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Thursday, March 9th, 2017
NCCN Guidelines Panel for Neuroendocrine Tumors

Dear Ms. McClure,

On behalf of Lexicon Pharmaceuticals, Inc., I respectfully request the NCCN Guidelines Panel for Neuroendocrine Tumors to review the enclosed data for inclusion of Xermelo™ (telotristat ethyl) in the guidelines and the associated Drugs and Biologics Compendium™.

**Specific changes:** We recommend inclusion of Xermelo™ based on category 1 evidence from two phase 3 randomized clinical trials (TELESTAR and TELECAST), for the treatment of carcinoid syndrome (CS) in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy, recommending 250 mg po tid as initial therapy, and with consideration that 500 mg po tid may be beneficial in patients not adequately responding to initial therapy with 250 mg tid.

**FDA clearance:** Xermelo™, a tryptophan hydroxylase inhibitor indicated for the treatment of CS diarrhea in combination with SSA therapy in adults inadequately controlled by SSA therapy was approved by the FDA on February 28th, 2017 (www.accessdata.fda.gov/drugsatfda_docs/label/2017/208794s000lbl.pdf)[1].

**Rationale for recommended change:** The efficacy and safety of Xermelo™ has been demonstrated in two phase 2 studies[2,3] and two phase 3 randomized clinical trials conducted in patients with neuroendocrine tumors (NETs) and CS (TELESTAR[4] and TELECAST[5]).

**Citation of literature support and complete articles supporting recommended change:**

- TELESTAR[4] was an international, multicenter, randomized, double-blind, placebo-controlled phase 3 trial designed to assess the safety and efficacy of TE in patients with CS not adequately controlled with SSA therapy. Patients (N = 135) experiencing four or more bowel movements (BMs) per day despite stable-dose somatostatin analog (SSA) therapy received (1:1:1) placebo, TE 250 mg, or TE 500 mg three times per day orally during a 12-week double-blind treatment period. The primary end point was change from baseline in BM frequency. In an open-label extension, 115 patients subsequently received TE 500 mg. Estimated differences in BM frequency per day versus placebo averaged over 12 weeks were –0.81for TE 250 mg ($P < .001$) and –0.69 for TE 500 mg ($P < .001$). At week 12, mean BM frequency reductions per day for placebo, TE 250 mg, and TE 500 mg were –0.9, –1.7, and –2.1, respectively. Responses, predefined as a BM frequency reduction ≥ 30% from baseline for ≥ 50% of the double-blind treatment period, were observed in 20%, 44%, and 42% of patients given placebo, TE 250 mg, and TE 500 mg, respectively. Both TE dosages significantly reduced mean urinary 5-hydroxyindole acetic (u5-HIAA) acid versus placebo at week 12 ($P < .001$). TE was tolerated with no increase in serious adverse events or discontinuations due to adverse events vs. placebo. Follow-up of patients during the open-label treatment supported the efficacy and safety of TE.
    - Conclusion: Among patients with CS not adequately controlled by SSAs, treatment with TE was generally safe and well tolerated and resulted in significant reductions in BM frequency and u5-HIAA.

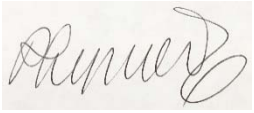
- Additional observations: (1) Primary efficacy results support TE 250 mg as a starting dose, (2) results for bowel movement frequency reduction at Week 12, stool consistency, urgency, short-acting rescue use, and u5-HIAA favored the 500 mg dose. Its long-term safety supported its use in CS. TE 500 mg may be beneficial in patients not adequately responding to initial therapy with TE 250 mg, and (3) TELESTAR is the first successful (and largest) randomized placebo-controlled study to assess symptom control in patients with CS.

- The TELECAST[5] phase 3 study is a companion study to the phase 3 double-blind, placebo-controlled TELESTAR study, and included patients on SSAs with <4 BMs/day and ≥1 CS sign/symptom. Patients not on SSAs were allowed with ≥1 CS sign/symptom, including ≥4 BMs/day. Both primary safety and efficacy endpoints were met. The safety results of this study support those observed in TELESTAR. TE significantly reduced u5-HIAA levels and BM frequency in patients with CS, consistent with the results of TELESTAR. Durable response was observed in 40% of patients receiving TE 250 mg tid and TE 500 mg tid, compared to 0% on placebo.

A recent update of the European Neuroendocrine Tumor Society (ENETS) consensus guidelines highlighted TELESTAR as one of three "well-constructed phase III trials in NET have an impact on the current treatment recommendations and therapeutic algorithm." They indicated that, if approved, TE "can be recommended in addition to SSA for refractory diarrhea in carcinoid syndrome patients.[6]" The North American Neuroendocrine Tumor Society (NANETS) published a set of consensus guidelines in 2010. In 2013 NANETS published a set of consensus tables intended to complement the guidelines as reference for the practicing physician. The manuscript indicates that no prospective data exists to support the dose-escalation or interval shortening for SSAs ("as these have never been tested in a rigorous and/or randomized fashion".)[7] A multidisciplinary panel of experts recently updated the Canadian evidence-based consensus guidelines for the diagnosis and management of well differentiated gastroenterohepatic NETs, and TE (unapproved in Canada) was given a category 1 recommendation for patients with continued CS-related diarrhea despite SSA use ("symptoms refractory to SSAs".)[8]

The following information is enclosed with our submission in support of our respectful request to include Xermelo™ (telotristat ethyl) 250 mg and 500 mg in the NCCN Guidelines Panel for Neuroendocrine Tumors and the associated Drugs and Biologics Compendium™: Kulke MH, et al.[4], Pavel M, et al.[5], and Xermelo™ US Prescribing Information[1]. We appreciate the panel's thorough consideration of our submission and would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors to some of the references in the list cited below.

Sincerely yours,



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**Literature support:** [1] Xermelo™ US Prescribing Information. Accessed on March 7th, 2017 at www.accessdata.fda.gov/drugsatfda_docs/label/2017/208794s000lbl.pdf; [2] Kulke MH, et al. Telotristat Etiprate, a Novel Serotonin Synthesis Inhibitor, in Patients with Carcinoid Syndrome and Diarrhea Not Adequately Controlled by Octreotide. *Endocr Relat Cancer*. 2014; 21(5):705-714; [3] Pavel M, et al. Telotristat etiprate for carcinoid syndrome: A single-arm, multicenter trial. *J Clin Endocrinol Metab*. 2015; 100:1511-1519; [4] Kulke MH et al. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. *J Clin Oncol.* 2017; 35(1):14-23; [5] Pavel M, et al. Safety and Efficacy Results of Telotristat Ethyl in Patients With Carcinoid Syndrome During the Double-blind Treatment Period of the TELECAST Phase 3 Clinical Trial. Presented at the *9th NANETS Annual Symposium* on Sep 30th, 2016 (Abstract #174); [6] Pavel M, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology*. 2016; 103:172–185; [7] Kunz P, et al. Consensus Guidelines for the Management and Treatment of Neuroendocrine Tumors. *Pancreas*. 2013; 42: 557-577; and [8] Singh S, et al. Diagnosis and management of gastrointestinal neuroendocrine tumors: An evidence-based Canadian consensus. *Cancer Treat Rev*. 47 (2016) 32–45.