalence rates for the target population are not published, but have been estimated based on the current prevalence data available for NETs as of January 1, 2004 of approximately 103,312 cases in the United States.[8] It is believed that carcinoid tumors represent about half of all NETs, or approximately

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[1] Turga, et al. Recent Progress in the Understanding, Diagnosis, and Treatment of Gastroenteropancreatic Neuroendocrine Tumors. Ca Cancer J Clin 2011; 61:113-132

[2] Neuroendocrine tumors (NETs). Cancer Treatment Centers of America. http://www.cancercenter.com/neuroendocrine-tumors/ accessed 9/13/2016

[3] Santacroce L (Ed), Espat NJ, et al. Malignant Carcnoid Syndrome. Medscape, WebMD. Updated 03/07/2016, accessed 08/04/2016 http://emedicine.medscape.com/article/282515-overview

[4] Evers, M. Carcinoid Syndrome. Merck Manuals. Updated November 2015, accessed 9/13/2016. http://www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/carcinoid-tumors/carcinoid-syndrome

[5] McCormick D. Carcinoid tumors and syndrome. Gastroenterol Nurs. 2002;25:105-111

[6] Bourdreaux JP. The NANETS Consensus Guideline for the Diagnosis and Management of Neuroendocrine Tumors. Pancreas 2010; 39:753-766

[7] Robiolio PA, et al. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catherization and echocardiography. Circulation. 1995;92:790-795

[8] Yao JC, et al. One Hundred Years After "Carcinoid": Epidemiology of and Prognostic Factors for Neuroendocrine Tumors in 35,825 Cases in the United States. J Clin Oncol. 2008, June 20; 26:3063-72

51,656 cases and in clinical practice, it has been estimated that 10% of patients with carcinoid tumors will develop CS, or approximately 5,166 cases.[9] Of these, around 75% will experience diarrhea resulting in a rough estimate of a prevalence of 3,874 cases of CS associated with diarrhea. Because telotristat ethyl is indicated for patients who have not achieved satisfactory control of diarrhea with standard therapy, the target population is likely lower and meets the threshold requirements for orphan-product designation.

3.2 Description of Current Treatment Options[6,10]

Somatostatin analogues (octreotide, lanreotide) are the first line therapy for CS. SSAs work by inhibiting the release of serotonin and other bioactive peptides and amines produced by NETs to provide control of flushing, diarrhea, and other symptoms. Results from the recent studies PROMID (Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors) and CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) demonstrated the antiproliferative effects of octreotide long acting release (LAR) and lanreotide Autogel and justify the use of SSAs to reduce tumor proliferation.[11,12]

Table 1: Somatostatin analogues approved for CS

Drug (Date Approved)	Indication	Dosing and Administration for NET	Warnings and Precautions	Risk Management Approaches
Sandostatin (1988) **Sandostatin LAR Depot (1998)** **(octreotide)**	Acromegaly Carcinoid Tumors Vasoactive Intestinal Peptide Tumors (VIPomas)	100-600 mcg/day in 2-4 divided doses subcutaneous (SC) injection 20 mg SC every 4 weeks (LAR)	Gallstones, hyper/ hypoglycemia, bradycardia, pancreatitis, low vitamin B12 Dose must be adjusted for renal function	No REMS No Boxed Warning
Somatuline Depot (2007) **(lanreotide)**	Acromegaly Gastroenteropancreatic Neuroendocrine Tumors	120 mg SC every 4 weeks	Gallstones, hyper/ hypoglycemia, bradycardia, hypertension	No REMS No Boxed Warning

Octreotide is available in a short acting aqueous formulation and a long acting release (LAR) depot while lanreotide is only available as a long acting depot. The short acting formulation is generally used initially to determine the effective dose and tolerability. The patient can then be transitioned to a long acting

[9] Tomassetti P, et al. Epidemiology, clinical features and diagnosis of gastroenteropancreatic endocrine tumors. Annals of Oncology 2001; 12(Suppl. 2): S95-S99
[10] Clinical Overview
[11] Caplin ME, et al. Lanreotide in metastatin enteropancreatic neuroendocrine tumors. N Engl J Med 2014;371(3):224-33
[12] Rinke A. et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009;27(28):4656-63

formulation. The short acting formulation can also be used as a rescue injection when the patient is experiencing severe symptoms.

Patients often have decreasing response to SSAs over weeks to months resulting in resurgence of symptoms including diarrhea and flushing. Sixty percent of patients stop responding after 3 months of octreotide treatment. This may be due to an increase of metastatic tumor cells or a decrease in cell surface receptors.[13] When this occurs, it is an accepted practice to continue SSA therapy while initiating additional treatments.[14]

Surgical debulking of tumors, radiation, various liver-directed therapies and chemotherapy may be attempted to reduce overall tumor burden and associated serotonin production.

4 Benefit Assessment

The efficacy of telotristat ethyl for the treatment of CS is supported by a pivotal Phase 3 trial, LX301, and a companion Phase 3 trial, LX303. Both LX301 and LX303 are multicenter, randomized, placebo controlled, double blind studies evaluating the efficacy and safety of telotristat ethyl 250 mg and 500 mg TID vs. placebo in patients with CS for 12 weeks followed by a 36 week open label extension (OLE) period which is currently ongoing. Additionally, LX302, a multicenter, open label, long term 86 week extension study is currently ongoing to further evaluate safety and efficacy for telotristat ethyl. Safety and efficacy data was also incorporated from two phase 2 trials, LX202 and LX203. LX202 was a double-blind, placebo controlled study while LX203 was an open-label, single-arm, dose escalating study.

LX301 and LX303 enrolled adult patients with well differentiated metastatic NETs. LX301 required patients to have ≥ 4 bowel movements (BMs) per day, documented history of CS, and be on stable dose SSA therapy for at least 3 months. The companion study, Study LX303, had a similar study design to LX301 and was designed to expand the population enrolled by the LX301 study to patients with CS whose primary symptoms were not GI related and may have been naïve to SSA therapy by enrolling patients with CS who were not eligible for LX301 including patients not on stable dose SSA therapy or those who had < 4 BMs/day. The purpose of LX303 was to provide confirmation of the pharmacodynamic effect and safety of telotristat ethyl in a broader patient population, but one in whom potential benefits of telotristat ethyl could be demonstrated. LX302 enrolled patients who completed the OLE of any Phase 2 or Phase 3 telotristat ethyl study. Exclusion criteria for all three Phase 3 studies included clinically significant abnormal laboratory values, electrocardiogram findings, medical history or physical examination findings that would compromise the outcome of the study. Patients were also excluded if they had ≥12 watery BMs/day or had stool examinations positive for infectious diarrhea.

[13] Cuevas-Ramos D, Fleseriu M. Somatostatin receptor ligands and resistance to treatment in pituitary adenomas. J Mol Endocrinol 2014; 52:R223-40

[14] Strossberg JR, et al. Clinical Benefits of Above-Standard Dose of Octreotide LAR in Patients with Neuroendocrine Tumors for Control of Carcinoid Syndrome Symptoms: A multicenter Retrospective Chart Review Study. The Oncologist. 2014;19(9):930-936

The primary efficacy endpoint for LX301 was change in frequency from baseline number of daily BMs averaged over the 12 weeks of treatment. A durable response was defined as a reduction of at least 30% in BM frequency from baseline for at least 50% of the double blind trial (DBT) period. Secondary endpoints included several key measures of efficacy relevant to patients with CS including 24-hour urinary 5-HIAA excretion, number of cutaneous flushing episodes, and abdominal pain. Additional outcomes relative to gastrointestinal (GI) manifestations of CS included urgency to defecate, nausea, stool consistency as well as subjective measures of symptom relief.

The primary efficacy endpoint in LX303 was the pharmacodynamic effect of telotristat ethyl as measured by percent change from baseline in the 24 hour urinary 5-HIAA levels at week 12. Secondary endpoints were the same as in LX301 with the addition of change from baseline in the number of BMs/day and durable response, frequency of rescue short acting SSA used to treat CS symptoms, and number of daily BMs in patients not on SSA therapy at baseline.

LX301 and LX303 Results

Patients enrolled in LX301 (N=135) and LX303 (N=76) were randomized 1:1:1 to telotristat ethyl 250 mg TID, 500 mg TID or placebo. Both doses of telotristat ethyl significantly reduced BM frequency vs. placebo averaged over the DBT period ($p \leq 0.004$ in both studies) supporting the primary endpoint for LX301. Reductions from baseline of approximately 2 BMs/day were observed throughout the OLE period of LX301. The durable response showed statistical significance for the 500 mg TID dose ($p \leq 0.02$) but not for the 250 mg dose in study LX301 and in both doses ($p \leq 0.001$) in study LX303. Both studies demonstrated statistically significant reductions in urinary 5-HIAA with both doses of telotristat ethyl supporting the primary endpoint for LX303. No significant difference in flushing or abdominal pain was seen compared to control.

The Applicant concluded that when taken together, both studies showed that both doses of telotristat ethyl reduced the frequency of BMs averaged over the 12 week DBT period compared to placebo and resulted in a durable response. Both studies showed that the proportion of days with ≥30% reduction in BM frequency was greater and time to first sustained ≥30% reduction in BM frequency was shorter for both doses of telotristat ethyl compared to placebo. Both studies showed that telotristat ethyl reduced urinary 5-HIAA from baseline over the 12 week period. Both studies showed that telotristat ethyl 500mg TID resulted in improvement in stool consistency (a trend in LX301 but statistically significant in LX303) and reduced the urgency to defecate (only for the 500mg TID dose in LX301, but both doses in LX303). Additionally, there was a trend towards reduced burden of short-acting octreotide rescue therapy with 500mg TID which was clinically meaningful.

The clinical reviewer agrees that the evidence submitted supports the effectiveness of telotristat ethyl in the treatment of CS diarrhea caused by 5-HT secreting carcinoid tumors. The reduction of daily bowel movements correlated with the reduction of urinary 5-HIAA levels and the time to the first occurrence of sustained $\geq$30% improvement from baseline in BM frequency during the DBT period shows faster improvements in telotristat ethyl treated groups compared to placebo. Telotristat ethyl did not reduce the episodes of cutaneous flushing or abdominal pain, therefore should not be used to treat symptoms

of CS other than diarrhea. Furthermore, telotristat ethyl benefits the treatment of 5-HT mediated refractory CS diarrhea, but does not have therapeutic effects on non-5-HT mediated CS diarrhea.

5 Risk assessment

The overall safety analyses integrated data from 239 patients from two Phase 2 studies and three ongoing Phase 3 studies. 34% of patients experienced at least one serious adverse event (SAE) with abdominal pain being the most common (7.1%). The most common adverse events (AEs) seen in ≥ 5% of subjects included nausea, abdominal pain, decreased appetite, depression and diarrhea.

5.1 Serious Adverse Events (SAEs)

The investigators evaluated all treatment emergent adverse events with regard to the maximum intensity and relationship to the study drug and categorized them as mild (aware of event but easily tolerated), moderate (discomfort enough to cause interference with usual activity), or severe (incapacitating so that the patient is unable to work or perform usual activities). An SAE was defined as any event that resulted in any of the following outcomes: death, a life threatening treatment emergent adverse event, inpatient hospitalization or prolonging of an existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Additionally, important medical events that did not result in death, were not life-threatening, or did not require hospitalization could have been considered serious when, based upon appropriate medical judgement, they may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed.

A total of 16 patients died (6.7%). Two of these deaths were identified as possibly being related to the study drug by the investigators. One patient randomized to telotristat ethyl 500 mg TID in study LX301 died of cardiac arrest on study Day 13. Cardiac arrest was reported as possibly related to the study drug by the Investigator, but as unlikely related by the Applicant due to probable contribution of pain management difficulties in this event. The clinical reviewer agrees with the Applicant in that the cardiac arrest appears to be due to the respiratory distress associated with morphine overdose as well as the underlying metastatic carcinoid tumor and there was no sufficient evidence to support a causal relationship to telotristat ethyl. Another patient, originally enrolled in LX203, died of acute liver failure which will be described in section 5.2.1 below.

5.2 Adverse Events of Special Interest (AESIs)

5.2.1 Hepatic Enzyme Abnormalities

Administration of telotristat ethyl was associated with elevation in hepatic enzymes, particularly gamma-glutamyl transferase (GGT) which occurred in 8.4% of the overall safety population. In the overall safety population, 39 patients experienced a total of 78 AESIs related to hepatic enzyme abnormalities. 45 events were determined to be possibly, probably, or definitely related to the study drug by the investigators. Six events were determined to be severe, the rest being mild or moderate. One event was listed as a SAE due to increased transaminases which resulted in hospitalization. The event resolved after the study drug was interrupted and it was later restarted at the lower dose (250 mg

TID). Increased GGT was a contributing factor for study withdrawal for two patients. Both patients were enrolled in study LX301. One patient experienced GGT increase that was considered severe and not related to the study drug by the investigators, and did not resolve after study drug was discontinued. The patient's hepatic enzymes were all elevated at baseline and increased further while taking telotristat ethyl 250mg TID. The second patient experienced increased GGT and alkaline phosphatase (ALP) which was considered moderate and not related by the investigators, and did not resolve after study drug was discontinued. In this patient, the study drug discontinuation and study withdrawal were also due to several other adverse events including abdominal pain and decreased appetite among other things. At baseline, the patient's ALP was normal but the GGT was elevated.

Additionally, there were seven events of ascites, three events of liver disorder, two events of hepatectomy, and one event each of acute hepatic failure, chronic hepatic failure, hepatic failure, cholangitis, cholestasis and septic shock. These events occurred in patients with underlying metastatic NET with liver involvement and there were no cases of drug induced liver injury. Two events of moderate ascites were reported as SAEs due to hospitalization, although the hepatic enzymes remained within normal limits. The events were determined to be unrelated to the study drug for both patients and resolved in 7-9 days. The clinical reviewer notes that the pattern and incidence of SAEs observed during the clinical development of telotristat ethyl in patients with CS were consistent with characteristics of this population. In the presence of metastatic tumors, the SAEs were related to tumor progression in the liver, such as hepatic failure.

One death due to acute liver failure was reported as possibly related to study drug by investigator. The patient, who originally enrolled in the Phase 2 study, LX203, died after enrolling in the extension study, LX302. This patient took telotristat ethyl for approximately 3 years and 10 months. The patient had underlying metastatic NET with extensive liver metastasis (80% replacement) and pre-existing liver fibrosis possibly due to alcohol. Laboratory results near the time of death did not suggest drug induced liver injury. The acute liver failure was reported as possibly related to the study drug by the Investigator, but as unlikely related by the Applicant due to the underlying extensive liver metastasis and pre-existing liver fibrosis. The clinical reviewer concurs that the acute liver failure appears to be associated with the pre-existing conditions of alcoholic liver fibrosis and metastatic NET to the liver and agrees with the Applicant that the death was most likely due to the patient's underlying disease.

Most patients in the studies had underlying metastatic NET with liver involvement and the most common cause of death in patients with metastatic NET is liver failure due to progression of liver metastases. The clinical reviewer observed that no patients met Hy's Law criteria of ALT/AST $\geq$ 3x upper limit of normal in association with bilirubin elevation to > 2x upper limit of normal in these studies which suggests that the elevations of ALT, AST, ALP, and GGT are not associated with meaningful hepatic injuries. Given the sample size and presence of hepatic metastases in the population, there are uncertainties with regard to the risk of liver injury. The Applicant has recommended (b) (4) .

5.2.2 GI Disorders

GI disorders were the most frequently reported adverse events experienced by 66.9% of CS patients in the overall safety analysis. Abdominal pain was the most common GI symptom reported by 32.2% followed by nausea reported by 31% of patients treated with telotristat ethyl. Nausea occurred early after treatment initiation, and had a dose response which was likely related to delay in gastric emptying. In animal studies, telotristat ethyl caused a significant dose-dependent delay in GI transit and gastric emptying likely due to reduction in systemic serotonin levels as evidenced by decreased urinary 5-HIAA.

Constipation was reported by 2 (3%), 4 (6%), and 5 (7%) patients in the placebo, telotristat ethyl 250 mg TID and 500 mg TID treatments groups, respectively, in the placebo-controlled safety analyses and in 28 (11.7%) patients in the overall safety analysis. Of these 28 patients, 26 had NET of GI origin, one patient had NET of mesenteric origin and one had NET of unknown origin. Seven patients had more than one episode of constipation reported, four patients required hospitalization, four patients received a dose reduction and four patients discontinued the study drug.

Several cases were identified as SAEs including three cases of constipation requiring hospitalization, two cases of fecaloma, and one case each of small bowel obstruction, ileus, and intestinal obstruction with subileus. Each of these cases had confounders including underlying disease of metastatic GI tumor and concomitant medications that may have contributed to the GI events. The Applicant stated that although these events are often confounded by the patients' underlying conditions or concomitant medications, a role of telotristat ethyl in the development of these events cannot be ruled out based on its mechanism of action.

The clinical reviewer notes that because most of the SAEs occurred during the open-label phase, a definitive causal relationship cannot be established. All of the cases of constipation SAEs involved patients with underlying metastatic carcinoid tumor of the GI tract and included confounders such as advanced age and concomitant medications (ex. opioids and loperamide). Progression of abdominal metastases can lead to death by causing small bowel obstruction, GI hemorrhage, perforation or peritonitis. The clinical reviewer commented that the role of telotristat ethyl in causing constipation and in exacerbation of the underlying conditions cannot be ruled out.

Patients who will likely use telotristat ethyl face a severe underlying condition and regular use of concomitant medications that could contribute to GI SAEs. The risk of constipation will be communicated in the labeling. The Applicant has recommended in the Warnings and Precautions section of the labeling that patients on telotristat ethyl should be monitored for signs and symptoms of constipation. (b) (4)

5.2.3 Depression

Because of the mechanism of action of TPH inhibition resulting in decreased production of serotonin, AEs related to depression were investigated. At the request of the Agency, a specific procedure was used to screen for and follow up on depression. A two question depression screening tool was added to

clinical study procedures through a protocol amendment for each Phase 3 study. At that time, Phase 3 studies were ongoing with patients enrolled under previous versions of the protocols.

Nineteen events in the DBT period and 52 events in the overall safety population were identified as depression, depressed mood or decreased interest; none were serious. Three of the events were reported as possibly or definitely related to the study drug in the DBT period, one in each arm: placebo, 250 mg and 500 mg. One event potentially met the Diagnostic and Statistical Manual of Mental Disorders IV criteria for major depressive disorder. The patient was randomized to telotristat ethyl 250 mg TID and had no previous history of depression. At 60 days, he reported symptoms of depression that were considered moderate. The Investigator initially considered it definitely related to the study drug, however, it was later stated that disease progression contributed to the symptoms. The event resolved after study drug was interrupted and the patient eventually discontinued the study due to withdrawal of consent.

Depression is an underlying disorder of CS patients. All patients had metastatic cancer at baseline and depression was commonly reported in their medical histories. Many events occurred in patients with underlying conditions, concomitant medication or personal circumstances that could contribute to the development of depression related events. The Applicant provided patient narratives for depression related AESIs for patients enrolled in studies LX301 and LX303 which included three incidences that did not occur until the patient was enrolled in the open label extension study, LX302. Of the 43 cases, 19 (44%) had a history of depression, anxiety or insomnia and 16 (37%) were on concomitant therapy indicated for depression, anxiety or insomnia at baseline.

The clinical reviewer notes that there was a numerical imbalance in the incidence of AESIs related to depression for the telotristat ethyl 500mg tid treatment group compared with that for the placebo and telotristat ethyl 250mg tid treatment groups for the placebo-controlled safety population. These events were reported by the investigators as mild or moderate in intensity and generally did not limit treatment. There were no AESIs related to depression reported as an SAE.

All events were mild or moderate in intensity and generally did not require treatment or limit study drug therapy. However, due to the mechanism of action, the role of telotristat ethyl in depression cannot be ruled out.

6 Expected Postmarket Use

Telotristat ethyl will be prescribed in an outpatient setting generally by prescribers who are specialists. No additional post marketing requirements beyond routine pharmacovigilance and labeling have been recommended at the time of this review.

7 Evaluating the Need for a REMS

Carcinoid Syndrome is a rare, highly debilitating condition that develops in patients with metastatic NET commonly originating in the GI tract, pancreas, and lung with metastases most frequently to the liver. Carcinoid syndrome is characterized by flushing, severe diarrhea, abdominal pain, wheezing, and

valvular heart disease. The standard of care is use of a SSAs; however, symptoms often become refractory to treatment.

Although Phase 3 trials and open label extension studies are still ongoing, based on the results from the data so far, telotristat ethyl uses a novel mechanism of action and was shown to reduce BM frequency by 2 BM per day from baseline over 48 weeks in 20-40% of patients with diarrhea refractory to SSA therapy. Additionally, telotristat ethyl may have a positive impact on related symptoms including trends toward improvement in stool consistency, reduction in number of days with urgency to defecate, and reduced burden of short-acting octreotide rescue therapy, but no improvements were seen with regard to flushing or abdominal pain.

The most common AEs were nausea, abdominal pain, decreased appetite, depression and diarrhea which were mostly mild to moderate in severity. GI disorders, specifically nausea and constipation, increases in hepatic enzymes, and depression were considered as AESI's, however, due to the existence of significant confounding factors, it is unclear if they are due to drug effect or the underlying disease state. Patients with CS may have metastatic NET with common tumor locations in the GI tract and the liver and many patients in the clinical trials were depressed at baseline.

The risks identified in the proposed labeling include (b) (4) warnings and precautions: (b) (4) Monitoring for signs and symptoms of constipation; telotristat ethyl reduces bowel movement frequency. Furthermore, the Labeling recommends: (b) (4) Additionally, the risk of depression is proposed to be added to the Adverse Reactions section of the label. At the time of this review, labeling negotiations are ongoing.

Overall, AEs were mostly mild to moderate and were reversible with discontinuation or interruption of the drug. Healthcare providers who treat CS are typically specialists and are familiar with the risks of increases in hepatic enzymes, and GI disorders in this patient population as well as the importance of patient monitoring and many patients were depressed at baseline. AESIs seen can occur even without use of the drug secondary to the underlying disease state. Additionally, due to the severity and rarity of the disease state and the unmet medical need among patients with CS, telotristat ethyl was granted orphan drug status with fast track designation. Based on the available data, risk mitigation measures beyond professional labeling are not necessary for telotristat ethyl for the proposed indication of the (b) (4) treatment of diarrhea in patients with carcinoid syndrome (CS) not adequately controlled with long acting SSAs. Therefore, DRISK and DGIEP have determined that a REMS is not warranted at this time.

8 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for telotristat ethyl beyond routine pharmacovigilance and labeling.

9 Conclusions and Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of telotristat outweigh its risks. Telotristat ethyl has been granted orphan drug status for a small target population diagnosed with metastatic NET. In general, healthcare providers who treat CS are familiar with the risks of depression, abnormal liver function tests, as well as GI symptoms which may be due to the underlying disease condition and are aware of the importance of patient monitoring.

Should DGIEP have any concerns or questions, or if new safety information becomes available, please send a consult to DRISK

10 Appendices

10.1 Materials Reviewed

The following is a list of materials informing this review:

1. Applicant. Original submission NDA 208794 for telotristat ethyl, received 03/30/2016
    a. Section 2.5 Clinical Overview
    b. Section 2.7.3 Summary of Clinical Efficacy
    c. Section 2.7.4 Summary of Clinical Safety
2. Applicant. Proposed Prescribing Information for Xermelo (telotristat ethyl), received 03/30/2016, amended on 06/30/2016
3. Mid-cycle Meeting Background Package for telotristat ethyl, dated 07/10/2016
4. Gao, Wen-Yi. Clinical Review, Division of Neurology Products for telotristat ethyl, dated 1/12/2016

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/s/

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