



NDA 208794

**NDA APPROVAL**

Lexicon Pharmaceuticals, Inc.  
Attention: Penny Logan, M.S.  
Regulatory Affairs Manager  
8800 Technology Forest Place  
The Woodlands, TX 77381

Dear Ms. Logan:

Please refer to your New Drug Application (NDA) dated and received on March 30, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XERMELO (telotristat ethyl) tablets, 250 mg.

We also refer to our approval letter dated February 28, 2017, which contained the following error: the Portable Document Format (PDF) carton and immediate container labels, which were attached as enclosures to the approval letter, were submitted with multiple invisible layers (dated December 7, 2017; eCTD sequence number 0044). As a result, while finalizing the approval letter, the invisible layers were inappropriately rendered and resulted in an inaccurate portrayal of the carton and immediate container labels.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain February 28, 2017, the date of the original approval letter.

We additionally acknowledge receipt of your major amendment dated September 2, 2016, which extended the goal date by three months.

This new drug application provides for the use of XERMELO (telotristat ethyl) tablets for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

**APPROVAL & LABELING**

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

## **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

## **CARTON AND IMMEDIATE CONTAINER LABELS**

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 208794.**” Approval of this submission by FDA is not required before the labeling is used.

## **MARKET PACKAGE**

Please submit one market package of the drug product when it is available to the following address:

Benjamin Vali  
Food and Drug Administration  
Center for Drug Evaluation and Research  
White Oak Building 22, Room: 5245  
10903 New Hampshire Avenue  
Silver Spring, Maryland  
Use zip code **20903** if shipping via United States Postal Service (USPS).  
Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

## **ADVISORY COMMITTEE**

Your application for telotristat ethyl was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease and outside expertise was not necessary.

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

## **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity associated with XERMELO (telotristat ethyl), and an unexpected serious risk of toxicity due to drug interaction of XERMELO (telotristat ethyl) and its major metabolites with CYP enzymes and major transporters. Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3152-1 A 2-year rat carcinogenicity study.

The timetable you submitted on February 24, 2017 states that you will conduct this study according to the following schedule:

Study Completion:	09/2017
Final Report Submission:	09/2018

3152-2 *In vitro* drug interaction study(ies) to evaluate potential inhibition of CYP2C9 by telotristat ethyl, inhibition of CYP2B6 and CYP2C8 by telotristat, and inhibition of major CYP enzymes (1A2, 2B6, 2C8, 2C9, 2C19, and 2D6) by LP-951757, a major metabolite of telotristat ethyl.

The timetable you submitted on February 24, 2017 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2017  
Study Completion: 09/2017  
Final Report Submission: 11/2017

3152-3 *In vitro* drug interaction study(ies) to evaluate potential induction of CYP1A2, CYP2B6, and UGT by telotristat ethyl and its major metabolites, telotristat and LP-951757.

The timetable you submitted on February 24, 2017 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2017  
Study Completion: 09/2017  
Final Report Submission: 11/2017

3152-4 *In vitro* drug interaction study(ies) to evaluate potential inhibition of major transporters (BCRP, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3) by LP-951757, a major metabolite of telotristat ethyl.

The timetable you submitted on February 24, 2017 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2017  
Study Completion: 09/2017  
Final Report Submission: 11/2017

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of drug toxicity in patients with moderate and severe hepatic impairment treated with Xermelo (telotristat ethyl).

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3152-5 A clinical trial to investigate the pharmacokinetic profile of Xermelo (telotristat ethyl) and evaluate the potential for toxicity in patients with moderate and severe hepatic impairment.

The timetable you submitted on February 24, 2017 states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 06/2017  
Trial Completion: 04/2018  
Final Report Submission: 07/2018

Submit the protocol(s) to your IND 078749, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording

in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o),” “Required Postmarketing Final Report Under 505(o),” “Required Postmarketing Correspondence Under 505(o).”**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

#### **POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitment:

3152-6 Evaluation of concomitant gastric acid reducers on the pharmacokinetics of Xermelo (telotristat ethyl).

The timetable you submitted on February 24, 2017 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2017
Study Completion:	02/2018
Final Report Submission:	04/2018

Submit clinical protocols to your IND 078749 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,”** or **“Postmarketing Commitment Correspondence.”**

## **PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

## **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

## **MEDWATCH-TO-MANUFACTURER PROGRAM**

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

**POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Benjamin Vali, Regulatory Project Manager, at (301) 796-4261 or [benjamin.vali@fda.hhs.gov](mailto:benjamin.vali@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Julie Beitz, M.D.  
Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure(s):  
Content of Labeling  
Carton and Container Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JULIE G BEITZ  
02/28/2017