CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208794Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 208794 SUPPL # HFD # 180

Trade Name: XERMELO

Generic Name: telotristat ethyl

Applicant Name: Lexicon Pharmaceuticals, Inc.

Approval Date, If Known: February 28, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (c) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the

application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES ☐ NO ☐
Explain:

Investigation #2

IND # YES ☐ NO ☐
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES ☐
Explain:

NO ☐
Explain:

Investigation #2

YES ☐ NO ☐
Explain: Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Benjamin P Vali
Title: Regulatory Project Manager, Division of Gastroenterology and Inborn Errors Products
Date: February 27, 2017

Name of Division Director signing form: Donna J Griebel
Title: Director, Division of Gastroenterology and Inborn Errors Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BENJAMIN P VALI
02/27/2017

DONNA J GRIEBEL
02/27/2017

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA #: 208794 | Supplement Number: | NDA Supplement Type (e.g., SE5):

Division Name: DGIEP | PDUFA Goal Date: February 28, 2017 | Stamp Date: March 30, 2016

Proprietary Name: Xermelo

Established/Generic Name: telitristat ethyl

Dosage Form: Tablets

Applicant/Sponsor: Lexicon Pharmaceuticals, Inc.

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1)
(2)
(3)
(4)

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: For the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Benjamin Vali
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BENJAMIN P VALI
02/07/2017

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 208794 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: XERMELO Established/Proper Name: telotristat ethyl Dosage Form: Tablets, 250 mg		Applicant: Lexicon Pharmaceuticals, Inc. Agent for Applicant (if applicable):
RPM: Benjamin Vali		Division: Division of Gastroenterology and Inborn Errors Products (DGIEP)

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is February 28, 2017	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain – **Not applicable as this is a traditional/regular approval action based on clinical trial data.**	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only): Type 1
(confirm chemical classification at time of approval)

☒ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approval Action on **28Feb2017**
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included (28Feb2017)
• Original applicant-proposed labeling	☒ Included (30Mar2016)
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☒ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☐ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included (07Dec2016)
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	☒ 21Jul2016 ☒ 08Dec2016; 18Jul2016
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ 18May2016 DMEPA: ☒ 14Nov2016 DMPP/PLT (DRISK): ☒ None OPDP: ☒ 21Dec2016 COA: ☒ None CSS: ☒ None Product Quality ☒ 03Jan2017 Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ 12Jul2016 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC: Not Applicable If PeRC review not necessary, explain: This program obtained Orphan Drug Designation and was consequently exempt from PREA.	N/A (Pediatric Page Included; 07Feb2017)
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	Review Extension – Major Amendment: 14Sep2016 Information Request: 17Aug2016 Information Request: 12Aug2016 Priority Review Designation: 27May2016
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ 24Feb2015
• EOP2 meeting *(indicate date of mtg)*	☒ 11Apr2012
• Mid-cycle Communication *(indicate date of mtg)*	☒ 20July2016
• Late-cycle Meeting *(indicate date of mtg)*	☒ 08Dec2016
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	Pre-NDA (CMC-only): 11Feb2015 EOP2 (CMC-only): 14Aug2012
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ 28Feb2017
Division Director Summary Review *(indicate date for each review)*	☒ 28Feb2017
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ 29Jan2017
PMR/PMC Development Templates *(indicate total number)*	☒ 5 FDAAA PMRs and 1 506B-reportable PMC

Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	☒ Addendum: 28Feb2017 Final: 12Jan2017
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Financial Disclosure review addressed in Section 13.2 of the primary clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ COA Staff: 23Nov2016 ☒ DPMH: 04Oct2016 ☒ QT-IRT: 11Aug2016
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ 20Oct2016
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	N/A N/A ☒ 17Jan2017
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	17Nov2016 (letter) 30Sep2016 (letter) ☒ 24Aug2016 (letter) 12Aug2016 (review) 09Aug2016 (letter) 05Jul2016 (letter)
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☒ Main Review (03Dec2016) ☒ COA Review (29Nov2016)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ 01Dec2016
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ 09Jan2017
• Supervisory Review(s) *(indicate date for each review)*	☒ 02Feb2017
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ 31Dec2016
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ 11Aug2016
❖ ECAC/CAC report/memo of meeting	☒ Included in P/T review (pgs. 174-175)
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☒ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☒ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	Amendment Memo: 12Jan2017 Drug Substance: 10Aug2016 Drug Product: 31Aug2016 Environmental Assessment: 26Oct2016 ☒ Labeling: 31Aug2016 Process: 12Sep2016 Facilities: 15Aug2016 Biopharmaceutics: 05Oct2016 Methods Validation: 30Aug2016 Executive Summary: 28Nov2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	26Oct2016
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Initial: 15Aug2016 Confirmation: 27Feb2017 ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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/s/

BENJAMIN P VALI
03/02/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208794

**REVIEW EXTENSION –
MAJOR AMENDMENT**

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) received March 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xermelo (telotristat ethyl) tablets, 250 mg.

On September 2, 2016, we received your major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is February 28, 2017.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 28, 2016. Additionally, the planned date for the Late Cycle Meeting has been changed to December 14, 2016.

If you have any questions, call Benjamin Vali, Regulatory Project Manager, at (301) 796-4261.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

BENJAMIN P VALI
09/14/2016
Signing on behalf of Brian Strongin

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208794

MID-CYCLE COMMUNICATION

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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XERMELO (telotristat etiprate) tablets, 250 mg. We also refer to the teleconference between representatives of your firm and the FDA on July 20, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application. A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-4261.

Sincerely,

{See appended electronic signature page}

Benjamin Vali, M.S.
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time:	July 20, 2016, 3:30 PM – 4:30 PM (EST)
Application Number:	NDA 208794
Product Name:	XERMELO (telotristat etiprate)
Indication:	(b) (4) treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy
Applicant Name:	Lexicon Pharmaceuticals, Inc.
Meeting Chair:	Dr. Stephanie Omokaro
Meeting Recorder:	Mr. Brian Strongin

FDA ATTENDEES

Julie Beitz, M.D.	Director, Office of Drug Evaluation III (ODEIII) / Immediate Office (IO)
Donna Griebel, M.D.	Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Stephanie Omokaro, M.D.	Cross Discipline Team Leader, DGIEP
Wen-Yi Gao, M.D., Ph.D.	Medical Officer, DGIEP
David Joseph, Ph.D.	Pharmacology/Toxicology Team Leader, DGIEP
Ke Zhang, Ph.D.	Pharmacology/Toxicology Reviewer, DGIEP
Sue Chih Lee, Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP) / Division of Clinical Pharmacology III (DCPIII)
Insook Kim, Ph.D.	Clinical Pharmacology Reviewer, OCP / DCPIII
Yeh-Fong Chen, Ph.D.	Statistical Team Leader, Office of Biostatistics (OB) / Division of Biometrics III (DBIII)
Scott Komo, Ph.D.	Statistical Reviewer, OB / DBIV
George Kordzakhia, Ph.D.	Statistical Reviewer, OB / DBIII
Lili Garrard, Ph.D.	Statistical Reviewer, OB / DBIII
Danuta Gromek-Woods, Ph.D.	CMC Application Technical Lead, Office of Pharmaceutical Quality (OPQ) / Office of New Drug Products (ONDP) / Division of New Drug Products 2 (DNDP 2)
Susan Leibenhaut, M.D.	Medical Officer, Office of Scientific Investigations (OSI)
Truong Quach, Pharm.D.	Regulatory Business Process Manager (RBPM), OPQ / Office of Program and Regulatory Operations (OPRO)
Brian Strongin, R.Ph., M.B.A.	Chief, Project Management Staff, DGIEP

APPLICANT ATTENDEES

Lexicon Pharmaceuticals, Inc.

Lonnel Coats	President and Chief Executive Officer
Jeff Wade, J.D.	Chief Financial Officer and Executive Vice President, Corporate and Administrative Affairs
Alan Main, Ph.D.	Executive Vice President, CMC and Supply Operations
Praveen Tyle, Ph.D.	Executive Vice President, Research and Development
Pablo Lapuerta, M.D.	Executive Vice President and Chief Medical Officer
John R. Cutt, Ph.D.	Vice President, Regulatory Affairs and Quality Assurance
Kenneth Kassler-Taub, Ph.D.	Vice President, Clinical Operations
Alan Wilson, Ph.D.	Vice President, DMPK, Toxicology, and Pathology
Suman Wason, M.D.	Vice President, Clinical Development
William Heydorn, Ph.D.	Senior Vice President, Preclinical Development
Phil Banks, M.S.	Executive Director, Biostatistics
Rosanna Fleming, M.S.	Senior Director, Biostatistics
Wenjun Jiang, M.D.	Senior Director, Pharmacovigilance and Drug Safety
Penny Logan, M.S.	Manager, Regulatory Affairs

1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

Clinical/Statistics:

We are in the process of reviewing your response to our information request regarding the psychometric report. We are interested in the evidence available to support that a 30% reduction in bowel movements is clinically meaningful. It is critical to establish that a 30% reduction is meaningful to patients. We are interested in the distribution of percent reduction of bowel movements and have requested this distribution across responders. For example, if most responders had a 50% – 100% reduction in diarrhea, the 30% reduction issue may be less of a concern.

We are considering the mechanism of action of the drug and the pathophysiology of the underlying disease and how this might impact the expected treatment response. For example, the drug would only be expected to work for serotonin-induced diarrhea. However, patients with

neuroendocrine tumors may have multiple etiologies for their diarrhea. Please submit the proportion of patients in the neuroendocrine population who have serotonin-induced diarrhea, and the proportion of patients with serotonin-induced diarrhea whose diarrhea is primarily caused by serotonin.

Please provide analyses of the time course for reduction of diarrhea across the population and by patient or direct us to where these analyses (graphs) are within the NDA submission.

We are reviewing the safety database for any evidence of GI bleeding or severe adverse events of abdominal pain that may be associated with hospitalization in light of the non-clinical findings of drug-induced necrosis in the stomach.

We are carefully evaluating the potential for the drug to increase the risk of serious depression symptoms.

Nonclinical:
We do not have any concerns at this time.

Clinical Pharmacology:
In vitro studies: We will send an information request for these data. These are not complete response (CR) issues, but are important for labeling purposes.

- Some study reports do not include results for model substrates (i.e., for substrate studies) or model inhibitors (i.e., positive controls for inhibition studies).
- The interaction potential for major metabolites, regardless of their pharmacological activities, needs to be evaluated.

In vivo drug-drug interaction (DDI): Based on the following observations, we will send an information request for you to present exploratory analyses to address whether there is an impact on efficacy.

- Short-acting octreotide (s.c. three doses of 200 mcg: 600 mcg/day) decreased mean C_{max} and AUC of the active metabolite by 79% and 65%, respectively, in healthy subjects. The mechanism is unclear.
- Effects of short-acting octreotide at lower doses or the long-acting release (LAR) depot formulation of octreotide or lanreotide on the PK of Xermelo are unknown.
- Concomitant somatostatin analogue (SSA) therapy in phase 3 trials: The majority of patients were on octreotide LAR depot formulation at 30 mg or lanreotide LAR depot formulation at 120 mg. The potential impact on efficacy is unknown.

Chemistry/Biopharmaceutics:
We do not have any concerns at this time.

3.0 INFORMATION REQUESTS

Here are the outstanding information requests (IRs) for your application at the time of this meeting:

- June 29, 2016 Clinical Pharmacology IR

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

We do not have any concerns at this time.

5.0 ADVISORY COMMITTEE MEETING

There is no advisory committee meeting planned.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting (LCM) is September 20, 2016. In addition, please note the following projected milestone dates. It should be noted that these dates may change, and you will be notified accordingly:

Labeling, REMS, and PMR/PMC to Applicant: September 6, 2016
LCM Background Package: September 15, 2016
PDUFA Action: November 30, 2016

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/s/

BENJAMIN P VALI
09/02/2016

Vali, Benjamin P

From: Vali, Benjamin P
Sent: Friday, August 12, 2016 11:00 PM
To: Logan, Penny (PLogan@lexpharma.com); Cutt, John (jcutt@lexpharma.com)
Subject: NDA 208794 - Xermelo (telotristat etiprate) for Carcinoid Syndrome: Requests for Information

Importance: High

Dear Penny and John,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xermelo (telotristat etiprate). We are conducting a review of your NDA and have the following requests for information.

Please formally submit your written responses to the NDA as soon as possible. Please also provide a true and exact electronic (via email) courtesy copy of these formal responses to me.

Medication Error Prevention

1. [redacted] (b) (4), submit samples of the proposed 28-day case, containing weekly boxes and blister day packs (NDC 70183-125-84 [redacted] (b) (4)).

Chemistry, Manufacturing, and Controls (CMC)

2. You have proposed [redacted] (b) (4)

3. Furthermore, make the following changes to the carton/container labels:

   i. The established name should be changed to "telotristat ethyl" [redacted] (b) (4) where it appears on carton and container labels.

   ii. The following equivalence statement should be added on the side panel of the carton label:

   Each tablet contains:
   Telotristat Ethyl 250 mg
   (equivalent to 328 mg Telotristat Etiprate)

   iii. Lot number, expiration date, storage condition and bar code should be added to the blister shellpak.

Clinical

4. Provide patient narratives from the safety population of studies LX1601-1-301-CS and LX1601-1-303-CS and include major clinical laboratory results of the following adverse events of special interest

(AESI): (1) hepatic enzyme abnormality; (2) depression; and (3) constipation. Also, provide detailed narratives of all patients who died during study LX1601-1-301-CS. If you have already submitted this information, direct us to its location within your application.

5. For both studies LX1601-1-301-CS and LX1601-1-303-CS, provide subgroup analyses for narcotics usage, i.e., patients who were being administered concomitant narcotics vs. those who were not being administered concomitant narcotics. These subgroup analyses should be conducted for the primary and key secondary endpoints of each aforementioned study.

Clinical Pharmacology

6. We note that the proportion of patients who used octreotide or lanreotide was different across treatment groups in your phase 3 trials. Provide an analysis of efficacy by type of somatostatin analog used in these trials including the comparison of efficacy between subgroups of patients on octreotide and lanreotide.

7. Provide a subgroup analysis for efficacy by concomitant usage of gastric acid reducing agents and anti-diarrheal drugs.
   i. Efficacy comparisons between patients who did and patients who did not use gastric acid blocking drugs (e.g., proton-pump inhibitors (PPI)).
   ii. Efficacy comparisons between patients who did and patients who did not use concomitant anti-diarrheal drugs (loperamide).

8. Provide analysis datasets, corresponding to the analysis requests made in items 6 and 7 above, in SAS transport format (i.e., File_Name.xpt).

9. In dedicated drug-drug interaction study LX1606.109, there was a substantial decrease in the systemic exposure to telotristat ethyl and its active metabolite by concomitant octreotide acetate injection (i.e., Sandostatin). We note that the majority of patients in the phase 3 clinical trials received octreotide or lanreotide in depot formulation. We have a concern that patients who receive octreotide injections may not benefit from telotristat ethyl based on the decrease in systemic exposure. Provide a rationale with supporting data to support your proposal to use telotristat ethyl in combination with a somatostatin analog, including, but not limited to, whether telotristat ethyl can be efficacious when telotristat ethyl is administered with somatostatin analog injection. Additionally provide the underlying mechanism for drug interaction between octreotide and telotristat ethyl and how the observed drug interaction with octreotide injection is relevant to potential interactions between telotristat ethyl and octreotide (or lanreotide) administered in depot formulation.

Biostatistics

10. Regarding study LX1601-1-301-CS, for both absolute (i.e., raw) change from baseline in overall bowel movements (BMs) and relative (i.e., percent) change from baseline in overall BMs, provide the following correlation coefficients and scatter plots to assess the relationship between BM frequency and the four proposed anchors.
    i. Biserial correlation:
        - Subject global assessment of adequate relief of Carcinoid Syndrome symptoms associated with GI symptoms
        - Change in BM and reported clinically meaningful change (from Exit Interview)
    ii. Polyserial correlation:
        - Perception of change in BMs (not collapsed, from Exit Interview)

- Satisfaction with study medication-relief of Carcinoid Syndrome (not collapsed, from Exit Interview)

11. In the LX1606-1-301 COS Psychometric Report, Table 5 of Section 5.1 lists a SAS dataset (i.e., Patient_Interview_Data.sas7bdat) for the Patient Exit Interview study. However, this Patient Exit Interview SAS dataset was not included in the original NDA submission made on March 30, 2016. Hence provide the Patient Exit Interview SAS dataset; if you have already submitted this dataset, direct us to its location within your application.

Please let me know if you have any questions.

Kind regards,
Ben

Benjamin Vali, MS
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
10903 New Hampshire Ave., WO22-RM5231
Silver Spring, MD 20903
Phone: 301-796-4261
Fax: 301-796-9904

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/s/

BENJAMIN P VALI
08/18/2016

Vali, Benjamin P

From: Vali, Benjamin P
Sent: Monday, August 15, 2016 2:26 PM
To: Cutt, John (jcutt@lexpharma.com)
Cc: Logan, Penny (PLogan@lexpharma.com)
Subject: RE: NDA 208794 - Xermelo (telotristat etiprate) for Carcinoid Syndrome: Requests for Information

Dear John,

It was great to speak with you today. I wanted to let you know that in regards to requests 8 and 11 below, please additionally provide the corresponding data definition files. Note that in order to hasten the submission process, these metadata files can be submitted in Define.PDF format as opposed to the usually recommended Define-XML format.

Please let me know if you have any questions.

Kind regards,
Ben

Benjamin Vali, MS
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
10903 New Hampshire Ave., WO22-RM5231
Silver Spring, MD 20903
Phone: 301-796-4261
Fax: 301-796-9904

From: Vali, Benjamin P
Sent: Monday, August 15, 2016 8:02 AM
To: 'Logan, Penny'
Cc: Cutt, John (jcutt@lexpharma.com)
Subject: RE: NDA 208794 - Xermelo (telotristat etiprate) for Carcinoid Syndrome: Requests for Information

Dear Penny,

Yes, please submit responses as they are ready (i.e., a rolling submission). This will be much more efficient than waiting to submit as one big response.

Thanks,
Ben

From: Logan, Penny [mailto:PLogan@lexpharma.com]
Sent: Saturday, August 13, 2016 9:11 AM
To: Vali, Benjamin P
Subject: Re: NDA 208794 - Xermelo (telotristat etiprate) for Carcinoid Syndrome: Requests for Information

Hi Ben,

As some of these responses are quicker to generate, do you want these responses returned as they are ready or would you rather we submit as one big response?

Have a good weekend!

Thanks,
Penny L.

On Aug 12, 2016, at 9:59 PM, Vali, Benjamin P <benjamin.vali@fda.hhs.gov> wrote:

> Dear Penny and John,
>
> Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xermelo (telotristat etiprate). We are conducting a review of your NDA and have the following requests for information.
>
> **Please formally submit your written responses to the NDA as soon as possible. Please also provide a true and exact electronic (via email) courtesy copy of these formal responses to me.**
>
> **Medication Error Prevention**
>
> 1. [redacted] (b) (4), submit samples of the proposed 28-day case, containing weekly boxes and blister day packs (NDC 70183-125-84 [redacted] (b) (4)).
>
> **Chemistry, Manufacturing, and Controls (CMC)**
>
> 2. You have proposed [redacted] (b) (4)
>
> 3. Furthermore, make the following changes to the carton/container labels:

i. The established name should be changed to "telotristat ethyl" [redacted] (b) (4) where it appears on carton and container labels.

ii. The following equivalence statement should be added on the side panel of the carton label:

Each tablet contains:
Telotristat Ethyl 250 mg
(equivalent to 328 mg Telotristat Etiprate)

iii. Lot number, expiration date, storage condition and bar code should be added to the blister shellpak.

Clinical

4. Provide patient narratives from the safety population of studies LX1601-1-301-CS and LX1601-1-303-CS and include major clinical laboratory results of the following adverse events of special interest (AESI): (1) hepatic enzyme abnormality; (2) depression; and (3) constipation. Also, provide detailed narratives of all patients who died during study LX1601-1-301-CS. If you have already submitted this information, direct us to its location within your application.

5. For both studies LX1601-1-301-CS and LX1601-1-303-CS, provide subgroup analyses for narcotics usage, i.e., patients who were being administered concomitant narcotics vs. those who were not being administered concomitant narcotics. These subgroup analyses should be conducted for the primary and key secondary endpoints of each aforementioned study.

Clinical Pharmacology

6. We note that the proportion of patients who used octreotide or lanreotide was different across treatment groups in your phase 3 trials. Provide an analysis of efficacy by type of somatostatin analog used in these trials including the comparison of efficacy between subgroups of patients on octreotide and lanreotide.

7. Provide a subgroup analysis for efficacy by concomitant usage of gastric acid reducing agents and anti-diarrheal drugs.

iv. Efficacy comparisons between patients who did and patients who did not use gastric acid blocking drugs (e.g., proton-pump inhibitors (PPI)).

v. Efficacy comparisons between patients who did and patients who did not use concomitant anti-diarrheal drugs (loperamide).

8. Provide analysis datasets, corresponding to the analysis requests made in items 6 and 7 above, in SAS transport format (i.e., File_Name.xpt).

9. In dedicated drug-drug interaction study LX1606.109, there was a substantial decrease in the systemic exposure to telotristat ethyl and its active metabolite by concomitant octreotide acetate injection (i.e., Sandostatin). We note that the majority of patients in the phase 3 clinical trials received octreotide or lanreotide in depot formulation. We have a concern that patients who receive octreotide injections may not benefit from telotristat ethyl based on the decrease in systemic exposure. Provide a rationale with supporting data to support your proposal to use telotristat ethyl in combination with a somatostatin analog, including, but not limited to, whether telotristat ethyl can be efficacious when telotristat ethyl is administered with somatostatin analog injection. Additionally provide the underlying mechanism for drug interaction between octreotide and telotristat ethyl and how the observed drug interaction with octreotide injection is relevant to potential interactions between telotristat ethyl and octreotide (or lanreotide) administered in depot formulation.

Biostatistics

10. Regarding study LX1601-1-301-CS, for both absolute (i.e., raw) change from baseline in overall bowel movements (BMs) and relative (i.e., percent) change from baseline in overall BMs, provide the following correlation coefficients and scatter plots to assess the relationship between BM frequency and the four proposed anchors.

vi. Biserial correlation:

- Subject global assessment of adequate relief of Carcinoid Syndrome symptoms associated with GI symptoms
- Change in BM and reported clinically meaningful change (from Exit Interview)

vii. Polyserial correlation:

- Perception of change in BMs (not collapsed, from Exit Interview)
- Satisfaction with study medication-relief of Carcinoid Syndrome (not collapsed, from Exit Interview)

11. In the LX1606-1-301 COS Psychometric Report, Table 5 of Section 5.1 lists a SAS dataset (i.e., Patient_Interview_Data.sas7bdat) for the Patient Exit Interview study. However, this Patient Exit Interview SAS dataset was not included in the original NDA submission made on March 30, 2016. Hence provide the Patient Exit Interview SAS dataset; if you have already submitted this dataset, direct us to its location within your application.

Please let me know if you have any questions.

Kind regards,
Ben

Secure Email
Secure email between CDER and sponsors is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). It is the only way FDA can communicate confidential information to you via email. If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

Benjamin Vali, MS
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
10903 New Hampshire Ave., WO22-RM5231
Silver Spring, MD 20903
Phone: 301-796-4261
Fax: 301-796-9904

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/s/

BENJAMIN P VALI
08/18/2016

Vali, Benjamin P

From: Vali, Benjamin P
Sent: Wednesday, August 17, 2016 6:41 PM
To: Logan, Penny (PLogan@lexpharma.com); Cutt, John (jcutt@lexpharma.com)
Subject: NDA 208794 - Xermelo (telotristat ethyl) for Carcinoid Syndrome: Requests for Information

Importance: High

Dear Penny and John,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xermelo (telotristat ethyl). We are conducting a review of your NDA and have the following requests for information.

Please formally submit your written responses to the NDA as soon as possible. Please also provide a true and exact electronic (via email) courtesy copy of these formal responses to me.

Clinical

1. For all patients from the safety population of studies LX1601-1-301-CS and LX1601-1-303-CS, provide focused patient narrative information regarding serious adverse events (SAEs) and non-SAEs for the following adverse events of special interest (AESI): (1) hepatic enzyme abnormality, (2) depression, and (3) constipation. Each AESI SAE and non-SAE patient narrative should also include major clinical laboratory results in addition to the following patient information:

   (1) Hepatic Enzyme Abnormality
   a. unique subject identifier
   b. age
   c. gender
   d. race
   e. history of hepatic enzyme abnormalities
   f. primary tumor location
   g. presence of metastasis and location
   h. tumor grade
   i. temporal relationship, i.e., time-to-onset
   j. concomitant medication
   k. required study drug dose adjustment (yes/no) and actual adjusted dose
   l. duration of hepatic enzyme abnormality
   m. whether hepatic enzyme abnormality resolved after treatment discontinuation (i.e., outcome status: ongoing, resolved, etc.)
   n. required hospitalization (yes/no)
   o. required clinic or emergency room visit (yes/no)
   p. study discontinuation (yes/no)

   (2) Depression
   a. unique subject identifier
   b. age

c. gender
d. race
e. history of depression
f. primary tumor location
g. presence of metastasis and location
h. tumor grade
i. temporal relationship, i.e., time-to-onset
j. concomitant medication
k. required study drug dose adjustment (yes/no) and actual adjusted dose
l. duration of depression
m. whether depression resolved after treatment discontinuation (i.e., outcome status: ongoing, resolved, etc.)
n. required hospitalization (yes/no)
o. required clinic or emergency room visit (yes/no)
p. study discontinuation (yes/no)

(3) Constipation

a. unique subject identifier
b. age
c. gender
d. race
e. history of intestinal obstruction and reason
f. prior surgeries and reasons
g. previous pathological diagnosis, i.e., information provided by previous endoscopic biopsy or by open section biopsy, including evaluation of the depth of tumor invasion and involvement of mesentery
h. primary tumor location
i. presence of metastasis and location
j. tumor grade
k. temporal relationship, i.e., time-to-onset
l. concomitant medication
m. required study drug dose adjustment (yes/no) and actual adjusted dose
n. duration of constipation
o. whether constipation resolved after treatment discontinuation (i.e., outcome status: ongoing, resolved, etc.)
p. presence of ascites (yes/no)
q. required hospitalization (yes/no)
r. required clinic or emergency room visit (yes/no)
s. study discontinuation (yes/no)

For administrative purposes, we ask that you additionally resubmit all previously submitted AESI patient narratives within this submission. This will result in all desired patient narrative information being co-located and thereby enabling a more streamlined regulatory review.

2. Additionally, present the data already requested in #1 above in line listing form, i.e., for each AESI group: the unique subject identifier in rows and the remaining previously requested AESI specific information (e.g., items b through p under Hepatic Enzyme Abnormality) in columns for all occurrences of SAEs and non-SAEs.

Clinical Pharmacology

3. Provide rationale and relevant analyses as to how the concomitant usage of antidiarrheal medicine affects (or does not affect) the efficacy of telotristat ethyl. Provide summary and individual listings for usage of concomitant anti-diarrheal medications in terms of dose, duration, and timing of initiation and discontinuation as well as frequency if used as a rescue.

Please let me know if you have any questions.

Kind regards,
Ben

Benjamin Vali, MS
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III/Center for Drug Evaluation and Research
10903 New Hampshire Ave., WO22-RM5231
Silver Spring, MD 20903
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/s/

BENJAMIN P VALI
08/18/2016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208794

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Lexicon Pharmaceuticals, Inc.
8800 Technology Forest Place
The Woodlands, TX 77381

ATTENTION: Penny Logan, MS
Regulatory Affairs Manager

Dear Ms. Logan:

Please refer to your New Drug Application (NDA) dated and received March 30, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Telotristat Etiprate Tablets, 250 mg.

We also refer to your correspondence, dated and received April 26, 2016, requesting review of your proposed proprietary name, Xermelo.

We have completed our review of the proposed proprietary name, Xermelo and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 26, 2016, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Ginneh Stowe, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4049. For any other information regarding this application, contact Brian Strongin, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

GINNEH D STOWE
07/20/2016

LUBNA A MERCHANT on behalf of TODD D BRIDGES
07/21/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208794

PRIORITY REVIEW DESIGNATION

Lexicon Pharmaceuticals
Attention: Penny Logan, MS
Regulatory Affairs Manager
8800 Technology Forest Place
The Woodlands, Texas 77381-1160

Dear Ms. Logan:

Please refer to your new Drug Application (NDA) dated March 30, 2016, received March 30 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Xermelo (telotristat etiprate) Tablets.

We also refer to your submission(s) dated April 22, 2016; April 26, 2016; May 4, 2016; May 12, 2016 and May 20, 2016.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is November 30, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 8, 2016.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before June 12, 2016.

If you have any questions, call Brian Strongin, R.Ph., MBA,Chief, Regulatory Project Management Staff, at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and
Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
05/27/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 078749

MEETING MINUTES

Lexicon Pharmaceuticals, Inc.
Attention: Penny Logan, MS
Regulatory Affairs Manager
8800 Technology Forest Place
The Woodlands, Texas 77381-1160

Dear Ms. Logan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Telotristat (LX1606) Capsules.

We also refer to the Pre-NDA meeting between representatives of your firm and the FDA on February 24, 2015.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., MBA
Chief, Project Management Staff
Division of Gastroenterology and
Inborn Errors of Metabolism
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA Meeting
Meeting Date and Time:	February 24, 2015 12 Noon
Meeting Location:	White Oak Building #22, Conference Room 1309
Application Number:	IND 078749
Product Name:	Telotristat (LX1606) Capsules
Indication:	Treatment of GI symptoms associated with carcinoid syndrome in patients who no longer respond to standard of care with somatostatin
Sponsor/Applicant Name:	Lexicon Pharmaceuticals, Inc

FDA ATTENDEES

Julie Beitz, M.D.	Director, Office of Drug Evaluation III (ODE III)
Amy Egan, M.D.	Deputy Director, ODE III
Donna Griebel, M.D.	Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Dragos Roman, M.D.	Acting Deputy Director, DGIEP
Joyce Korvick, M.D	Deputy Director for Safety, DGIEP
Ruyi He, M.D.	Medical Team Leader, DGIEP
Karyn Berry, M.D.	Medical Officer, DGIEP
Sue Chih Lee, Ph.D.	Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III
Insook Kim, Ph.D.	Reviewer, Division of Clinical Pharmacology III
Yeh-Fong, Chen Ph.D.	Supervisory Statistician, Division of Biometrics III
David Joseph, Ph.D.	Supervisory Pharmacologist, DGIEP
Ke Zhang, Ph.D.	Pharmacology Reviewer
Marie Kowblansky, Ph.D.	Chemistry, Manufacturing and Controls Team Leader Office of New Drug Quality Assurance
Maria Walsh, MSN	Associate Director for Regulatory Affairs, Office of Drug Evaluation III
Kathryn O'Connell, M.D.	Medical Officer, Division of Neurology Drug Products
Susan Leibenhaut, M.D.	Medical Officer, Office of Scientific Investigations
Gabriella Anic, M.D.	Epidemiologist, Division of Epidemiology I
Kira Leishear, M.D.	Epidemiologist, Division of Epidemiology I
Brian Strongin, R.Ph., MBA	Chief, Project Management Staff, DGIEP
Christopher Sese	Eastern Research Group, Independent Assessor
Patrick Zhou	Eastern Research Group, Independent Assessor

SPONSOR ATTENDEES

Lexicon Pharmaceuticals, Inc.

Phil Banks, MS, FRS, MS, FRS Executive Director, Biostatistics
Lonnel Coats, President and CEO
John R. Cutt, PhD, Vice President, Regulatory Affairs
William Heydorn, PhD, Senior Vice President, Preclinical Development
Pablo Lapuerta, MD, Executive Vice President and Chief Medical Officer
Penny Logan, MS, Regulatory Affairs Manager
John Northcott, Vice President, Marketing, Commercial and Operations
Suman Wason, MD, Vice President, Clinical Development
Alan Wilson, PhD, Vice President, DMPK
Winston Wu, PhD, Vice President, Chemical Development

Ipsen Pharma

Sophie Delobel, Regulatory Project Manager
Douglas Fleming, MD, Medical Development Director, Endocrinology
Josie Gayton, Research and Development Project Leader
Claire Gendreau Catania, Regulatory Project Manager

BACKGROUND

Lexicon is developing LX1606 (telotristat ediprate) for the treatment of GI symptoms associated with carcinoid syndrome in patients that no longer respond to standard care with somatostatin analogs. This development program was designated as a Fast Track development program on May 19, 2008. LX1606 was designated as an orphan drug on March 9, 2012.

An end-of-phase 2 meeting with the sponsor was held April 11, 2012 and follow-up meetings were held July 9, 2013 and October 9, 2013.

A special protocol assessment for a protocol titled, "Proposed 104-Week Repeated Dose Oral (Gavage) Carcinogenicity Study in Sprague-Dawley Rats" was submitted November 20, 2014. An Agreement letter was dated December 17, 2014.

A pre-NDA meeting request was dated December 18, 2014.

DISCUSSION

1. Does the agency agree that Lexicon's proposal for the content of Module 5 is acceptable to fulfill the requirements for the filing of the NDA submission? Specifically Lexicon would like the Division's comments and agreement on the following topics regarding the content of Module 5:

    a. Clinical study reports to be included in Section 5.3 -

    FDA Response:

Yes. Please note that Study Tagging Files (STFs) are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008). http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf

b. Case report forms to be submitted in the NDA -

FDA Response:
Yes. Case report forms need to be referenced under the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Do not use m5.3.7 as a heading element in the index.xml.

c. Patient profiles

FDA Response:

We will provide a response as post-meeting comments that will be added to the final meeting minutes.

d. Proposal to address the requirements for the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS).

FDA Response:
Your proposed placement of ISE and ISS is acceptable.

For the content of Module 5, please refer to the OSI comments provided as Attachment A and Attachment 1 to the minutes.

2. Does the Agency agree that the proposed overall and long-term safety exposure database is adequate for submission of a complete NDA in this orphan indication?

FDA Response:

We have a concern regarding your timeline of submission for the long-term safety exposure database. The long-term safety data must be submitted at the time of NDA filing. We cannot agree with your proposal for submission of data for 45 patients exposed for at least one year before you provide information on the

estimated number of patients with carcinoid syndrome refractory to somatostatin analogues in the United States. Please provide your estimate and we will further consider your proposal.

As a fast track designated drug product, you may consider submitting completed portions of your application or "rolling submission." The review clock will not begin though until a complete NDA has been submitted.

Discussion:

Lexicon will gather information and will present a package that reviews all patients taking 250 mg and 500 mg for exposure estimates up to 48 and 52 weeks. They will also estimate the impact of a rolling submission for supplying safety exposure data.

3. Can the Agency comment on Lexicon's preliminary justification for applying for a priority NDA review for telotristat etiprate?

   FDA Response:

   Your request for priority review will be evaluated once the NDA has been formally submitted and a decision will be made at the time of filing. Please refer to the Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf.

4. Does the Agency agree that the proposed safety integration plan and presentation of the data for the ISS and 120-Day Safety Update are acceptable to fulfill the requirements for submission of the NDA?

   FDA Response:

   No, we do not agree. We cannot agree with your proposal to submit only cut-off data from long-term open-label portion of the pivotal study LX 1606.1-301-CS, the long term open-label LX1606.1-302-CS and short-term and long-term portions of study LX 1606.1-303-CS at this time without further information. See response to question #2.

   The safety data should be presented separately in healthy subjects and in patients with CS (all phase 2 and 3 trials combined). In addition, present the data by dosing regimen, including for all of these subgroups.

Discussion:

For the sake of completeness lexicon will provide an integrated table that includes adverse events from all of the placebo controlled phase 2 and 3 trials in patients with carcinoid syndrome.

5. Does the Agency agree that no renal or hepatic impairment studies with telotristat etiprate (LX1606) are required?

FDA Response:

The following responses refer to the need for studies pre- or post- approval. We cannot agree that no hepatic impairment studies are needed based on the limited information provided to us. According to your preliminary PK data, the Tmax for the active metabolite, LX1033 appears to be delayed compared to that for the parent drug, LX1606. This result suggests that a role of liver in the formation of the active metabolite of LX1606 cannot be ruled out. Therefore we recommend that the potential effect of liver impairment on the pharmacokinetics of the active metabolite be studied if the proposed drug is likely to be used by patients with hepatic impairment. Please provide information regarding the proportion of patients who may be expected to have varying degrees of hepatic impairment.

According to your preliminary summary data, the contribution of renal excretion to the overall elimination of LX1606 appears to be minor. However, it is premature for us to agree that no additional study is needed for the use of the proposed product in patients with renal impairment. It is our current recommendation to study the effects of renal impairment on PK even if the drug is mainly eliminated via metabolism.[1] For the use of the proposed product by the patients with renal impairment, you must provide an adequate justification, including but not limited to, the available PK and/or safety data in patients with varying degree of renal impairment from phase 3 trials in your NDA submission.

[1] Guidance for Industry Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling; http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf

Discussion:
Lexicon proposed to look for more references regarding hepatic impairment in the CS population and to review liver function data from the 301 trial and determine if a study in liver function impaired patients will need to be studied post-approval.
Regarding renal impaired patients – Lexicon will provide safety data and population PK data from their trials, examining both renal and hepatic impairment as covariates. The FDA found this plan acceptable.

6. Does the Agency agree that there is adequate coverage of the major human metabolites in Lexicon's preclinical toxicology studies, and that there are no metabolites of toxicological concern?

FDA Response:

We agree that the nonclinical and clinical PK data in your meeting package appear to support the safety of the two major metabolites (LP-778902 and LP-951757) in men, based on the studies in male healthy volunteers and male rats. However, you need to determine whether there is a gender difference in the metabolism of the parent drug (e.g. clarify whether exposure to LP-951757 in females is supported by the rat exposure to this metabolite). To address this issue, you may evaluate the exposure to LP-951757 in female subjects and/or identify the enzyme which mediates the conversion of M2 to LP-951757 (page 29 of your meeting package), and provide a convincing rationale indicating that this enzymatic activity in females is comparable to that in males.

In addition, you need to clarify whether the other metabolites detected in humans (P1 and P2) were also identified in animal studies.

Discussion:

Lexicon proposed to assess the production of LP-951757 in hepatocytes from human males and females. Lexicon also proposes to assess levels of 757 after dosing with LX1606 in female rats. These data will be used to assess whether there is any indication of a gender difference in the production of 757.

This plan is acceptable to the Division.

7. Does the Agency agree that the LX1606-related microscopic findings in the glandular and non-glandular stomach of the rat are of limited clinical relevance?

FDA Response:
This issue will be addressed in our review of the NDA.

8. (e-mailed to DGIEP 2/17/15):

As noted in Question 8 of the Pre-NDA meeting briefing document submitted on 23 January 2015, (b) (4), an (b) (4) impurity that has been identified in the telotristat etiprate drug substance, was found to be weakly positive in the Ames test. This compound gave a 2.3 fold increase in revertant colonies at the high concentration of 5000 µg/plate in the presence of Aroclor™ 1254 – induced rat liver S9 for a single strain (TA100). The Ames assay was repeated with the same lot of material, and the results were confirmed. As shown in the attached Certificate of Analysis, the lot of material used in these tests was (b) (4)% weight percent (b) (4). Subsequent to the submission of the briefing document, Lexicon repeated the Ames assay again using a more purified batch of (b) (4) in strains TA98 and TA100 in the presence of Aroclor™ 1254 – induced rat liver S9. Results from this assay have just become available and are shown below. As can be seen, using this more purified batch of material, there was no increase in revertant colonies in this assay. While an official Certificate of Analysis is not yet available, it is expected that the purity of this new batch of (b) (4) will exceed (b) (4)%. These findings suggest that a (b) (4) is responsible for the initial findings in the Ames assay.

Lexicon is planning to repeat the full Ames assay one more time to confirm these recent results. Assuming the repeat of the full Ames assay with this more pure batch of material comes back negative, Lexicon does not plan to perform any additional assessments with (b) (4).

a. Does the Agency agree with this approach?

FDA Response:
Yes, we agree. However, we recommend that both batches of impurity, (b) (4) (i.e. the Ames positive batch with (b) (4) % purity and Ames negative batch with > (b) (4) % purity) be tested in the confirmatory test that you propose to conduct (full Ames test). In addition, full reports of the initial Ames tests with the (b) (4) % purity batch and the follow-up Ames tests conducted thereafter should be included in the original submission of the NDA.

b. And does FDA still agree with Lexicon's proposal from the April 11, 2012 EOP2 Meeting to submit the 2-year rat carcinogenicity study post-NDA approval?

FDA Response:
Yes, we agree. However, you should provide a safety update of the ongoing 2-year carcinogenicity study during the NDA review cycle.

Discussion:
Lexicon agrees to conduct the confirmatory full Ames test using both batches of (b) (4). They also agree to provide a safety update from the two year rat carcinogenicity study during the NDA review cycle as part of the 120-day Safety Update. Lexicon acknowledges the receipt of the agency's response to their SPA regarding the doses for their 2 year rat carcinogenicity study. They would like to discuss the doses of LX1606 proposed by the agency outside of this meeting. Lexicon will submit a plan for CAC review. This plan is acceptable to the Division

Study Number: 8310730
Experiment Number: 8310730 Confirm 2 Date Plated: 09-Feb-2015
Assay Conditions: Date Counted: 11-Feb-2015

With metabolic activation

Strain	Compound	Conc. Level (µg/plate)	Mean	Standard Deviation	Fold Increase	Revertant Numbers Per Plate
TA98	Dimethyl Sulfoxide	-	25.0	6.1	-	18 M N, 28 M N, 29 M N
	(b) (4)	5000	20.7	2.1	0.8	19 M P N, 20 M P N, 23 M P N
		3300	22.7	7.1	0.9	15 M P N, 24 M P N, 29 M P N
		1600	23.0	8.7	0.9	27 M P N, 29 M P N, 13 M P N
		1200	14.7	4.0	0.6	19 M P N, 14 M P N, 11 M P N
		800	21.3	5.5	0.9	24 M P N, 15 M P N, 25 M P N
		500	13.7	6.0	0.5	8 M P N, 13 M P N, 20 M P N
		160	24.0	2.6	1.0	27 M N, 22 M N, 23 M N
		50.0	22.0	1.7	0.9	23 M N, 20 M N, 23 M N
	BP	2.5	381.7	33.2	15.3	353 N, 374 N, 418 N
TA100	Dimethyl Sulfoxide	-	120.7	11.0	-	128 M N, 108 M N, 126 M N
	(b) (4)	5000	127.3	16.2	1.1	119 M P N, 146 M P N, 117 M P N
		3300	124.0	4.6	1.0	128 M P N, 119 M P N, 125 M P N
		1600	127.3	6.5	1.1	127 M P N, 134 M P N, 121 M P N
		1200	124.7	8.6	1.0	117 M P N, 123 M P N, 134 M P N
		800	134.3	8.1	1.1	125 M P N, 139 M P N, 139 M P N
		500	108.3	15.3	0.9	125 M P N, 105 M P N, 95 M P N
		160	115.3	11.0	1.0	103 M N, 124 M N, 119 M N
		50.0	118.7	7.5	1.0	110 M N, 123 M N, 123 M N
	2AA	2.5	1458.3	66.8	12.1	1466 N, 1521 N, 1388 N

Positive controls		Postfixes	
BP	Benzo{a}pyrene	M	Plate counted manually
2AA	2-aminoanthracene	N	Normal background bacterial lawn
		P	Precipitation of test article observed

9. Does the Agency agree with the proposed (b) (4) limit for telotristat etiprate?

FDA Response:

No, we do not agree with your proposed limit for [redacted] (i.e. [redacted] ppm based on the proposed PDE of [redacted] µg/day from [redacted]). Specifically, the Agency is not convinced that the study used to support the PDE estimate of [redacted] µg was adequate, based on the methods used, to allow for a reasonable PDE estimate ([redacted]). However, we understand that compliance with the acceptable intake for mutagenic impurities (1.5 µg/day as per ICH M7) may be difficult or impossible for your drug, due to the expected maximum daily dose ([redacted] mg telotristat etiprate, corresponding to an acceptable limit of ~ [redacted] ppm for [redacted] in the drug substance). Therefore, the Agency requests further dialogue on this issue, so that we can better understand the technical issues that limit your ability to control the levels of [redacted], and determine the acceptability of alternative proposals for limits. Please evaluate your manufacturing process to determine the minimum [redacted] level that you can consistently achieve (a data based approach will be required for this purpose). Submit this information for review and request a meeting with the Agency to discuss this information and obtain further guidance on how to proceed.

Discussion:
Lexicon contended that they have no problems controlling [redacted]. Lexicon proposes that testing for [redacted] is not required based on historical manufacturing data and will then request a Type C Written Response Only meeting request to discuss this further.

ISSUES REQUIRING FURTHER DISCUSSION

None

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 3, 2015 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

ACTION ITEMS

Action Item/Description	Owner
Provide an integrated table that includes adverse events from all of the placebo controlled phase 2 and 3 trials in patients with carcinoid syndrome.	Lexicon

Action Item/Description	Owner
Look for more references regarding hepatic impairment in the CS population and review liver function data from the 301 trial and determine if a study in liver function impaired patients will need to be studied post-approval.	Lexicon
Regarding renal impaired patients –provide safety data and population PK data from their trials, examining both renal and hepatic impairment as covariates.	Lexicon
Assess the production of LP-951757 in hepatocytes from human males and females. Assess levels of 757 after dosing with LX1606 in female rats. These data will be used to assess whether there is any indication of a gender difference in the production of 757.	Lexicon
Conduct the confirmatory full Ames test using both batches of (b) (4).	Lexicon
Provide a safety update from the two year rat carcinogenicity study during the NDA review cycle as part of the 120-day Safety Update.	Lexicon
Discuss the doses of LX1606 proposed by the agency for their 2 year rat carcinogenicity study. Lexicon will submit a plan for CAC review.	Lexicon
Request a Type C meeting to discuss proposed (b) (4) limit for telotristat etiprate	Lexicon

POST-MEETING COMMENTS
The sponsor submitted a proposal regarding the safety information to be included in the planned NDA on March 5, 2015. The Division found the proposal acceptable.

ATTACHMENTS AND HANDOUTS

Attachment A

Attachment 1

Sponsor's Slides

Attachment A

OSI Request Refer to Question #1

The Office of Scientific Investigations (OSI) requests that the following items be provided in the NDA submission to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

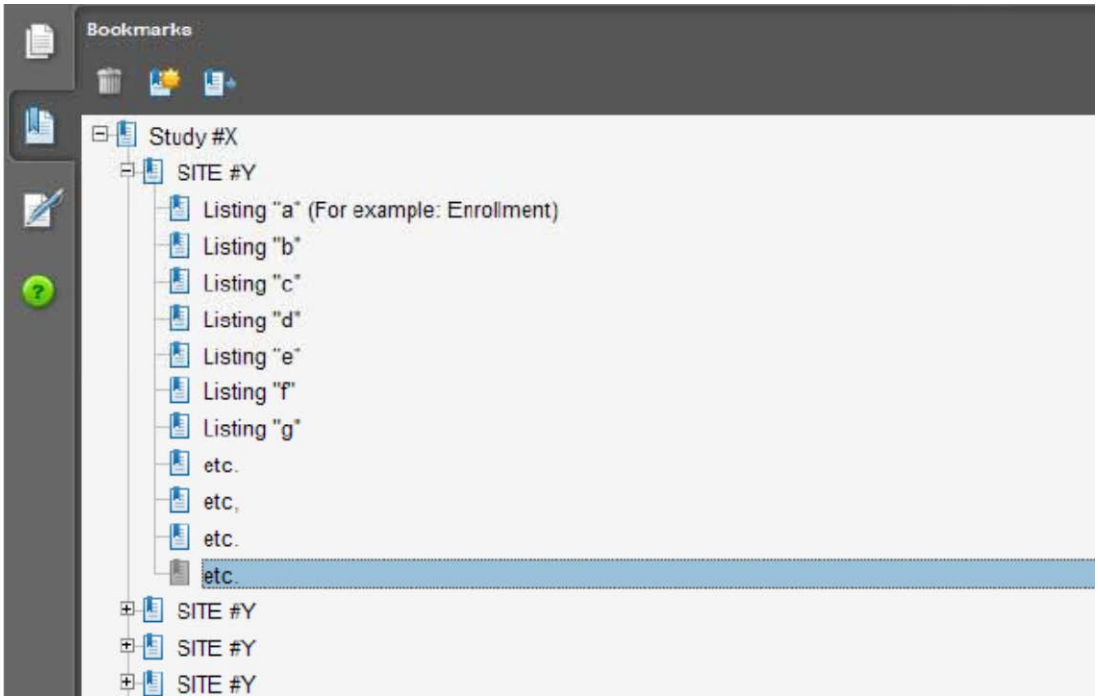
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[2]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

[2] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

For general help with eCTD submissions: ESUB@fda.hhs.gov

6 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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.

/s/

BRIAN K STRONGIN
03/24/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 078749

MEETING MINUTES

Lexicon Pharmaceuticals
Attention: Penny Logan
Regulatory Affairs Manager
8800 Technology Forest Place
The woodlands, TX 77381

Dear Ms. Logan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Telotristat (LX1606) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on February 11, 2015. The purpose of the meeting was to discuss CMC questions.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Laya Keyvan, Regulatory Project Manager at (240) 402-4598.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA (CMC Only)
Meeting Date and Time:	February 11, 2015, 1:30-2:30 pm EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1417 Silver Spring, Maryland 20903
Application Number:	IND 078749
Product Name:	Telotristat (LX1606) Capsules
Indication:	For treatment of gastrointestinal symptoms associated with carcinoid syndrome in patients who no longer respond to standard care with somatostatin analogs.
Applicant Name:	Lexicon Pharmaceuticals
Meeting Chair:	Marie Kowblansky, PhD
Meeting Recorder:	Laya Keyvan, MS, MBA

FDA ATTENDEES
Marie Kowblansky, PhD, CMC Team Leader, OPQ
Tapash Ghosh, PhD, Biopharmaceutics Branch chief, OPQ
Tien-Mien Chen, PhD, Biopharmaceutics Acting Team Leader, OPQ
Mei Ou, PhD, Biopharmaceutics reviewer, OPQ
Laya Keyvan, MS, MBA, Product Quality Regulatory Project Manager, OPQ

SPONSOR ATTENDEES
Lexicon Pharmaceuticals, Inc.
Alan Main, Ph.D., Executive Vice President, Pharmaceutical Research
John R. Cutt, Ph.D., Vice President, Regulatory Affairs
William Heydorn, Ph.D., Senior Vice President, Preclinical Development
Wenxue (Winston) Wu, Ph.D., Vice President, Chemical Development
Jinling Chen, Ph.D., Executive Director, Pharmaceutics
Donna Kapples, MS, Director Regulatory, CMC
Penny Logan, MS, Regulatory Affairs Manager

Ipsen Pharma
Nicole Cohen, Ph.D., Director, Head of Global CMC Regulatory

1.0 BACKGROUND

Lexicon Pharmaceutical Inc. submitted a meeting request on November 25, 2014 for IND 078749 Telotristat (LX1606) Capsules. This Type B meeting request is to discuss CMC questions. Telotristat etiprate is being developed for the treatment of gastrointestinal symptoms associated with carcinoid syndrome in patients who no longer respond to standard care with somatostatin analogs.

2.0 DISCUSSION

2.1. Category/Discipline A

Question 1a: *Does the Agency agree that the CMC filed documentation will be complete, at time of submission, based on the proposed table of contents (TOC) for Module 3 for the original NDA?*

FDA Response to Question 1a:
Since your proposed Table of Contents is in agreement with ICH M4Q, we have no objections to the content of your proposed submission.

Question 1b: *Does the Agency have a preference whether one drug substance section, 3.2.S, is submitted for two drug substance manufacturers or separate sections for each manufacturer?*

FDA Response to Question 1b:
We leave that up to you; either way is acceptable. Please note, however, since you will be using different analytical methods at the two sites, both methods will need to be validated.

Question 1c: *Does the Agency agree that it is acceptable that the compendial excipients will be combined into one P4 document (containing P41, P42, P43 and P44 information)?*

FDA Response to Question 1c:
Yes, we agree.

Question 1d: *Does the Agency agree that it is acceptable that the information for the non-compendial excipient ((b) (4) coating) will be filed in P41, P42, P43 and P44?*

FDA Response to Question 1d:
Yes, that will be acceptable.

Question 2: *Does the Agency agree that the Heavy Metals test USP<231> is sufficient for approval for drug substance testing?*

FDA Response to Question 2:
No, we do not agree. Your product will need to conform to the ICH Guidance for elemental impurities ICH Q3D.

Question 3: *Does the Agency agree that the LX1606 tablet dissolution method is appropriate for the immediate release Telotristat etiprate tablets and it is:*

a. sufficiently discriminatory

FDA Response to Question 3a:
No, we do not agree that the method is sufficiently discriminatory. You have not shown the effect of various physical properties of the drug substance such as particle size on the dissolution properties. Also, the method did not discriminate between tablets of different hardness.

Clarify, if the prodrug can release the active moiety in the dissolution media (with various pH conditions) and if the analytical method is specific for the prodrug only or nonspecific, i.e., for a mixture of both the prodrug and the active moiety.

Meeting Minutes:

1. The Agency agreed that the dissolution method is a Quality Control method.
2. Ideally, the dissolution method should be able to discriminate between bioequivalent and bioinequivalent batches and Q value equals to (b) (4)% or better will be ideal for an immediate release product.
3. It was discussed and agreed that the dissolution of the drug product is not dependent on the (b) (4) of the LX1606 drug substance because of (b) (4). Therefore, the Agency is not expecting Lexicon to make additional batches on (b) (4) for additional dissolution testing studies.
4. The (b) (4) will remain monitored (b) (4)
5. Testing for disintegration is not necessary because dissolution testing is performed.
6. The Agency recommended setting appropriate dissolution acceptance criteria upon review of all the release and stability data as well as the dissolution profile data of the clinically tested batch(es).
7. FDA agreed that the IVIVC study is not required for the NDA.

b. sufficiently clinically relevant

FDA Response to Question 3b:
We could not answer this question at this time. Whether your method is clinically relevant or not will depend largely on whether the method can discriminate between bioequivalent and bioinequivalent batches as mentioned earlier.

Question 4: *If Lexicon decides to launch with a child resistant blister, does the Agency agree that the registration stability (RS) data for the non-child resistant blister is representative of the child resistant (CR) blister, therefore the shelf life of the CR blister will be established based on the RS of the non-CR blister?*

FDA Response to Question 4:
We find your proposal to use stability data from the non-child resistant blister to support commercial packaging in a child-resistant blister acceptable based on the following information provided in the briefing package: 1) the material in contact with the product will be the same for both the child-resistant and non-resistant blisters, 2) same design for both blister types, and 3) the only difference between the child-resistant and non-resistant blister packaging is the thickness of the lidding.

Question 5: *Does the Agency agree that the shelf life of the drug product is established based on satisfactory stability data of the drug product and is independent of the drug substance manufacturer (providing that the drug substance manufacturing processes are equivalent and produce the same quality material)?*

FDA Response to Question 5:
No, we do not agree. Generally we expect at least some stability data for product manufactured with drug substance from a new site. In your particular case, since you will be providing 36 months of stability data for three batches of product manufactured with drug substance from (b) (4) and 12 months of data for drug product with drug substance from (b) (4), it will be acceptable to base expiration dating for the product on stability data for product manufactured with drug substance from (b) (4) provided that the stability trends are comparable for product manufactured from drug substance from both sites.

Question 6: *Does the Agency agree that one executed batch record will be sufficient for filing?*

FDA Response to Question 6:
Yes, it is acceptable to submit only one representative executed batch record for the registration batch, however, a Master batch record for the commercial product should also be provided.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MOO JHONG RHEE
02/24/2015
Chief, Branch V

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 78749

MEETING MINUTES

Lexicon Pharmaceuticals, Inc.
Attention: Melissa Green
Director
350 Carter Road
Princeton, NJ 08540

Dear Ms. Green:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LX1606 Oral Tablets.

We also refer to the telecon between representatives of your firm and the FDA on August 14, 2012. The purpose of the meeting was to CMC issues

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3877.

Sincerely,

{See appended electronic signature page}

Cathy Tran-Zwanetz
Regulatory Health Project Manager
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	CMC Meeting
Meeting Date and Time:	August 14, 2012 at 2:00 PM EST
Meeting Location:	FDA White Oak, Building 22, Room 1415
Application Number:	IND 78749
Product Name:	LX 1606 Oral Capsules
Indication:	Gastrointestinal Symptoms associated with carcinoid syndrome
Sponsor Name:	Lexicon Pharmaceuticals, Inc.
Meeting Chair:	Marie Kowblansky, Ph.D.
Meeting Recorder:	Cathy Tran-Zwanetz

FDA ATTENDEES

Office of New Drug Quality Assessment
Marie Kowblansky, Ph.D., CMC Lead
Zhengfang Ge, Ph.D., ONDQA Reviewer
Cathy Tran-Zwanetz, Regulatory Project Manager

Office of New Drugs- Gastroenterology Drug Products
Sushanta Chakder, Ph.D., Supervisory Pharmacologist

SPONSOR ATTENDEES

Alan Main, PhD – Executive Vice President Pharmaceutical Research
Wenxue (Winston) Wu, PhD – Vice President, Chemical Development
William Heydorn, PhD – Vice President, Preclinical Development
John Cutt, PhD – Vice President, Regulatory Affairs
Melissa Green – Director, Regulatory Affairs
Justin Kilby – Regulatory Compliance Manager
Penny Logan – Senior Regulatory Affairs Specialist

1.0 BACKGROUND

Lexicon's plans to submit a Phase 3 protocol by the end of August 2012 to initiate in September 2012. The purpose of this meeting is for the Sponsor to gain input from the Agency on the proposed development plan of the drug substance and drug product. Preliminary meeting comments were sent on Thursday, August 9, 2012 to the sponsor.

2.0 DISCUSSION

DRUG SUBSTANCE

1. Does the agency agree with the specifications as proposed?

FDA Response:
Your proposed drug substance specification is generally acceptable, with the following comments.

Does the agency agree that:

a) The impurity identification threshold of (b) (4)% and qualification threshold of (b) (4)% can be applied to the release of the drug substance?

FDA Response:
We agree with your proposed identification and qualification thresholds for impurities in the drug substance, but to support qualification of (b) (4), you need to provide documentation to assure that the completed toxicity studies with the drug substance containing these impurities are sufficient. Alternatively, you should conduct a toxicity study to support qualification, as per ICH guidance Q3A(R2), or reduce the limits to ≤ (b) (4)%. Genotoxicity studies (Ames test, chromosomal aberration test) with the individual impurities may also be needed for qualification at any proposed limit > (b) (4)%.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

b) The particle size specification limit of (b) (4) µm (D90) is acceptable?

FDA Response:
In view of the high solubility of this drug substance, your proposed particle size specification limit is reasonable.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

c) It is acceptable not to test (b) (4), polymorphism, residual metal catalysts, and microbiological quality attributes?

FDA Response:
It is possible that you may not need to test for some of the above variables in the commercial product, but this decision will be made at the time your NDA is reviewed. You should continue to collect the above data and provide justification in the NDA submission why such testing is not required on the basis of all your batch data. The maximum (b) (4) levels will need to respectively conform to levels recommended in *FDA Draft Guidance for Industry Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches; December 2008 and The United States Pharmacopoeia.*

Discussion:
It seems that the proposed (b) (4) limits are not necessarily in agreement with FDA guidance, the sponsor will further justify their (b) (4) limit in a future submission. Their proposal will be reviewed by the FDA (toxicology group) and a written response will be sent to the sponsor.

2 Does the Agency agree with the starting material designations?

FDA Response:
Your designation of (b) (4) as starting materials is acceptable in view of the information you have submitted in the briefing package regarding characterization, identification of impurity profiles, fate of impurities, and stability. Since these starting materials are not commercially available, when you submit your NDA you will need to resubmit all this information, as well as the synthetic pathway for each, starting with commercially available materials. In the NDA submission, you will also need to provide a commitment that you will notify the Agency if there are any changes to the routes of synthesis.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

Drug Product

1. Does the agency agree with the proposed release specifications for the telotristat etiprate (b) (4) coated tablets? Does the agency agree that:
    1) The proposed release specifications for the telotristat etiprate (b) (4) coated tablets, 250 mg (as free base), is acceptable for use with Phase 3 clinical trial material?

2) The related substances specification is acceptable for use with Phase 3 clinical trial material?

FDA Response:
Your proposed drug product specification is generally acceptable for the purpose of Phase 3 trials, but your proposed total impurity limit of (b) (4) will be further evaluated at the time of NDA submission. To support qualification of (b) (4) you need to provide documentation to assure that the completed toxicity studies with the drug substance containing these impurities are sufficient. Alternatively, you should conduct a toxicity study to support qualification, as per ICH guidance Q3B(R2), or reduce the limits to ≤ (b) (4)%. Genotoxicity studies (Ames test, chromosomal aberration test) with the individual impurities may also be needed for qualification at any proposed limit > (b) (4)%.

Also, the proposal to use HPLC retention time as the only identification test for the drug product is insufficient. Per ICH Q6A you will need either two non-specific identification tests (e.g. two chromatographic procedures where separation is based on different principles or a single procedure with a combination of tests) or one specific test (e.g. infrared spectroscopy) for identification.

With regard to the proposed dissolution test, please note that the acceptance criterion of Q = (b) (4)% at (b) (4) minutes is not supported by the available data. The following comments are provided in order to establish a meaningful, discriminating dissolution test and appropriate acceptance criterion.

1. **Dissolution Test: Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:**

a. **solubility data for the drug substance in the proposed dissolution medium, and as a function of pH;**

b. **detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant is used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least (b) (4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;**

c. **provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and**

d. include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

2. Dissolution Acceptance Criterion: For the selection of the dissolution acceptance criterion of your immediate release product, the following points should be considered:

a. The dissolution profile data (i.e., 15, 20, 30, 45, and 60 minutes, n=12) from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value).

b. The in vitro dissolution profile should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.

c. The selection of the specification time point should be where Q= (b) (4) % dissolution occurs.

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

Discussion:
The sponsor accepted the responses. The FDA clarified that if Ames test was negative then no second in vitro test would be required.

2. Does the agency agree with the proposed microbial testing plan?

FDA Response:
Your proposed microbial testing plan is acceptable for this solid oral dosage form.

Discussion:
The sponsor accepted the responses, and no further discussion was needed.

3. Does the agency agree with this stability plan?

FDA Response:
Yes, we agree. Your plan to use 75% RH for samples stored at 30°C is acceptable since it represents harsher conditions than the 60% recommended by ICH.

Discussion:

The sponsor accepted the responses, and no further discussion was needed.

3. 0 ACTION ITEMS

The Sponsor may provide justification for their proposed (b) (4) *limits and the FDA will provide a written response once that information is received..*

4.0 CONCURRENCE

{See appended electronic signature page}

Cathy Tran-Zwanetz
Regulatory Health Project Manager for Quality
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

{See appended electronic signature page}

Marie Kowblansky, Ph.D.
CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CATHERINE A TRAN-ZWANETZ
09/12/2012

MARIE KOWBLANSKY
09/12/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 078749

MEETING MINUTES

Lexicon Pharmaceuticals, Inc.
Attention: Melissa Green, MS, MBA
Director, Regulatory Affairs
8800 Technology Forest Place
The Woodlands, TX 77381

Dear Ms. Green:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LX1606 (telotristat etiprate) Tablets, 250 mg.

We also refer to the meeting between representatives of your firm and the FDA on April 11, 2012. This was an end of phase 2 meeting to discuss your phase 3 program and the timing of nonclinical studies.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2307.

Sincerely,

{See appended electronic signature page}

Matthew Scherer, MBA
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of phase 2
Meeting Date and Time:	April 11, 2012, 10:00 to 11:00 am
Meeting Location:	White Oak, Building 22, Room 1315
Application Number:	IND 078749
Product Name:	LX1606 (telotristat etiprate)
Indication:	treatment of gastrointestinal symptoms associated with carcinoid syndrome
Sponsor/Applicant Name:	Lexicon Pharmaceuticals
Meeting Chair:	Ruyi He
Meeting Recorder:	Matthew Scherer

FDA ATTENDEES

Andrew Mulberg, MD, FAAP, CPI, Deputy Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Ruyi He, MD, Medical Team Leader, DGIEP
Karyn Berry, MD, Medial Officer, DGIEP
Michael Welch, PhD, Deputy Director, Division of Biometrics III
David Joseph, PhD, Supervisory Pharmacologist, DGIEP
Ke Zhang, PhD, Pharmacologist, DGIEP
Insook Kim, PhD, Clinical Pharmacologist, Division of Clinical Pharmacology III
Matthew Scherer, MBA, Senior Regulatory Project Manager, DGIEP

SPONSOR ATTENDEES

Brian Zambrowicz, PhD, Executive Vice President and Chief Scientific Officer, Lexicon
Pablo Lapuerta, MD, Senior Vice President, Clinical Development and Chief Medical Officer, Lexicon
Linda Law, MD, Medical Director, Clinical Development, Lexicon
Phillip Banks, Senior Director, Biostatistics & Data Management, Lexicon
William Heydorn, PhD, Vice President, Preclinical Development, Lexicon
Melissa Green Director, Regulatory Affairs, Lexicon
(b) (4), Consultant to Lexicon. (b) (4)
(b) (4), Consultant to Lexicon, (b) (4)

1. BACKGROUND

Lexicon is developing telotristat etiprate for the treatment of GI symptoms associated with carcinoid syndrome in patients who no longer respond to standard care for somatostatin analogs. This is an end of phase 2 meeting to discuss to following:

- Phase 3 program and trial design
- Clinical pharmacology program
- Nonclinical program

2. DISCUSSION

CLINICAL

Question 1.1. Does the Agency agree that the protocol design for Study LX1606.1-301-CS is appropriate for an approvable marketing application, especially with regards to:

- population to be enrolled
- primary efficacy endpoints
- secondary efficacy endpoints
- dose and regimen
- duration of dosing
- escape and rescue criteria and the potential for randomized withdrawal
- sample size for the double-blind portion of the trial

FDA Response:
We do not agree with including patients in the trial who are on lanreotide. In your proposed protocol you plan to include patients who have failed SSAs and you plan to allow patients to continue their SSA, either octreotide or lanreotide. According to the label, lanreotide does not have the indication for treatment of symptoms related to carcinoid syndrome. Therefore, patients who are on lanreotide should not be included in the trial.

It is unclear that a decrease in stool frequency is more clinically meaningful to patients than improvement in stool formulation (consistency). You should provide data to justify the use of your proposed primary endpoint, "reducing the number of bowel movements over the 12-week double blind portion of the study" and your durability definition of proportion of responders with ≥ 25% reduction in daily number of BM for ≥ 50% of time over the double-blind portion of the study.

We do not agree with the use of a global assessment such as "adequate relief" as a key secondary endpoint [redacted] (b) (4) **. General terms such as adequate, satisfactory and relief are unlikely to be interpreted consistently among patients. Patient reported ratings of change may not be uniformly understood or describe the full range of possible treatment effects. It is unclear how the 11 point scale will be used and if this is a validated PRO.**

We recommend using urgency as an exploratory endpoint because it is unlikely to be interpreted consistently among patients.

We cannot agree to the dose selected for your phase 3 trial. Three patients per arm is inadequate to make any meaningful conclusions regarding dose selection. In addition, based on Tables 1, 2 and 4 in the briefing package, a dose-response is not seen. Please justify why 500 mg three times a day was selected as the dose to be studied in phase 3. You may need to conduct an adequately powered dose response study.

A 12-week duration of dosing for the double-blind portion of the trial is acceptable. We would like to see sustained treatment effect and durability.

It is acceptable to use short-acting octreotide as rescue therapy. You will have to account for this in the efficacy analysis (i.e., these patients will be considered treatment failures in the primary efficacy analysis).

Meeting Discussion
FDA noted that Lexicon should justify its choice of a primary endpoint and present data to show that it reflects the most meaningful effect in the patient population. Lexicon should also justify the magnitude of a clinically meaningful change in the endpoint measurement. FDA further noted that both consistency and frequency are both likely to be important endpoints (i.e., primary or key secondary).

FDA agreed that adequate relief may be useful in designing phase 3 trials including justifying the relevance of the magnitude of bowel movement change. FDA reiterated that, as a secondary endpoint, adequate relief (b) (4) ***in a patient population to be studied in phase 3.***

Lexicon understands that it will be their decision on whether or not the single phase 3 trial will include more than 1 dose and will try to balance the desire for robust data and additional support for dose selection.

FDA will further consider the implications of potential lanreotide use in patients outside of the US.

Question 1.2. Assuming positive efficacy results are observed in Study LX1606.1-301-CS, would this study provide sufficient demonstration of efficacy for an approvable marketing application for telotristat etiprate?

FDA Response:
Generally, we recommend two adequate and well-controlled studies to demonstrate efficacy. However, we recognize that a limited number of patients that may be available to enroll in phase 3 trials; if only one phase 3 trial is conducted it will have to demonstrate statistically robust evidence of important clinical benefit.

Question 2.1. Does the Agency agree that determination of the need for hepatic and/or renal impairment studies can be made following the results of the planned 14C-AME study?

FDA Response:
Your proposal is acceptable.

Question 2.2. Does the Agency agree that population PK analysis for the effect of age, gender, BMI and race in the target population can be performed as part of the Phase 3 study?

FDA Response:
Your proposal is generally acceptable. Nonetheless, depending on the results of analysis and/or the importance of a covariate in the target population, a dedicated confirmatory study may be needed to guide dosage adjustment for specific subpopulations. We also recommend that you evaluate the exposure-response relationship for efficacy and/or safety as appropriate.

Question 2.3. Does the Agency agree that administration of telotristat etiprate with food in Phase 3 will support approval of a label reflecting instructions to dose telotristat etiprate with meals?

FDA Response:
In general, the administration of a product in relation to meal intake in phase 3 trial will support labeling. Please provide a rationale why telotristat etiprate needs to be administered with meals.

It is unclear if the food effect study was done with the to-be-marketed formulation. If not, we recommend that effects of food on PK of telotristat be studied using the to-be-marketed formulation for the potential flexibility for dosage administration.

In addition, we recommend that you address if different types of food, e.g., protein-rich vs. protein-low diet, would affect the PD of telotristat. In particular, we recommend you address the effects of tryptophan content in meals on the efficacy of telostristat.

Question 2.4. Does the Agency agree that the proposed PK studies will support a Phase 3 program and will support approval of the NDA?

FDA Response:
Your approach is generally acceptable. However we cannot comment on the sufficiency of your PK information in supporting a phase 3 program because only limited information is available at this point.

We recommend that multiple-dose PK be characterized following administration of the to-be-marketed product.

Question 3.1. Does the Agency agree with the plan for cytochrome P450 and transporter nonclinical studies?

FDA Response:
We recommend that you determine not only the effects of telotristat and LX1033 on CYP enzymes and transporters but also if telostristat and/or LX1033 are a substrate of CYP enzymes and/or transporters.

We recommend that the effect of telostristat and LX1033 on uptake transporters be evaluated based on the measurable systemic exposure. You may conduct *in vitro* studies to assess the necessity of *in vivo* studies. Please see the DRAFT Guidance For Industry: *Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations* (February 2012) for more details.[1]

Question 3.2. Does the Agency agree that the only DDI study required will be with octreotide?

FDA Response:
Because of limited information, we can not comment on whether no additional DDI studies would be needed. Please see the response to Question 3.1.

Question 3.3. Does the Agency agree that, assuming the safety findings from the LX1606.1-301-CS trial are consistent with the profile observed in studies LX1606.1-202-CS and LX1606.1-203-CS, the proposed safety database is adequate for the NDA to support approval in the proposed indication?

FDA Response:
The adequacy of the proposed safety database will be a review issue. For chronic indications, we require long term safety studies, i.e., at least 12 months. Please see ICH guidance E1A for additional details. We will need to review your full protocol and your completed clinical study reports to determine if your safety monitoring is adequate. We are consulting the Division of Transplant and Ophthalmology Products to obtain recommendations on monitoring of potential ocular adverse reactions. We are also consulting the Division of Psychiatry Products regarding additional safety monitoring needed to assess the use of SSRI's.

Question 3.4. Does the Agency agree that the treatment of patients with ulcerative colitis and other indications can contribute relevant safety data to support approval?

FDA Response:
Yes, this safety data may be supportive.

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

Question 3.5. Lexicon can submit the safety data from the open-label extension phase of the Phase 3 study on a rolling basis after the initial filing of the NDA?

FDA Response:
No. Applications, including safety data, should be complete at the time of NDA submission.

You have been given fast-track status for this drug development program; therefore you may be eligible for a rolling review of your NDA. Under a rolling review program, we will generally only accept complete sections (e.g., clinical data section). Refer to the Guidance for Industry: *Fast Track Drug Development Programs –Designation, Development, and Application Review* (January 2006) for more information.[2] Also note that, under a rolling review, the review clock will not begin until a complete NDA has been submitted.

NONCLINICAL

Question 4. Does the Agency agree with the content and timing of this proposal [i.e., content and timing of nonclinical package]?
Specifically, does the agency agree that results from carcinogenicity studies with LX1606 can be submitted post-NDA approval?

FDA Response:
Yes, we agree.

Question 5. Does the Agency agree with the proposal that additional studies to evaluate the immunotoxicity of LX1606 are not necessary?

FDA Response:
Yes, we agree.

Question 6. Does the Agency agree with the proposal that additional non-clinical abuse liability assessment is not required for LX1606?

FDA Response:
Yes, we agree.

Question 7. Does the agency agree with the proposal that no further photosafety testing is necessary with LX1606, assuming there is no evidence of dermal or ocular distribution of radioactivity in pigmented rats following dosing with 14C-LX1606?

FDA Response:
We are consulting with the Division of Transplant and Ophthalmology Products to determine whether additional recommendations are needed to address the potential for ocular injury due to photoactivation of LX1606 and/or LX1033. We will communicate the response from DTOP at a later date.

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079736.pdf

Additional comments from the FDA

- **We recommend that you evaluate the effect of hepatic and renal function on the urinary and plasma 5-HIAA in your future trials.**

- **We recommend that you address the effect of telostristat on the alternative tryptophan metabolism pathway (e.g., vitamin B synthesis pathway).**

3. OTHER COMMENTS

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

4. ISSUES REQUIRING FURTHER DISCUSSION

None

5. ACTION ITEMS

- DGIEP to consult the Division of Transplant and Ophthalmology Products and provide additional comment regarding monitoring of ocular adverse events.

- DGIEP to further consider the implications of potential lanreotide use in study patients outside of the US.

6. ATTACHMENTS AND HANDOUTS

Lexicon made available the following article to support discussion:

Beaumont, JL, Cella, D, Phan, AT, et al. Comparison of Health-Related Quality of Life in Patients With Neuroendocrine Tumors With Quality of Life in the General US Population, *Pancreas*, 2012;41(3):461-466

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/s/

MATTHEW C SCHERER
05/11/2012

LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208794

LATE-CYCLE MEETING MINUTES

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 March 30, 2016, 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 the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on December 8, 2016. A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Benjamin Vali, Regulatory Project Manager at (301) 796-4261.

Sincerely,

{See appended electronic signature page}

Stephanie O. Omokaro, M.D.
Cross-Discipline Team Leader
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: December 8, 2016 (2:30 PM – 4:00 PM EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: NDA 208794
Product Name: XERMELO (telotristat ethyl)
Applicant Name: Lexicon Pharmaceuticals, Inc.

Meeting Chair: Dr. Stephanie O. Omokaro
Meeting Recorder: Mr. Benjamin Vali

FDA ATTENDEES

Office of Drug Evaluation III (ODEIII) / Immediate Office (IO)
Julie Beitz, M.D., Office Director
Amy Egan, M.D., Deputy Office Director

Division of Gastroenterology and Inborn Errors Products (DGIEP)
Donna Griebel, M.D., Division Director
Joette Meyer, Pharm. D., Associate Director for Labeling
Stephanie O. Omokaro, M.D., Cross-Discipline Team Leader
Wen-Yi Gao, M.D., Ph.D., Medical Officer
David Joseph, Ph.D., Pharmacology/Toxicology Team Leader
Ke Zhang, Ph.D., Pharmacology/Toxicology Reviewer
Brian Strongin, R.Ph., M.B.A., Chief, Project Management Staff
Kevin Bugin, M.S., R.A.C., Chief, Project Management Staff
Benjamin Vali, M.S., Regulatory Project Manager

Office of Clinical Pharmacology (OCP) / Division of Clinical Pharmacology III (DCPIII)
Insook Kim, Ph.D., Clinical Pharmacology Reviewer
Shen Li, Ph.D., Clinical Pharmacology Reviewer

Office of Biostatistics (OB)
Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III (DBIII)
George Kordzakhia, Ph.D., Statistical Reviewer, DBIII

Division of Pediatric and Maternal Health (DPMH)
Tamara Johnson, M.D., Medical Team Leader
Christos Mastroyannis, M.D., Medical Officer

Office of Surveillance and Epidemiology (OSE)
Mishale Mistry, Pharm.D., M.S., Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)
Donella Fitzgerald, Pharm.D., Team Leader (Acting), Division of Risk Management (DRISK)
Laura Zendel, Pharm.D., BCPS, Reviewer, DRISK
Joel Weissfeld, M.D., M.P.H., Medical Officer, Division of Epidemiology I (DEPI I)

Office of Pharmaceutical Quality (OPQ)
Zhengfang Ge, Ph.D., Drug Product Reviewer, Office of New Drug Products (ONDP)

Rare Diseases Program
Jonathan Goldsmith, M.D., F.A.C.P., Associate Director

EASTERN RESEARCH GROUP ATTENDEES
Peggah Khorrami, Independent Assessor

APPLICANT ATTENDEES
Lexicon Pharmaceuticals, Inc.
Penny Logan, M.S., Manager, Regulatory Affairs
John R. Cutt, Ph.D., Vice President, Regulatory Affairs and Quality Assurance
Pablo Lapuerta, M.D., Executive Vice President and Chief Medical Officer
Phil Banks, M.S., Executive Director, Biostatistics
William Heydorn, Ph.D., Senior Vice President, Preclinical Development
Wenjun Jiang, M.D., Senior Director, Pharmacovigilance and Drug Safety
Lonnel Coats, President and Chief Executive Officer
Alan Main, Ph.D., Executive Vice President, CMC and Supply Operations

Ipsen
Claire Gendreau, Senior Regulatory Project Manager
Josie Gayton, Head of R&D Project Management

1.0 BACKGROUND

NDA 208794: Submitted on March 30, 2016 for XERMELO (telotristat ethyl) tablets, 250 mg

Proposed indication (subject to change): In combination with a somatostatin analog, for the treatment of diarrhea associated with carcinoid syndrome in adult patients with diarrhea inadequately controlled by somatostatin analog therapy

PDUFA goal date: February 28, 2017

2.0 DISCUSSION

1. Introductory Comments

NDA 208794 was submitted on March 30, 2016 for XERMELO (telotristat ethyl) tablets, 250 mg, and was granted priority review status with a PDUFA goal date of November 30, 2016. The Mid-Cycle Communication (MCC) was made on July 20, 2016, and a solicited major amendment to the application review cycle was initiated on September 14, 2016 thereby revising the PDUFA goal date to February 28, 2017. The Agency issued their proposed revisions to the prescribing information (PI) on November 28, 2016, which was in response to Lexicon's updated labeling submitted on June 30, 2016. The Agency's November 28, 2016 communication also included proposed Postmarketing Requirements/Commitments (PMRs/PMCs). The Agency also issued the Background Package in preparation for this meeting on November 30, 2016. Lexicon formally responded to the Agency's November 28, 2016 and November 28, 2016 communications on December 7, 2016 (Supporting Document Number 45; eCTD sequence 0044). Lexicon additionally submitted a slide-deck on December 8, 2016 to help further aid the Late-Cycle Meeting (LCM) discussion. These slides are attached herein.

Meeting Discussion:
No additional discussion needed.

2. Discussion of Minor Review Issues

Clinical
In the controlled phase of study LX1606.301, the improvement of daily bowel movements (BMs) and the proportion of durable responses plateau at 250 mg TID. An increase of Xermelo to 500 mg TID did not improve the primary efficacy results. In the safety evaluation, 500 mg TID dosing increased the number of patients who developed constipation as a severe adverse event in both the controlled phase and the open-label extension phase. Based on our benefit-risk analysis, the lowest effective dose is recommended.

The u5-HIAA data from study LX1606.301 and study LX1606.303 are summarized in Section 12.2 of the prescribing information (PI). (b) (4)

Meeting Discussion:
Lexicon stated that (b) (4)

Carton and Container Labeling
We request revised carton and container labeling, incorporating the items below, to be submitted by December 12, 2016:

1. For All Container Labels and Carton Labeling (Daily dose packs, Weekly cartons, Monthly Cartons):
   a. Revise the terminology from [redacted] (b) (4) to "Daily dose pack" to clearly state that one pack is for one day's dose.

   b. Revise the product strength to express the strength per tablet (i.e., 250 mg per tablet) per FDA's Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf) in order to prevent confusion as to how much product is contained in a single unit.

2. For the Carton Labeling (7 day box and 28-day case):
   - Relocate the net quantity statement away from the product strength, such as to top right side of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.

Lexicon Response:
Lexicon acknowledges the FDA comments on the carton and container labeling. We would like to discuss the following regarding the packaging. Based upon preliminary feedback from FDA that the review team had no comments on the packaging labels (September 15th, 2016 teleconference between Lexicon and FDA to discuss the 3 month extension), Lexicon packaged [redacted] (b) (4) monthly cartons to be available for the initial launch. Lexicon proposes to use the [redacted] (b) (4) monthly cartons for launch, and commits to a Post-Marketing Requirement to implement the requested carton and container labeling changes post launch with an agreed upon timeline. Lexicon's justification to use these cartons is based on the following:

- **The population to be treated is a small orphan population who will have their drug dispensed by a specialty pharmacy. One hundred percent of all patients who will receive the drug will receive patient counseling on the product and the use of the product. Given the small number of patients who will receive Xermelo in the first [redacted] (b) (4) cartons, and the counseling they will receive by the specialty pharmacy, the risk of confusion or medication errors in this initial launch phase is minimized.**

Does FDA Agree?

Meeting Discussion:
The Agency agreed with Lexicon's proposal and does not require a PMR to address this issue. The Agency requested that the changes be implemented at the time of next printing.

3. Postmarketing Requirements/Postmarketing Commitments

Lexicon agreed and commits to the PMR and PMCs as proposed by the Agency on November 28, 2016, and the respective timelines indicated for each herein.

PMR: 2-Year Rat Carcinogenicity Study.

- Final Protocol Submission: Completed
- Study/Trial Completion: 09/15/2017
- Final Report Submission: 09/30/2018

PMC: Evaluation of hepatic impairment on the pharmacokinetics of Xermelo in patients with moderate or severe hepatic impairment.

- Final Protocol Submission: 05/31/2017
- Study/Trial Completion: 11/30/2017
- Final Report Submission: 02/28/2018

PMC: Evaluation of concomitant gastric acid reducers on the pharmacokinetics of Xermelo.

- Final Protocol Submission: 05/31/2017
- Study/Trial Completion: 02/28/2018
- Final Report Submission: 04/30/2018

PMC: Evaluation of drug interaction potential via 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 in *in vitro* studies.

- Final Protocol Submission: 3/1/2017
- Study/Trial Completion: 6/30/2017
- Final Report Submission: 8/31/2017

PMC: Evaluation of drug interaction potential via induction of CYP1A2, CYP2B6, and UGT by telotristat ethyl and its major metabolites, telotristat, and LP-951757 in *in vitro* studies.

- Final Protocol Submission: 3/1/2017
- Study/Trial Completion: 6/30/2017
- Final Report Submission: 8/31/2017

PMC: Evaluation of drug interaction potential via inhibition of major transporters (BCRP, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3) by LP-951757, a major metabolite of telotristat ethyl.

- Final Protocol Submission: 3/1/2017
- Study/Trial Completion: 6/30/2017
- Final Report Submission: 8/31/2017

Meeting Discussion:
The Agency agreed with Lexicon's proposed timelines for the PMR/PMCs.

4. Additional Applicant Data

Lexicon Proposal:
The Sponsor will use specialty pharmacies to dispense Xermelo to patients. The specialty pharmacies will contact patients via phone calls on a regular basis to ensure that the prescription is filled appropriately and Xermelo is taken as indicated. During these phone calls, the specialty pharmacies may come across adverse events. Although these adverse events are collected through phone calls to patients initiated by specialty pharmacies on behalf of the Sponsor, the Sponsor proposes to submit these adverse events to the FDA as spontaneous reports rather than solicited reports. Is the proposed approach agreeable to the FDA?

Meeting Discussion:
The Agency agreed with Lexicon's proposed approach for reporting adverse events as spontaneous reports.

5. Labeling Issues

In addition to further Agency comments/suggestions, clarification is requested by Lexicon on the FDA proposed labeling revisions from November 28, 2016, specifically the following sections in the PI: Section 5.1 (Warnings and Precautions: Constipation), Section 14 (Clinical Studies: Inclusion of Figure 1 – (b) (4) Section 1 (Indication), and Section 12.2 (Pharmacodynamics). Other points of clarification may also be requested by Lexicon.

Meeting Discussion:
In regards to Section 5.1 (Warnings and Precautions: Constipation), Lexicon presented their rationale that the (b) (4) ***. The Agency indicated that*** (b) (4) ***the drug reduces bowel movements and can cause constipation. The Agency stated that they will consider the currently proposed language in the PI, and Lexicon stated that they will propose further clarity on the role of adhesions and tumor progression in the development of severe constipation. The Agency indicated that the role of disease characteristics may not be appropriate to include in the Warnings and Precautions section of the PI. The Agency also requested that Lexicon provide further information in regards to the first case study.***

Regarding Section 14 (Clinical Studies: Inclusion of Figure 1 (b) (4) ***The Agency stated that they will consider including Lexicon's proposal to add Figure 1 or their proposed text.***

Regarding Section 1 (Indications and Usage), the Agency stated that Lexicon's proposal may be reasonable, however further internal discussion and consideration is needed.

For Section 12.2 (Pharmacodynamics), the Agency agreed to consider an additional qualitative statement in regards to the relative lack of reduction in u5-HIAA levels observed in placebo patients.

In regards to the additional points of clarification, i.e., Section 6 (Adverse Reactions) and then Section 8.1 (Pregnancy), the Agency indicated that the margin calculations were extrapolated from the 500 mg TID PK data, given the linearity. A full description of how the calculations were performed was agreed to be sent to Lexicon by the Agency in a separate post-meeting communication.

6. Review Plans

FDA plans to continue its review throughout the Labeling and PMR/PMC discussion period. The Wrap-up meeting is scheduled for January 26, 2017, with an action planned to be taken some time during February 2017.

Meeting Discussion:
No additional discussion needed.

7. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

Meeting Discussion:
No additional discussion needed.

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/s/

STEPHANIE O OMOKARO
12/08/2016