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RESEARCH**

APPLICATION NUMBER:

208794Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA # 208794
Product Name: Xermelo (telotristat ethyl) Tablets

PMR 3152-1
Description: A 2-year rat carcinogenicity study.

PMR 3152-1	Final Protocol Submission:	<u>Completed</u>
Schedule Milestones:	Study/Trial Completion:	<u>09/2017</u>
	Final Report Submission:	<u>09/2018</u>

1. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

- ☒ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The sponsor has previously agreed to conduct a carcinogenicity study, which is currently ongoing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the study is to evaluate the carcinogenic potential of the drug.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies, animal studies, and laboratory experiments)?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

2-year rat carcinogenicity study.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☒ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs?
- ☒ Are the objectives clear from the description of the PMR?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMR, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA # 208794
Product Name: Xermelo (telotristat ethyl) Tablets

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

PMR 3152-2	Final Protocol Submission:	<u>06/2017</u>
Schedule Milestones:	Study/Trial Completion:	<u>09/2017</u>
	Final Report Submission:	<u>11/2017</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

Because Xermelo is being used in a chronic manner, the chance of patients taking other medications concomitantly is higher. Therefore, we recommend *in vitro* studies to fully evaluate the drug interaction potential.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The drug interaction potential by telotristat ethyl and its major metabolites, telotristat and LP-951757, has not been fully studied. Thus, additional *in vitro* drug interaction studies should be conducted to fully assess the necessity of *in vivo* drug interaction studies and to update the labeling as appropriate.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

In vitro drug interaction studies to evaluate whether Xermelo is an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☒ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs?
- ☒ Are the objectives clear from the description of the PMR?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA # 208794
Product Name: Xermelo (telotristat ethyl) Tablets

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

PMR 3152-3	Final Protocol Submission:	06/2017
Schedule Milestones:	Study/Trial Completion:	09/2017
	Final Report Submission:	11/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

Because Xermelo is being used in a chronic manner, the chance of patients taking other medications concomitantly is higher. Therefore, *in vitro* studies are needed to fully evaluate the potential for drug interaction.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The drug interaction potential by telotristat ethyl and its major metabolites, telotristat and LP-951757, has not been fully studied. Thus, additional *in vitro* drug interaction studies should be conducted to fully assess the necessity of *in vivo* drug interaction studies and to update the labeling as appropriate.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

In vitro drug interaction studies to evaluate whether Xermelo is an inducer of CYP1A2, CYP2B6, and UGT.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☒ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs?
- ☒ Are the objectives clear from the description of the PMR?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA # 208794
Product Name: Xermelo (telotristat ethyl) Tablets

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

PMR 3152-4	Final Protocol Submission:	06/2017
Schedule Milestones:	Study/Trial Completion:	09/2017
	Final Report Submission:	11/2017

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

Because Xermelo is being used in a chronic manner, the chance of patients taking other medications concomitantly is higher. Therefore, *in vitro* studies are needed to fully evaluate the potential for drug interaction.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The drug interaction potential by telotristat ethyl and its major metabolites, telotristat and LP-951757, has not been fully studied. Thus, additional *in vitro* drug interaction studies should be conducted to fully assess the necessity of *in vivo* drug interaction studies and to update the labeling as appropriate.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

In vitro drug interaction studies to evaluate whether telotristat ethyl's major metabolite, LP-951757, is an inhibitor of major transporters (BCRP, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3).

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☒ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs?
- ☒ Are the objectives clear from the description of the PMR?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA #	208794		
Product Name:	Xermelo (telotristat ethyl) Tablets		
PMR 3152-5 Description:	A clinical trial to investigate the pharmacokinetic profile of Xermelo (telotristat ethyl) and evaluate the potential for toxicity in patients with moderate and severe hepatic impairment.		
PMR 3152-5 Schedule Milestones:	Final Protocol Submission:	06/2017	
	Trial Completion:	04/2018	
	Final Report Submission:	07/2018	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

Telotristat ethyl is metabolized by carboxylesterases to form the active metabolite, telotristat. Telotristat is further metabolized to form another major metabolite. As such the reduced liver function in patients with hepatic impairment can potentially change the pharmacokinetics of telotristat and increase the risk for toxicity. The potential effects of moderate and severe hepatic impairment on the PK of Xermelo were not studied. In addition, in the pivotal phase 3 trial, patients with moderate and severe hepatic impairment were excluded. Therefore, the PK and safety of Xermelo in patients with moderate and severe hepatic impairment are unavailable. The labeling will have no specific recommendation for patients with moderate and severe hepatic impairment. No dosage adjustment is necessary for patients with mild hepatic impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This PMR study is to evaluate the risk of (potential for) toxicity in patients with moderate and severe hepatic impairment and to clarify the labeling for patients with moderate and severe hepatic impairment in terms of a need for dosage adjustment. See response to Question 1.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☒ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial in which pharmacokinetics of Xermelo (telotristat ethyl) are investigated in patients with moderate and severe hepatic impairment. In this study, patients with hepatic impairment (b) (4) should be included.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☐ Other
-

5. Is the PMR clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs?
- ☒ Are the objectives clear from the description of the PMR?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

NDA #	208794		
Product Name:	Xermelo (telotristat ethyl) Tablets		
PMC 3152-6 Description:	Evaluation of concomitant gastric acid reducers on the pharmacokinetics of Xermelo (telotristat ethyl).		
PMC 3152-6 Schedule Milestones:	Final Protocol Submission:	05/2017	
	Study/Trial Completion:	02/2018	
	Final Report Submission:	04/2018	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☒ Theoretical concern
- ☐ Other

Telotristat ethyl has a pH-dependent solubility, i.e., the solubility decreases as the pH increases (> 71 mg/mL at pH 1 and 0.0083 mg/mL at pH 5 in phosphate buffer). As such in patients who are on gastric acid inhibitors, such as proton pump inhibitors, a lower absorption of Xermelo that may lead to reduced efficacy cannot be ruled out. In the phase 3 trial, 29-60% of patients were concurrently using acid related drugs including omeprazole, a proton pump inhibitor. In a subgroup analysis, loss of efficacy was not evident in patients who reportedly took gastric acid reducers. Nevertheless, exact information such as the dose and treatment duration was not required to be documented during the trial. Given the theoretical nature of the concern, this study can be conducted as a post-marketing study instead of a pre-approval requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This PMC study will be used to update the labeling by clarifying the potential effects of concurrent gastric acid reducers or the lack of such effects on the PK of Xermelo and the dosing recommendation, if needed, to ensure consistent efficacy in patients on concomitant gastric acid reducers.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- ☐ Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

(b) (4) drug interaction study (b) (4) to evaluate the effects of (b) (4) on (b) (4) the PK of telotristat ethyl, Xermelo.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies
- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials

- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
 - ☐ Immunogenicity as a marker of safety
 - ☐ Other (provide explanation)
-

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

-
- ☒ Other
Drug interaction study
-

5. Is the PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMCs?
- ☒ Are the objectives clear from the description of the PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

- ☐ Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- ☐ There is a significant question about the public health risks of an approved drug
- ☐ There is not enough existing information to assess these risks
- ☐ Information cannot be gained through a different kind of investigation
- ☐ The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- ☐ The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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
02/28/2017

STEPHANIE O OMOKARO
02/28/2017

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: Jan 3, 2017

From: Zhengfang Ge, Ph.D.
ONDP/Division II/Branch V

Through: Moo-Jhong Rhee, Ph.D.
Chief, ONDP/Division II/Branch V

To: CMC Review #1 of NDA 208794

Subject: Final labeling/labels

The Labeling review #1 has noted the following pending issues:

1. Regarding Highlight section
 - The established name should be changed to (telotristat ethy) tablets per CDER Salt Nomenclature policy
 - The Dosage Forms and Strengths should be displayed as “Tablets: 250 mg telotristat ethy”
2. Regarding # 3: Dosage Forms and Strengths
 - This section should be changed to “Tablets: 250mg telotristat ethyl is a white to”
3. Regarding #11: Description section
 - The 1st sentence should be changed to “Xermelo (telotristat ethyl) tablets contain telotristat ethyl as telotristat etiprate, a tryptophan hydroxylase inhibitor”
 - “Each Xermelo tablet contains 250 mg of telotristat ethyl (free base) which is equivalent to 328 mg telotristat etiprate” should be added.
 - (b) (4) should be removed from the active ingredients.
4. Regarding #16: How Supplied/Storage and Handling
 - In order to avoid potential medical errors using (b) (4), drug product samples have been requested through DMEPA. A final decision for a better description will be decided after receiving the drug product.

And because of these deficiencies, in the Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

On December 7, 2016, the applicant amended the labeling and the above issues are satisfactorily resolved. In addition, carton/container labels were also modified based on the recommendation from DMEPA (see the **Attachment**). These changes are acceptable from CMC perspective.

Recommendation:

This NDA is **now** recommended for approval from the labeling perspective.

Attachment: Final labeling and labels

Highlight

XERMELO (telotristat ethyl) tablets, for oral use

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 250 mg telotristat ethyl (3)

3. DOSAGE FORMS AND STRENGTHS

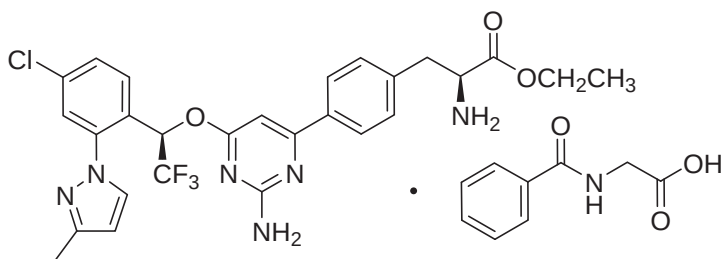
Tablets: 250 mg telotristat ethyl; white to off-white, coated and oval with “T-E” debossed on oneside and “250” debossed on the other side.

11. DESCRIPTION

Xermelo (telotristat ethyl) tablets contain telotristat ethyl as telotristat etiprate, a tryptophan hydroxylase inhibitor. Telotristat etiprate is the hippurate salt of telotristat ethyl [(S)-ethyl 2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoate], which undergoes hydrolysis to the active metabolite, (S)-2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)-2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoic acid.

The molecular formula of telotristat etiprate is $C_{27}H_{26}ClF_3N_6O_3 \cdot C_9H_9NO_3$ and its molecular weight is 754.2. The molecular weight of the free base (telotristat ethyl) is 575.0.

Chemical Structure:



Telotristat etiprate is a white to off-white solid. The solubility is a function of pH at 25°C; at pH 1 (0.1N HCl), the solubility is >71 mg/mL (8) at pH 3 phosphate buffer, the solubility is 0.30 mg/mL, at pHs 5–9, the solubility is negligible. In organic solvents, telotristat etiprate is freely soluble in methanol, soluble in acetone, and sparingly soluble in ethanol.

Each Xermelo tablet contains 250 mg of telotristat ethyl (free base) which is equivalent to 328 mg telotristat etiprate. The inactive ingredients of Xermelo tablets include: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose anhydrous, macrogol/PEG, magnesium stearate, polyvinyl alcohol [part hydrolyzed], talc and titanium dioxide.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

250 mg tablet: white to off-white coated oval tablet with “T-E” debossed on one side and “250” debossed on the other side.

Xermelo is dispensed in a monthly case for a total of 28 days of therapy. Each monthly case contains four weekly boxes. Each weekly box contains seven daily dose packs (day pack).

- NDC 70183-125-84: Monthly case of 84 tablets. Each child resistant daily dose pack (day pack) contains three 250 mg tablets.

Storage

Store at 25°C (77°F); excursions permitted to (b) (4) [see USP Controlled Room Temperature]

Label for 28 Day Case:



Label for 7-Day Box:

(b) (4)



Label for Daily Dose Pack:

(b) (4)





Moo Jhong
Rhee

Digitally signed by Moo Jhong Rhee
Date: 1/03/2017 04:37:54PM
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Zhengfang
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Date: 1/03/2017 04:36:54PM
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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: December 21, 2016

To: Benjamin Vali, MS
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products (DGIEP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

Subject: NDA # 208794 – XERMELO (telotristat ethyl) tablets, for oral use

Reference is made to DGIEP's consult request dated November 15, 2016, requesting review of the proposed Package Insert (PI) and Carton/Container labeling for XERMELO (telotristat ethyl) tablets, for oral use.

OPDP has reviewed the proposed PI entitled, "NDA 208794 - 07Dec2016 Applicant Response_Clean.docx" that was accessed via SharePoint on December 21, 2016, at 9:05am. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling entitled:

- te-ethyl-tablets-1x3-7-day-box-china-0044.pdf
- te-ethyl-tablets-1x3-7-day-box-switzerland-0044.pdf
- te-ethyl-tablets-1x3-28-day-case-china-0044.pdf
- te-ethyl-tablets-1x3-28-day-case-switzerland-0044.pdf
- te-ethyl-tablets-1x3-shellpak-china-0044.pdf
- te-ethyl-tablets-1x3-shellpak-switzerland-0044.pdf

that was accessed via SharePoint on December 8, 2016, at 10:00am. OPDP has no comments at this time on the proposed Carton/Container labeling.

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ADEWALE A ADELEYE
12/21/2016

CLINICAL OUTCOME ASSESSMENT CONSULT REVIEW

Template version: June 24, 2015

CLINICAL OUTCOME ASSESSMENT (COA)	AT 2016-106
TRACKING NUMBER	
IND/NDA/BLA NUMBER	NDA 208794
LETTER DATE/SUBMISSION NUMBER	
PDUFA GOAL DATE	February 28, 2017
DATE OF CONSULT REQUEST	March 23, 2016
REVIEW DIVISION	Division of Gastroenterology and Inborn Errors Products (DGIEP)
MEDICAL REVIEWER	Wenp-Yi Gao
REVIEW DIVISION PM	Brian Strongin
PRIMARY COA REVIEWER	Wen-Hung Chen
SECONDARY COA REVIEWER	
ASSOCIATE DIRECTOR, COA STAFF (ACTING)	Elektra Papadopoulos
REVIEW COMPLETION DATE	November 15, 2016
ESTABLISHED NAME	Telotristat etiprate
TRADE NAME	Xermelo
SPONSOR/APPLICANT	Lexicon Pharmaceuticals, Inc.
CLINICAL OUTCOME ASSESSMENT TYPE	Patient-reported outcome (PRO)
ENDPOINT(S) CONCEPT(S)	Frequency of bowel movement
MEASURE(S)	Number of bowel movement question in DiaryPRO
INDICATION	Telotristat etiprate is a tryptophan hydroxylase inhibitor indicated for the (b) (4) treatment of carcinoid syndrome (CS) in patients with metastatic neuroendocrine tumors who are receiving somatostatin analog (SSA) therapy.
INTENDED POPULATION(S)	Patients with metastatic neuroendocrine tumors who are receiving SSA therapy with inadequately controlled CS

Clinical Outcome Assessment Review

Wen-Hung Chen

NDA 208794

Telotristat etiprate (Xermelo)

BM Question in DiaryPRO

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment review is provided as a response to a request for consultation by the Division of Division of Gastroenterology and Inborn Errors Products (DGIEP) regarding NDA 208794. The Applicant used the Number of Bowel Movement question in the DiaryPRO for the measurement of frequency of bowel movement (BM) as the primary endpoint in a Phase 3 study, LX1606.1-301-CS (LX1606.301), and as the secondary endpoint in another Phase 3 study, LX1606.1-303-CS (LX1606.303), in males and females patients, age 18 and older, with histopathologically confirmed, well differentiated, metastatic neuroendocrine tumors (NETs) with a documented history of carcinoid syndrome (CS), currently experiencing ≥ 4 BMs/day (uncontrolled CS), on a stable-dose somatostatin analog (SSA) therapy. The targeted labeling claim is “Xermelo is a tryptophan hydroxylase inhibitor indicated (b) (4) for the treatment of (u) (4) ”.

The review concludes that the evidence submitted by the applicant is adequate to demonstrate that the Number of BM Question in the DiaryPRO is adequate to measure the frequency of BM in the proposed context of use. The patient exit interview study and PRO psychometric analysis suggested that reduction of two BMs or 30% from baseline per day was considered meaningful by the patients.

High-level comments:

- The “Number of BM Question” in the DiaryPRO is a single item asking patients the number of BM that they had in the past 24 hours. Patients recorded the number of daily BMs in the daily diary. The Number of BM Question in the DiaryPRO is adequate to measure the frequency of BM in the proposed context of use.
- Reduction of two BMs or 30% from baseline per day was considered meaningful by the patients interviewed in the patient-reported outcome sub-study (patient exit interviews conducted in study LX1606.301).
- However, “durable response” defined as “reduction of at least 30% in BM frequency from Baseline for at least 50% of the days of participation in the double-blinded trial period” was not appraised by the patients during the exit interviews. This definition is less rigorous than requiring 30% reduction per day during the study as the patients remarked during the exit interview. In addition, statistical testing of “durable response” was conducted as other efficacy analysis without controlling for multiplicity (i.e., Type I error).

Clinical Outcome Assessment Review

Wen-Hung Chen

NDA 208794

Telotristat etiprate (Xermelo)

BM Question in DiaryPRO

B. SUGGESTED COMMENTS TO SPONSOR/APPLICANT

No questions were submitted by the sponsor/applicant. In response to the Review Division's request for review, we have the following comments:

- Reduction of two BMs or 30% from baseline per day is considered meaningful by the patients interviewed in the patient-reported outcome sub-study (patient exit interviews conducted in study LX1606.301). However, this responder definition was not proposed as a study endpoint.
- “Durable response” defined as “reduction of at least 30% in BM frequency from Baseline for at least 50% of the days of participation in the double-blinded trial period” was not appraised by the patients during the exit interviews. In addition, statistical testing of “durable response” was conducted as other efficacy analysis without controlling for multiplicity (i.e., Type I error).

C. CLINICAL OUTCOME ASSESSMENT REVIEW

Materials reviewed:

- Study protocol: LX1606.1-301-CS, “A Phase 3, Randomized, Placebo-controlled, Parallel group, Multicenter, Double-blind Study to Evaluate the Efficacy and Safety of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome Not Adequately Controlled by Somatostatin Analog (SSA) Therapy”; Lexicon Pharmaceuticals, Inc., February 16, 2016
- Study protocol: LX1606.1-303-CS, “A Phase 3, Randomized, Placebo-controlled, Multicenter, Double-blind Study to Evaluate the Safety and Efficacy of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome”; Lexicon Pharmaceuticals, Inc., Mar 03, 2016
- Psychometric report: “Evaluation of Meaningful Change in Bowel Movement Frequency: TELESTAR Analyses”, Version 4, Lexicon Pharmaceuticals, Inc., February 23, 2016
- Patient exit interview substudy report: “Lx1606.301 Substudy: Assessing Treatment Benefit of Telotristat Etiprate in Patients with Carcinoid Syndrome: Patient Exit Interviews and Select Clinical Trial Results”, Lexicon Pharmaceuticals, Inc., January 22, 2016

Clinical Outcome Assessment Review

Wen-Hung Chen

NDA 208794

Telotristat etiprate (Xermelo)

BM Question in DiaryPRO

- Study report: “LX1606.1-301-CS INTERIM CLINICAL STUDY REPORT”, Lexicon Pharmaceuticals, Inc., February 16, 2016

1 CONTEXT OF USE (COU)

1.1 Target Study Population and Clinical Setting

The target study population is males and females patients, age 18 and older, with histopathologically confirmed, well differentiated, metastatic neuroendocrine tumors (NETs) with a documented history of carcinoid syndrome (CS), currently experiencing ≥ 4 BMs/day (uncontrolled CS), on a stable-dose somatostatin analog (SSA) therapy.

Study LX1606.1-303-CS is a companion study to the LX1606.1-301-CS trial will enroll patients on SSA therapy who have < 4 BMs per day with ≥ 1 sign/symptoms of CS or patients who are not on SSA therapy with ≥ 1 sign/symptoms of CS (see Inclusion criterion 4). Patients who have previously screened in the LX1606.1-301-CS study and have not met the study criteria may be eligible for this study.

Study LX1606.1.301-CS:

The key inclusion criteria for study LX1606.301 are as the followings:

1. Patients ≥ 18 years of age at the time of the Screening visit
2. Histopathologically-confirmed, well-differentiated metastatic NET with extent documented by computed tomography (CT), magnetic resonance imaging (MRI), or radionuclide imaging
3. A documented history of CS, and currently experiencing an average of ≥ 4 bowel movements per day during the Run-in Period. Confirmation of eligibility will be determined by measuring the mean number of BMs
4. Currently receiving a stable-dose SSA therapy. For the purposes of this study, stable-dose SSA therapy is defined as long acting release (LAR) or Depot SSA therapy or a continuous subcutaneous infusion via a pump. Patients must have been receiving the same dose level and frequency for at least 3 months prior to entering the Run-in Period

The key exclusion criteria for study LX1606.301 are as the followings:

1. Presence of diarrhea attributed to any condition(s) other than CS (including, but not limited to fat malabsorption or bile acid malabsorption)

Clinical Outcome Assessment Review

Wen-Hung Chen

NDA 208794

Telotristat etiprate (Xermelo)

BM Question in DiaryPRO

2. Presence of more than 12 watery BMs per day associated with volume contraction, dehydration, or hypotension compatible with a “pancreatic cholera”-type clinical syndrome, as judged by the Investigator
3. Positive stool examination for enteric pathogens, pathogenic ova or parasites, or *Clostridium difficile* at Screening
4. Karnofsky Performance Status $\leq 60\%$

Study LX1606.1-303-CS:

The key inclusion criteria for study LX1606.303 are as the followings:

1. Patients ≥ 18 years of age at the time of the Screening visit
2. All patients of reproductive potential must agree to use an adequate method of contraception (defined as having a failure rate of $<1\%$ per year) during the study and for 12 weeks after the Follow-up visit. Adequate methods of contraception for patient or partner include condoms with spermicidal gel, diaphragm with spermicidal gel, coil (intrauterine device), surgical sterilization, vasectomy, oral contraceptive pill, depot progesterone injections, progesterone implant, and abstinence during the study and for 12 weeks after the Follow-up visit. **Note:** For females, childbearing potential is defined as those who have not undergone surgical sterilization, or those who are not considered postmenopausal. Post menopause is defined as absence of menstruation for at least 2 years. If necessary, follicle-stimulating hormone (FSH) results >50 IU/L at Screening are confirmatory in the absence of a clear postmenopausal history.
3. Histopathologically-confirmed, well-differentiated metastatic (NET confirmed by computed tomography (CT), magnetic resonance imaging (MRI), or radionuclide imaging

The key exclusion criteria for study LX1606.303 are as the followings:

1. Presence of diarrhea attributed to any condition(s) other than CS including, but not limited to, fat malabsorption or bile acid malabsorption
2. Presence of >12 watery BMs per day associated with volume contraction, dehydration, or hypotension compatible with a “pancreatic cholera”-type clinical syndrome, as judged by the Investigator
3. Positive stool examination for enteric pathogens, pathogenic ova or parasites, or *Clostridium difficile* at Screening
4. Karnofsky Performance Status $\leq 60\%$

1.2 Clinical Trial Design, Protocol, and Analysis Plan

Clinical Outcome Assessment Review

Wen-Hung Chen

NDA 208794

Telotristat etiprate (Xermelo)

BM Question in DiaryPRO

Study LX1606.1.301-CS:

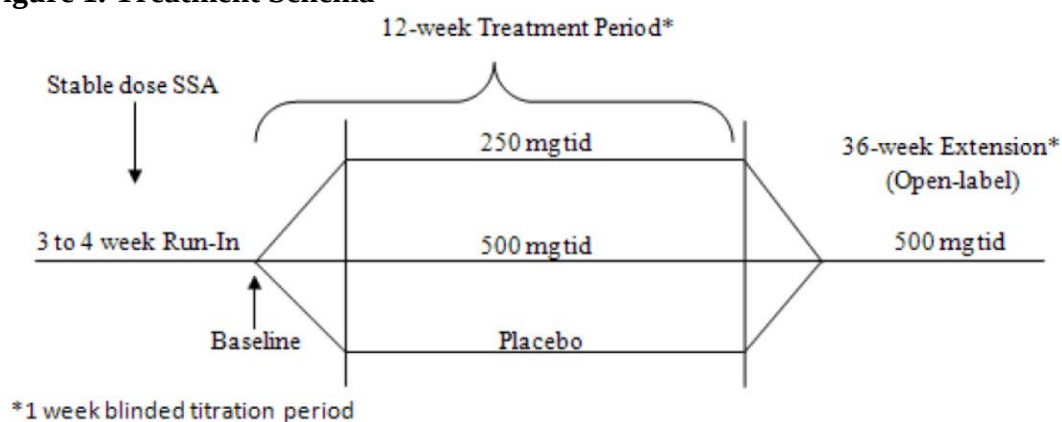
Study LX1606.301 was conducted as a Phase 3, randomized, placebo controlled, parallel-group, multicenter, double-blind study in patients with CS not adequately controlled by SSA therapy to evaluate 2 oral dose levels of telotristat etiprate, 250 and 500 mg 3 times daily (tid), versus placebo.

A minimum of 105 patients not adequately controlled by a stable-dose of octreotide therapy indicated for the treatment of CS and approved by the Food and Drug Administration (FDA) were expected to participate in this study.

After the Screening/Run-in Period, eligible patients were to be randomly assigned (1:1:1 ratio) on Day 1 to receive 1 of 2 oral dose levels of telotristat etiprate (250 or 500 mg) or placebo, each given tid for 12 consecutive weeks. A blinded titration was to occur during the first 7 days for patients assigned to 500 mg tid. During the titration, all patients were to take 2 tablets tid (1 × 250-mg telotristat etiprate tablet and 1 placebo tablet or 2 placebo tablets). After 7 days, patients were to receive their assigned treatment and dose level for the remaining 11 weeks of the DBT Period. All patients were to remain on their Baseline dosage of SSA therapy for the duration of the DBT Period.

The treatment schema is summarized in Figure 1.

Figure 1. Treatment Schema



Study LX1606.1-303-CS:

Study LX1606.303 was conducted as a Phase 3, randomized, placebo-controlled, parallel-group, multicenter, double-blind study in patients with CS to evaluate 2 oral dose levels of telotristat etiprate, 250 mg and 500 mg tid, versus placebo. Patients with histopathologically confirmed,

Clinical Outcome Assessment Review

Wen-Hung Chen

NDA 208794

Telotristat etiprate (Xermelo)

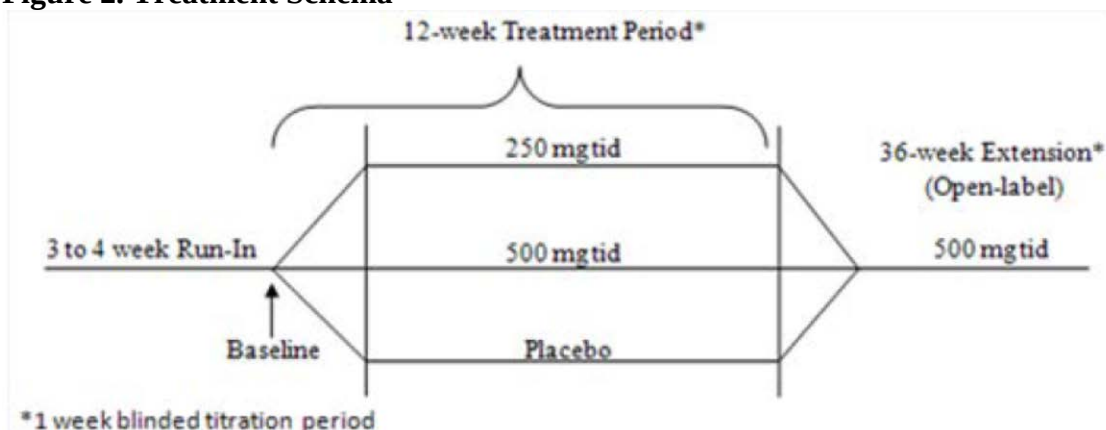
BM Question in DiaryPRO

well-differentiated NET and a documented history of CS were to be screened for this study. This companion study to the LX1606.1-301-CS study was designed to enroll patients receiving SSA therapy who had <4 BMs/day with ≥ 1 signs/symptoms of CS or patients who were not receiving SSA therapy with ≥ 1 signs/symptoms of CS (see inclusion criterion 4). Patients receiving SSA therapy with ≥ 4 BMs/day may have been considered for enrollment in the LX1606.1-301-CS study. Patients who were previously screened for the LX1606.1-301-CS study and did not meet the entry criteria may have been eligible for this study.

Patients were to enter into a Screening/Run-in Period of at least 3 weeks to establish Baseline symptoms. During the Run-in Period, no changes to SSA therapy were to occur. Patients receiving SSA therapy were to continue to receive stable-dose SSA therapy and those not currently receiving SSA therapy were to remain without SSA therapy in order to establish Baseline characteristics and symptomatology. For the purposes of this study, stable-dose SSA therapy was defined as LAR or depot SSA therapy or a continuous subcutaneous infusion via a pump at the same dose level and frequency for at least 3 months before the Run-in Period. In addition, therapy with rescue short-acting SSA was to be permitted as clinically indicated. Only patients who completed the Screening/Run-in Period and were $\geq 75\%$ compliant with diary entries were to be considered eligible for the DBT Period of the study. Patient diaries were to be completed at the end of each study day. In the daily diary, patients were to record the number of BMs over a 24-hour period, consistency of each BM based on the Bristol Stool Form Scale, abdominal pain, nausea, frequency of rescue SSA use, number of flushing episodes, and presence of urgency to defecate.

The treatment schema is summarized in Figure 2.

Figure 2. Treatment Schema



1.3 Endpoint Positioning

Study LX1606.1.301-CS:

Clinical Outcome Assessment Review

Wen-Hung Chen

NDA 208794

Telotristat etiprate (Xermelo)

BM Question in DiaryPRO

The primary efficacy endpoint is the change from Baseline in the number of daily BMs averaged over the 12-week double-blind portion (Treatment Period) of the trial.

Secondary efficacy endpoints include:

- Change from Baseline in urinary 5-HIAA levels at Week 12
- Change from Baseline in the number of daily cutaneous flushing episodes averaged across all time points
- Change from Baseline in abdominal pain averaged across all time points

Other efficacy endpoints of key interest include the following:

- Proportion of patients with durable response, defined as the proportion of responders with $\geq 30\%$ reduction in daily number of BMs for $\geq 50\%$ of time over the double-blind portion of the study
- Change from Baseline in overall and domain scores of the EORTC QLQ-C30 & GI.NET21 averaged across all time points and at each study visit where collected
- Change from Baseline in the daily number of cutaneous flushing episodes at each study week
- Change from Baseline in abdominal pain averaged at each study week
- Change from Baseline in BM frequency averaged at each study week
- Change from Baseline in stool consistency averaged across all time points and averaged at each study week
- Proportion of weeks in which patients report adequate relief of CS symptoms associated with GI symptoms
- Proportion of patients that report adequate relief of CS symptoms associated with GI symptoms at each study week
- Change from Baseline in subjective global assessment of CS symptoms on an 11- point NRS averaged across all time points and at each study week
- Proportion of days where urgency/immediate need to defecate is reported
- Proportion of days with reports of nausea
- Change from Baseline in the sensation/severity of nausea averaged across all time points and at each study week
- Number of days with $\geq 30\%$ reduction in number of BMs from individual Baseline mean
- Number of days with ≥ 1.5 reduction in number of BMs from individual Baseline mean
- Time to first $\geq 30\%$ worsening in BM frequency, defined as time to the first day of 2 consecutive weeks with a mean BM frequency at least 30% above the individual Baseline mean
- Time to first sustained $\geq 30\%$ improvement from Baseline in BM frequency, defined as time to the first day of a 2 consecutive weeks with a mean BM frequency at least 30% below the individual Baseline mean
- Others (see study protocol)

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Study LX1606.1.303-CS:

The primary efficacy endpoint of this study is the percent (%) change from Baseline in 24-hour urinary 5-HIAA levels at Week 12.

The secondary efficacy endpoints include:

- Change from Baseline in the number of daily BMs averaged over a 12-week treatment period
- Change from Baseline in stool consistency averaged across all time points
- Change from Baseline in the number of cutaneous flushing episodes
- Change from Baseline in abdominal pain averaged across all time points
- Change from Baseline in the frequency of rescue short-acting SSA is used to treat CS symptoms
- Change from Baseline in the number of daily BMs averaged over the 12-week treatment period and at each study week, among patients who are not on an SSA at Baseline

Other efficacy endpoints include the following:

- Pharmacodynamic (PD) effects of telotristat etiprate on 5-HIAA levels in urine over time versus Baseline
- Change from Baseline in BM frequency averaged at each study week
- Change from Baseline in stool consistency, as measured by the Bristol Stool Form Scale at each study week
- Proportion of patients who report adequate relief of CS symptoms associated with GI symptoms at each study week
- Number of days with $\geq 30\%$ reduction (each calculated separately) from individual Baseline mean
- Number of days with ≥ 1.5 reduction in the number of BMs from individual Baseline mean
- Time to first $\geq 30\%$ worsening in BM frequency, defined as time to the first day of 2 consecutive weeks with a mean BM frequency of $\geq 30\%$ above the individual Baseline mean
- Time to first sustained $\geq 30\%$ improvement from Baseline in BM frequency, defined as time to the first day of 2 consecutive weeks with a mean BM frequency of $\geq 30\%$ below the individual Baseline mean
- Durability, defined as the proportion of responders with $\geq 30\%$ reduction in daily number of BMs for $\geq 50\%$ of time over the double-blind portion of the study
- Others (see study protocol)

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1.4 Labeling or promotional claim(s) based on the COA

The targeted labeling claim is “Xermelo is a tryptophan hydroxylase inhibitor indicated (b) (4) for the treatment of (b) (4) (b) (4) ”.

2 CONCEPT OF INTEREST (COI) AND CONCEPTUAL FRAMEWORK

The concept of interest is the number of BM during the past 24 hours.

3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

The measurement of BM frequency has many precedents in scientific literature with regards to studies evaluating SSA therapy as a measure of efficacy for symptom control. The COA measures used is the patients recorded number of daily BMs as part of the electronic daily diary. It is a single item with direct input of the numbers of BM.

How many bowel
movements have you had in
the last 24 hours?



4 CONTENT VALIDITY

Content validity of the single item number of BM in the last 24 hours is supported by patient exit interviewed conducted as a substudy of Study LX1606.301.

The results of the exit interview substudy illustrated substantial burden that patients with CS experience. Among patients with CS who experienced ≥ 4 BMs per day at baseline, frequent and urgent BMs were the most salient symptoms to treat. Improvements in these symptoms may have allowed patients to better enjoy life, leave the house, and participate in social and other activities.

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A total of 35 patients were recruited across 16 clinical sites and 5 countries and completed the exit interview substudy. Patients' reported the following CS symptom experiences prior to starting the LX1606.301 clinical trial:

- Participants reported experiencing a number of CS symptoms before starting the trial.
- BM-related symptoms (ie, too frequent BMs, diarrhea, loose and watery stools, and urgent BMs) were reported most frequently; all 35 interview participants reported experiencing at least 1 BM-related CS symptom prior to starting the trial. Too frequent BMs was the most frequently reported CS symptom (n = 34, 97.1%).
- Participants also commonly described diarrhea as a multifaceted concept that included more than 1 BM related symptom (most commonly altered stool form, increased BM frequency, and urgency). Patients' descriptions of the CS symptoms that were most important to treat and the most bothersome were as follows:
- Patients identified diarrhea (n = 17), BM frequency (n = 9), and urgency (n = 5) as the single most important symptom to treat; all but 2 participants indicated that the same symptoms were the most bothersome CS symptoms.
- Among the participants who identified diarrhea as being one of the most important symptoms to treat, all ranked BM frequency or urgency as the single most important aspect of diarrhea to improve; none of these participants reported stool consistency as the single most important aspect of their diarrhea to improve.

Patients' descriptions of the impact of CS symptoms on their lives were as follows:

- The negative impacts of CS symptoms on social and/or physical activities/hobbies were reported most frequently, closely followed by emotional and energy areas.
- Interview participants indicated that certain CS symptoms had greater impact on their lives than others, with too frequent BMs followed by urgent BMs as the most commonly reported impactful symptom.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

Full analysis of measurement properties of the frequency of BM was not conducted. However, given that it is a simple single question recording the number of BM in the past 24 hours, full analysis is not needed.

The Application conducted ability to detect change analysis (responsiveness) of BM frequency to various levels of patient reported change (as assessed during the exit interview) and reported statistically significant differences in effect size estimates for the perception of change item for both overall change and change from Week 12. The limitation was the analysis was based on a

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small number of subjects interviewed (N=35) following completion of the Double-blind Treatment Period.

6 INTERPRETATION OF SCORES

An anchor-based analysis of thresholds of meaningful overall change in BM frequency was conducted among ITT patients using patient-reported adequate relief at Week 12, the EORTC QLQC30 Diarrhea Symptom domain, and responders on the EORTC GI.NET21 GI Symptoms Domain as the anchors. This analysis produced average BM changes among ITT patients who reported adequate relief at Week 12 (-1.90), responders on the EORTC QLQC30 Diarrhea Symptom domain (-1.71), and responders on the EORTC GI.NET21 GI Symptoms Domain (-1.88).

Anchor-based method applied to patient exit interview data based on patient response on the question: “Since your started the study medication, would you say that the number of your bowel movement now is...” yielded average change of -2.50 for overall change during the Double-blind Treatment Period and -3.14 for change between Baseline and Week 12 for those who responded with “a great deal better”. Based on the same anchor question, the average BM change was -0.87 for overall change during the Double-blind Treatment Period and -1.05 for change between Baseline and Week 12 for those who responded with “much better”.

Other exit interview items, such as “Satisfaction with relief of CS symptoms since starting study medications” yielded average BM change from -2.07 for overall Change and -2.43 for Change from Baseline to Week 12 for those who responded with “very satisfied”. Based on the same anchor question, the average BM change was -0.26 for overall change during the Double-blind Treatment Period and -0.67 for change between Baseline and Week 12 for those who responded with “somewhat satisfied”.

During the exit interview substudy, most participants reported that they would need to have at least a 30% reduction in the number of BMs per day for the change to be considered an improvement. The majority (n = 28; 82.4%) of participants were able to provide a response describing the smallest reduction in BM frequency that they considered meaningful (Table 1, Column 3). Across the 28 participants who answered this question, the amount of change required for an improvement in BM frequency to be meaningful varied from a range of 1 to 7 BMs per day from a range of pre-treatment of 3 to 15 BMs per day; 9 participants provided responses as low as 1, and 1 participant provided a response of 7 a day. The average minimal reduction needed was 2.6 bowel BMs per day. Of note, the amount of change required to be considered meaningful seemed to depend largely on number of BMs per day the participant typically experienced at the start of the study (Table 1, Column 2). Specifically, a trend was noted that suggested that the higher the typical stool frequency pre study, the larger the reduction needed to have a meaningful change (or to move toward “normalcy”). Therefore, when reduction

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was calculated as a percentage change, the majority of participants (n = 17/28, 60.7%) reported that they would need to see at least a 30% reduction (range 14%-64%) in the number of BMs per day for the change to be considered an improvement.

Table 1 Minimal Important Difference: Reduction in Bowel Movement Frequency (N = 34)

Participant	Average Daily BMs (Before Trial)	Minimal BM Reduction Needed n (%) ^a	BM Reduction = A Little Better ^b n (%) ^a
Column 1	Column 2	Column 3	Column 4
0101-001	9 (8-10)	3 (33)	2.5 (2-3; 28)
0101-003	6.5 (6-7)	2 (31)	3.5 (3-4; 54)
0101-004	4	1 (25)	—
0101-005	4.5 (4-5)	2 (44)	1.5 (1-2; 33)
0103-001	10 (8-12)	5 (4-6 ^c ; 50)	—
0103-002	4.5 (4-5)	1 (22)	1 (22)
0104-006	4.5 (3-6)	2 (44)	2 (44)
0106-002	5	2 (40)	1 (20)
0106-004	4.5 (4-5)	1 (22)	1.5 (1-2; 33)
0108-001	6 (4-8)	2.5 (2-3; 42)	2 (33)
0108-002	10	3 (30)	2 (20)
0108-003	10 (9-11)	5.5 (5-6 ^c ; 55)	3 (30)
0108-004	7	1 (14)	1 (14)
0108-005	3.5 (3-4)	1 (29)	1 (29)

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Participant	Average Daily BMs (Before Trial)	Minimal BM Reduction Needed n (% ^a)	BM Reduction = A Little Better ^b n (% ^a)
0108-006	14	–	4 (29)
0108-007	8	3 (38)	3 (38)
0108-008	11	1.5 (1-2;14)	4 (36)
0109-004	12.5 (10-15)	5 (40)	–
0109-005	6	2 (33)	1.5 (1-2; 25)
0109-007	10	–	–
0115-001	5	1 (20)	1 (20)
0115-002	10 (8-12)	5 ^c (50)	3.5 (3-4; 35)
0116-003	9 (4-14)	–	3 (33)
0603-001	13.5 (13-14)	–	–
0606-004	5	–	–
0606-007	9 (8-10)	5 (56)	–
0609-001	3.5 (3-4)	2 (57)	–
0702-003	5.5 (5-6)	–	1.5 (1-2;27)
0709-001	7 (4-10)	4.5 (4-5; 64)	2 (29)
0902-006	5 (3-7)	1 (20)	1 (20)
0902-009	3.5 (3-4)	1 (29)	–
2103-003	12	7 (58)	6 (50)
2103-004	4	1 (25)	1 (25)
2107-002	5.5 (5-6)	1.5(1-2;27)	1.5 (1-2; 27)
BM = bowel movement.			
Note: Where a range of numbers was reported, the midpoint was taken to compute percentages.			
^a Percentage denominator = the number of average daily BMs participant self-reported (column 1).			
^b Participant responses to “What bowel movement reduction constitutes “A little better?”			
^c Patient provided a percentage instead of a number when describing the minimal reduction needed (thus the number shown is derived based upon their average daily BM).			

Based on all findings, it is reasonable to define meaningful reduction of BM as reduction of 2 BM or 30% reduction from baseline per day.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The translation guide was provided for review. The translation guide described the process and guideline of the translation from translating English to Spanish for DiaryPRO. The translation process appears to be adequate.

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8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Not applicable.

9 REVIEW USER MANUAL

A detailed DiaryPRO site manual was provided. The manual describes how the study site coordinator would set up the system, train the patients on how to use the DiaryPRO (completing the Evening Report and charging the DiaryPRO every evening), and how to collect DiaryPRO from the patients. The site training manual appeared to be adequate.

10 KEY REFERENCES FOR MEASURE

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D. APPENDICES (INCLUDE COPY OF INSTRUMENT)

Append 1. DiaryPRO

APPEARS THIS WAY ON ORIGINAL

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Telotristat etiprate (Xermelo)

BM Question in DiaryPRO

DIARYpro screen shots

Patient setup screens:

(b) (4)



➤ Full text:

(b) (4)



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➤ If patient declines the following text will appear:



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(b) (4)



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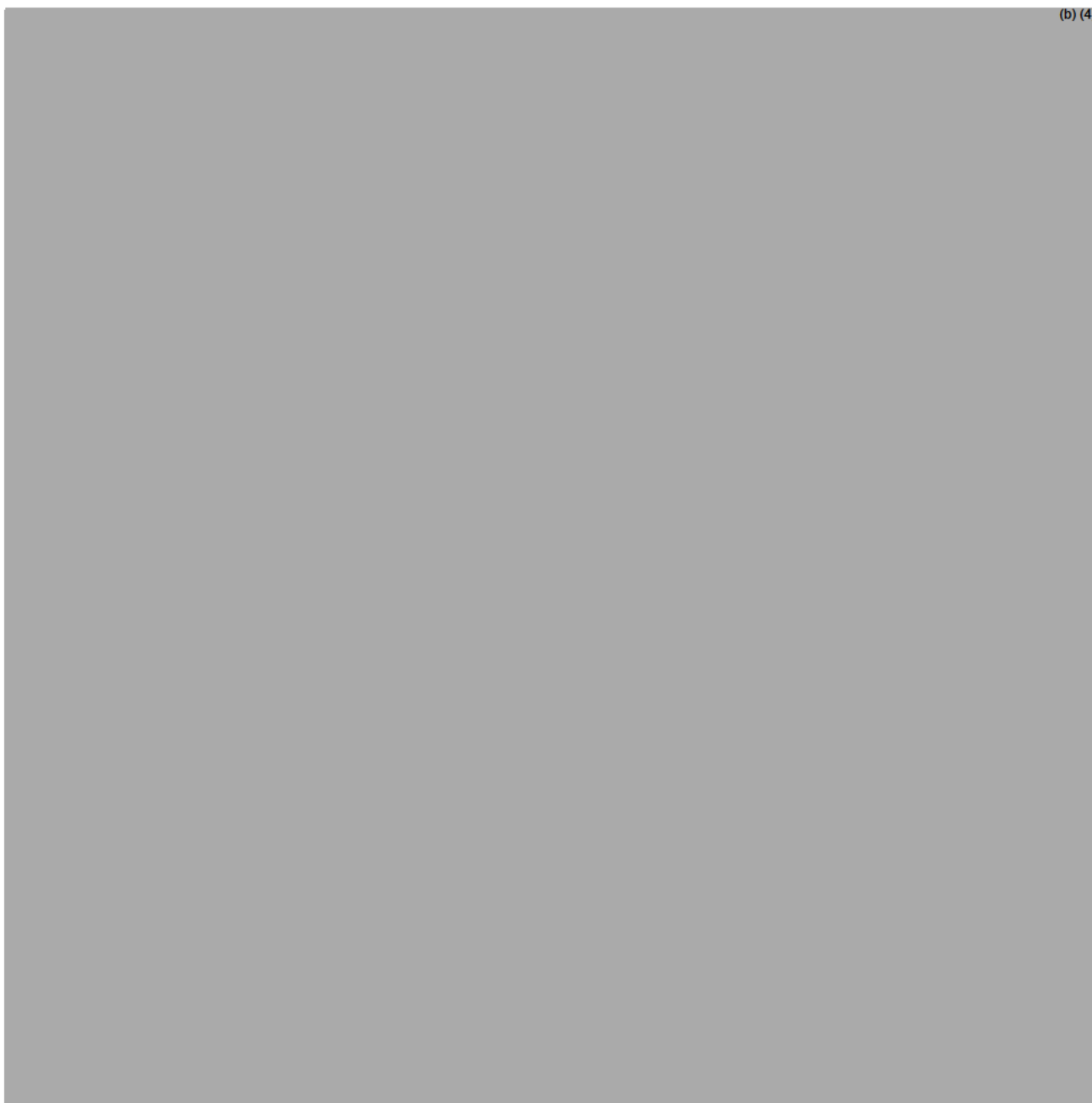
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DIARYpro screen shots

Patient Daily Diary Screens:



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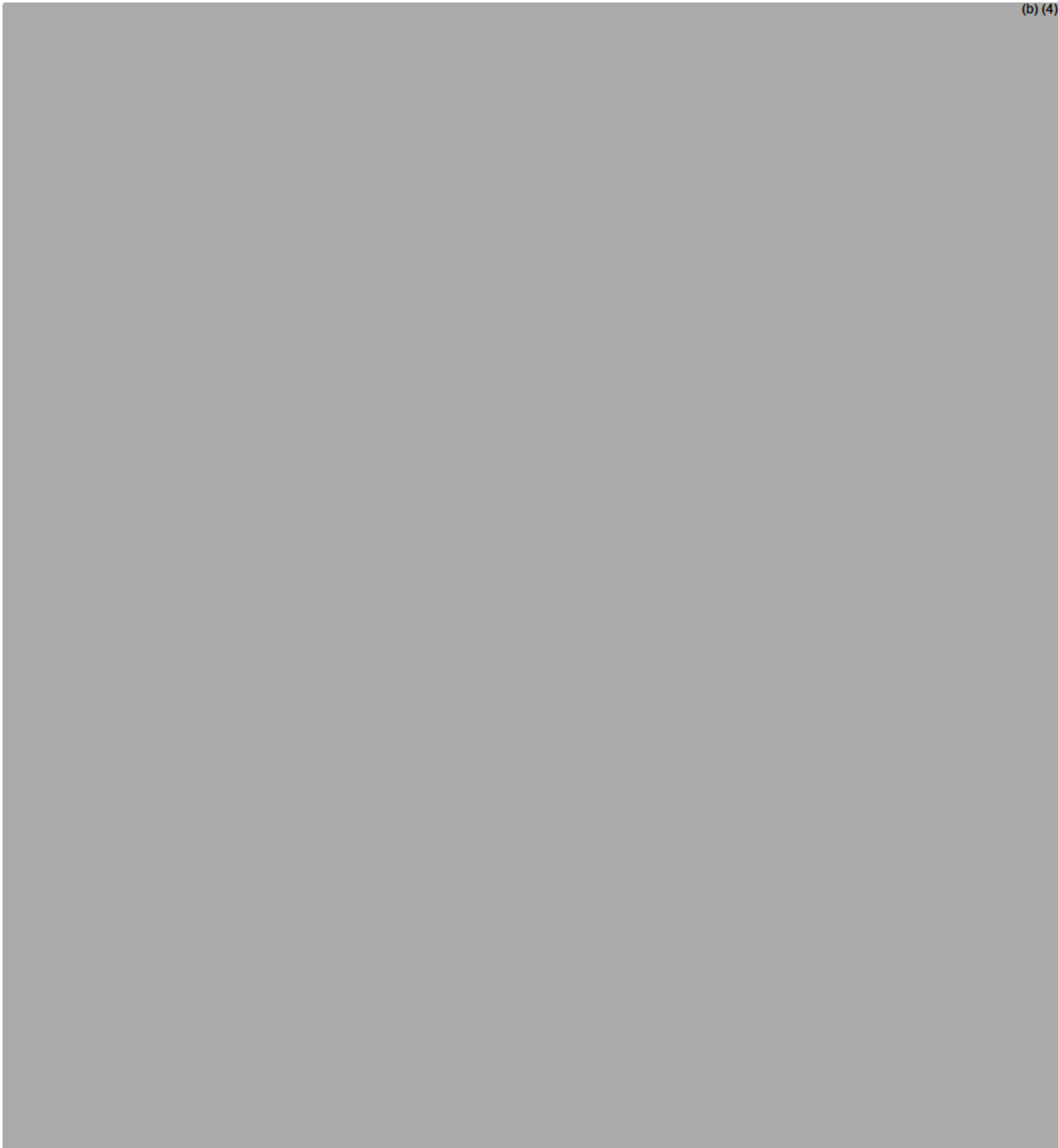
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DIARYpro screen shots

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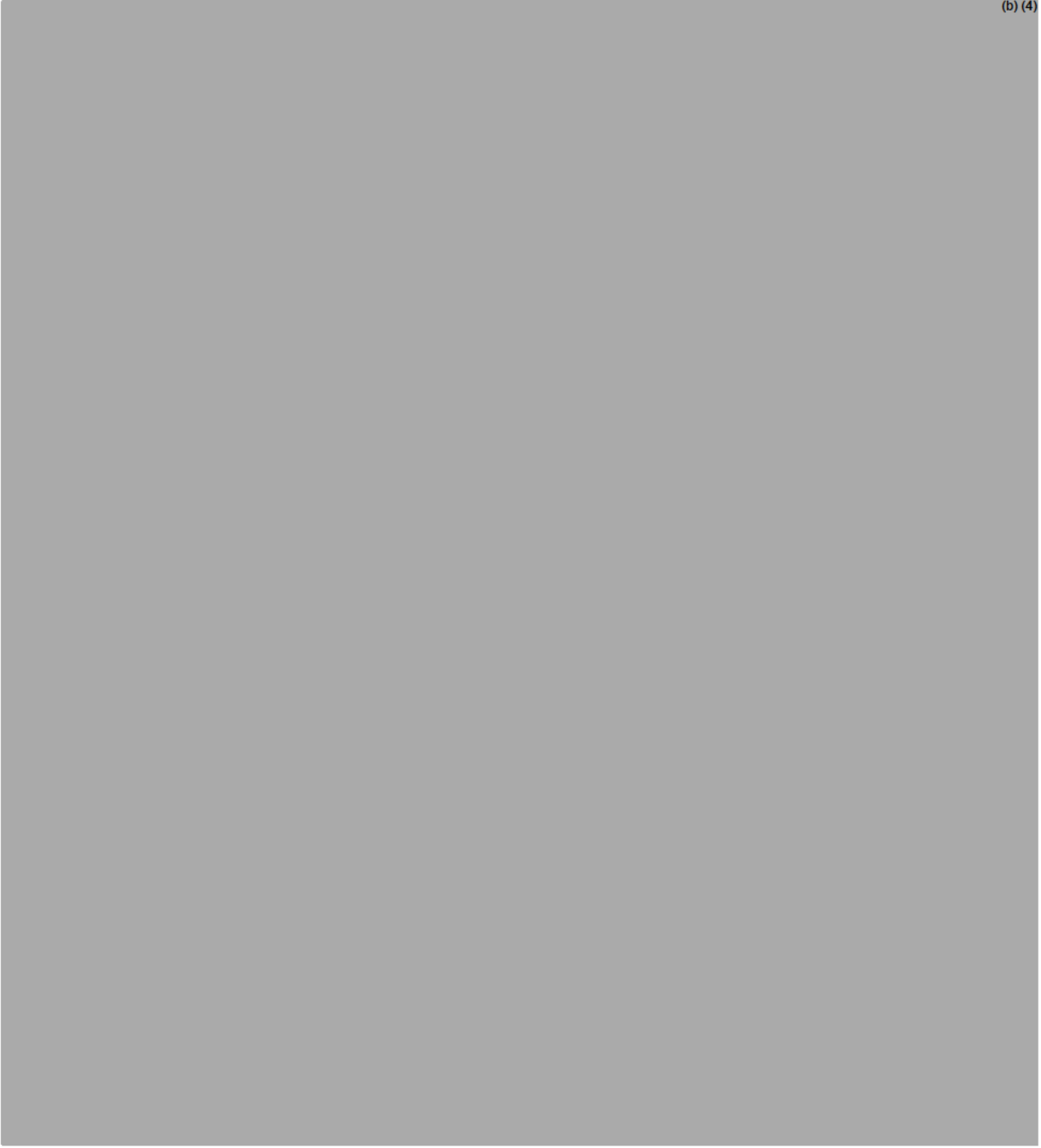
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/s/

WEN-HUNG CHEN

11/15/2016

ELEKTRA J PAPADOPOULOS

11/23/2016

LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 14, 2016
Requesting Office or Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Application Type and Number:	NDA 208794
Product Name and Strength:	Xermelo (telotristat ethyl) Tablets, 250 mg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Lexicon Pharmaceuticals
Submission Dates:	March 30, 2016 (Prescribing Information) August 23, 2016 (Container labels and Carton Labeling)
OSE RCM #:	2016-751
DMEPA Primary Reviewer:	Sherly Abraham, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review evaluates the labels and labeling for Xermelo (NDA 208794), a new molecular entity (NME) NDA, submitted on March 30, 2016. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed prescribing information, container labels and carton labeling for any areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C– N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E– N/A
Other	F– N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Lexicon Pharmaceuticals submitted a new molecular entity (NME) NDA for Xermelo (telotristat etiprate) for (b) (4) treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analog therapy. DGIEP issued a fast track designation for this application on May 19, 2008 and an orphan drug designation on March 9, 2012. We note that the product is available in a single strength of 250 mg. (b) (4)

(b) (4) The proposed packaging for the product is in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons. Each weekly carton contains seven daily dose packs. (b) (4)

(b) (4) . We identified areas in the Prescribing Information, container labels and carton labeling that can be improved to clarify the product dose and (b) (4) . Specifically, we recommend using (b) (4)

as the Applicant proposes. Additionally, we recommend relocating the net quantity statements away from the product strength to mitigate the risk that the net quantity is confused for the strength. We also recommend including the specific dose for the usual dose statement on the labels and labeling (b) (4). We provide recommendations for the Division in Section 4.1 and for Lexicon pharmaceuticals in 4.2 to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed prescribing information, container labels and carton labeling can be improved to increase the clarity of information on the label to promote the safe use of the product. Please see our letter-ready recommendations in Section 4.1 and 4.2 below:

4.1 RECOMMENDATIONS TO THE DIVISION

A. Full Prescribing Information: Section 16 How Supplied Section

1. We recommend revising this section to clearly state how the product is packaged and that the product is available in one strength, but different net quantities. For example: "Xermelo is dispensed in a monthly (b) (4) for a total of 28 days of therapy. Each monthly (b) (4) contains four weekly (b) (4). Each weekly (b) (4) contains seven daily dose packs.

250 mg tablet: white to off-white coated oval tablet with "T-E" debossed on one side and "250" debossed on the other side.

- NDC 70183-125-84: Monthly (b) (4) of 84 tablets. Each child resistant daily dose pack contains three 250 mg tablets.

(b) (4)

4.2 RECOMMENDATIONS TO LEXICON PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

A. All Container Labels and Carton Labeling (Daily dose packs, Weekly cartons, Monthly Cartons)

1. Revise the terminology from (b) (4) to "Daily dose pack" to clearly state that one pack is for one day's dose.
2. To avoid the confusion (b) (4), revise the "Dosage and Administration: See package insert" statement to either:

(b) (4)

3. As currently presented,

(b) (4)

(b) (4)

(b) (4)

B. Carton labeling (7 day box and 28-day case)

1. 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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xermelo submitted by Lexicon Pharmaceuticals on March 30, 2016.

Table 2. Relevant Product Information for Xermelo	
Initial Approval Date	N/A
Active Ingredient	telotristat etiprate
Indication	Treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy.
Route of Administration	oral
Dosage Form	tablets
Strength	250 mg
Dose and Frequency	(b) (4)
How Supplied	250 mg dose: 28 day case Contains 4 weekly boxes. Each weekly box contains 7 child-resistant blister day packs. Each day pack contains 3 tablets each. (b) (4)
Storage	Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature]
Container Closure	HDPE (b) (4) with Child Resistant Closure

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/s/

SHERLY ABRAHAM
11/14/2016

MISHALE P MISTRY
11/14/2016



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 20, 2016

To: Donna Griebel, M.D., Director
Division of Gastroenterology and Inborn Errors Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Martin S. Rusinowitz, M.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 208794** Telotristat Etiprate (Xermelo) Tablets
Indication: The (b) (4) treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy.
Dosage: 250 mg (b) (4) TID
Sponsor: Lexicon Pharmaceuticals, Inc.
PDUFA Goal Date: November 30, 2016

Materials Reviewed: DARRTS, NDA 208794, Sponsor Response to Information Request, 5/24/2016
DARRTS, NDA 208794, Information Request: Strongin, B, 5/20/2016
Sponsor's NDA 208794 Common Technical Document Summaries (2.2, 2.4, 2.5, 2.6, 2.7), Clinical Study Reports (5.3.3.4), 3/30/2016
DARRTS, IND 078749, Type B, End of Phase 2 Meeting Minutes, 4/11/2012

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I. SUMMARY

1. Background

Carcinoid Syndrome (CS) is the result of well-differentiated neuroendocrine tumors (NETs) secreting large amounts of serotonin (5-HT) and other vasoactive substances into the systemic circulation. These symptoms generally include cutaneous flushing, diarrhea, wheezing, abdominal pain, and valvular heart disease. Telotristat etiprate is an orally administered small molecule inhibitor of tryptophan hydroxylase, the rate limiting enzyme in the biosynthesis of serotonin. From the time of diagnosis of metastatic NETs, median survival is estimated to be approximately 31-75 months. The most frequent cause of death in patients with NETs is liver failure due to hepatic replacement by tumor. Due to the slow-growing nature of NETs and the prolonged course of the disease, about 50% of patients with CS will eventually develop heart disease which can lead to significant morbidity and mortality. Approximately 75% of patients with CS experience diarrhea, which may have the most direct impact on their lives.

Somatostatin analogs (SSAs), like lanreotide and octreotide, are the primary therapies for the relief of CS. They inhibit the release of serotonin by NETs and have become first-line therapy for CS. There are no approved treatment options for patients not adequately controlled on SSAs. Telotristat etiprate is being developed for the treatment of patients whose CS is not adequately controlled by SSAs alone. Telotristat etiprate may therefore potentially lessen the pathophysiology of CS by reducing 5-HT levels via inhibition of tryptophan hydroxylase (TPH), as compared with inhibition of the release of 5-HT with SSAs.

During the IND stage of development (IND 078749) a Type B End of phase 2 meeting was held between the Sponsor and the Division of Gastroenterology and Inborn Errors Products (DGIEP). The Sponsor asked, in Question 6, *Does the Agency agree with the proposal that additional non-clinical liability assessment is not required for LX1601?* DGIEP's response was, *Yes, we agree.* The Controlled Substance Staff (CSS) was not consulted during the IND stage of drug development.

After NDA 208784 was submitted to FDA on March 30, 2016, DGIEP, in an email correspondence dated May 20, 2016, the following information request was sent to the Sponsor:

Please submit (if applicable) the Abuse Liability Assessment, including a proposal for scheduling per 21 CFR 314.50(d) (5) (vii). You should indicate whether Xermelo has abuse potential. If you state that it has abuse potential then you are required to submit, at the time of NDA submission, information regarding the drug's abuse potential as well as a proposal for scheduling –justifying why you believe your drug should be placed in Schedule II, III, IV or V.

If Xermelo has no abuse potential, you still have to submit a statement stating that you propose that it should not be scheduled under the CSA (Controlled Substances Act) and the justification as to why it should not be scheduled.

In a submission dated May 24, 2016, the Sponsor responded that no formal abuse liability assessment was provided in the NDA submission, but that abuse potential was discussed in Sections 2.4, 2.5 and 2.6. (See Discussion for their review.) This was the first time CSS was consulted to review and assess Xermelo's abuse potential.

2. Conclusions

1. Nonclinical studies demonstrate that telotristat etiprate does not have abuse potential as it does not have central nervous system (CNS) activity. It is the hippurate salt form of an ethyl-ester prodrug (telotristat ethyl), designed as a prodrug (b) (4) of the active metabolite, LP-778902. At clinically relevant dose levels, it does not cross the blood brain barrier (BBB). Telotristat etiprate should, therefore, decrease peripherally elevated levels of 5-HT seen in CS without affecting 5-HT in the brain.

2. There were no adverse events (AEs) clearly attributable to a CNS effect (neurologic or psychiatric). At the request of DGIEP, in the event that telotristat etiprate might decrease CNS 5-HT resulting in depression, a special process was established for patients enrolled in Phase 3

studies to monitor depression-related AEs ('AEs of special interest'). All patients had metastatic cancer, at baseline, and depression was commonly reported in patients' medical histories.

3. Recommendations

1. The label for Xermelo should not include Section 9.0 (Abuse and Dependence); given that there are no data showing that the drug has abuse potential.
2. Xermelo should not be recommended for scheduling under the Controlled Substances Act.

II. Discussion

1. Chemistry

1.1 Substance Information

The pharmacological class for telotristat etiprate is a serotonin synthesis inhibitor. It has two chiral centers and there are no cis/trans isomers. It is the hippurate salt form of an ethyl-ester prodrug (telotristat ethyl), designed as a prodrug (b) (4) of the active metabolite, LP-778902.

2. Nonclinical Pharmacology

Telotristat etiprate is an orally administered small molecule inhibitor of TPH, the rate limiting enzyme in the biosynthesis of serotonin. Telotristat etiprate may therefore potentially lessen the pathophysiology of CS by reducing 5-HT levels via inhibition of TPH, as compared with inhibition of the release of 5-HT, the mechanism of action for the SSAs. Telotristat etiprate is a prodrug that is rapidly converted to the active metabolite LP-778902 in vivo.

Telotristat etiprate did not have any effect on brain 5-HT at doses up to 300 mg/kg/day (highest dose tested) in mice, rats or dogs. The tissue distribution of drug radioactivity was studied in rats following a single oral dose of 14C-LX1606 using quantitative whole body autoradiography with no measurable radioactivity.

3. Clinical Pharmacology

3.1 Absorption, Distribution, Metabolism, Elimination (ADME)

Following oral administration, telotristat etiprate dissociates to telotristat ethyl which is rapidly converted to its active metabolite LP-778902. At clinically relevant dose levels it does not cross

the blood brain barrier (BBB). Telotristat etiprate should, therefore, decrease peripherally elevated levels of 5-HT seen in CS without effecting 5-HT in the brain.

Plasma concentrations of telotristat ethyl were significantly lower than its active metabolite LP-778902 at all dose levels tested. Exposure of telotristat ethyl and LP-778902 increased with increase in dose. Population PK analysis showed that the PK of LP-778902 increased in an approximately dose proportional manner over the range of doses tested. Accumulation of telotristat ethyl and LP-778902 was minimal following multiple administration of telotristat etiprate in healthy subjects and in patients with CS.

Both telotristat ethyl and LP-778902 were highly bound to plasma proteins (> 99%). Telotristat ethyl undergoes ester hydrolysis to its active metabolite LP-778902. The only metabolite of LP-778902 was its pharmacologically inactive oxidative decarboxylated deaminated metabolite.

The major route of elimination is via the feces (92.78%) with < 1% in the urine. The half-life of telotristat ethyl following a single oral dose of 500 mg in healthy fasted subjects was estimated to be approximately 0.6 hours and that of LP-778902 was approximately 5 hours.

4. Clinical Studies

4.1 Human Abuse Potential Studies

None

4.2 Safety Profile, Adverse Events

The AEs in all the clinical trials detailed in Table 1 were reviewed. None were suggestive of being abuse-related AEs. The most common AEs included nausea, abdominal pain, fatigue, decreased appetite, abdominal pain upper, headache, gamma-glutamyl transferase increased, diarrhea, vomiting, cutaneous flushing, constipation, hypokalemia, flatulence, abdominal distention, urinary tract infection, dyspnea, pyrexia, and peripheral edema.

Table 1: Clinical Studies Included in this Review

Study ID	Phase	Objective	Design	Subjects	Dose Range	Duration
101-NRM	1	safety, tolerability, PK, PD, food effect	randomized, db, placebo controlled, ascending single-dose, healthy subjects	47	7 escalating oral single doses, 50-2000 mg	3 days
102-NRM	1	safety, tolerability, PK, PD	randomized, db, placebo controlled, ascending multiple-dose, healthy subjects	38	5 cohorts oral dosed for 14 days at: 100, 250, 500 mg qd, 500 mg bid, 500	16 days

					mg tid	
202-CS	2	safety, tolerability, efficacy, PK, urinary 5-HIAA	multicenter, randomized, db, placebo controlled, ascending dose, pts with carcinoid syndrome	22	150, 250, 350, 500 mg oral tid	184 weeks (4 wk db, 180 wk open label)
204-UC	2	safety, tolerability, efficacy, PK, urinary 5-HIAA	multicenter, randomized, db, placebo controlled, pts with ulcerative colitis	47	500 mg oral tid	10 weeks
301-CS	3	efficacy, PK, urinary 5-HIAA, QOL	randomized, placebo controlled, parallel-group, multicenter, db	117	200, 500 mg oral tid	48 weeks (12 wk db, 36 wk OLE)
302-CS	3	long term safety, tolerability, QOL	multicenter, open-label, long-term extension study, no placebo	71	250 mg oral tid	84 weeks
303-CS	3	safety, efficacy, urinary 5-HIAA	randomized, placebo controlled, parallel-group, multicenter, db	68	250, 500 mg tid	ongoing, interim results

4.3 Evidence of Abuse, Misuse and Diversion in Clinical Trials

There were no drug accountability issues reported and no findings of abuse, misuse or diversion in any clinical trials.

5. Regulatory Issues and Assessment

There is no nonclinical or clinical evidence to suggest an abuse potential of Telotristat Etiprate (Xermelo), it should not be recommended for scheduling under the Controlled Substances Act.

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/s/

MARTIN S RUSINOWITZ
10/20/2016

MICHAEL KLEIN
10/20/2016



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Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: August 20, 2016 **Date Consulted:** May 23, 2016

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, M.D., M.S., Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Division Director,
Division of Pediatric and Maternal Health

To: Division of Gastroenterology and Inborn Errors Products (DGIEP)

Drug: Xermelo (telotristat ethyl) Tablets for oral use

BLA: 208794

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For the (b) (4) treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy.

Applicant: Lexicon Pharmaceuticals, Inc.

Materials Reviewed:

- March 30, 2016, Applicants submission
- Applicant's proposed labeling
- May 23, 2016, DGIEP's request to DPMH-MHT for labeling review

Consult Question: Assist with Pregnancy and Lactation Labeling

REGULATORY HISTORY

The applicant submitted an original 505(b)(1) New Drug Application (NDA) for Xermelo (telotristat ethyl) Tablet for oral use, NDA 208794, on March 30, 2016. The proposed indication is for the treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors (NETs) who are receiving somatostatin analogue therapy. Fast Track Designation for telotristat ethyl was granted by the FDA on May 19, 2008. Pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act, Lexicon received Orphan Drug Designation for telotristat ethyl on March 9, 2012. The Division of Gastroenterology and Inborn Errors Products (DGIEP) consulted the Division of Pediatric and Maternal Health (DPMH) on May 23, 2016 to assist with reviewing the Pregnancy and Lactation subsections of labeling. (b) (4)

This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

BACKGROUND

Drug Characteristics

Xermelo (telotristat ethyl) is the hippurate salt of telotristat ethyl. Both telotristat ethyl and its active metabolite are inhibitors of L-tryptophan hydroxylase (the rate limiting step in serotonin biosynthesis). Through inhibition of TPH, telotristat ethyl reduces the production of serotonin, thus alleviating symptoms associated with carcinoid syndrome. Serotonin plays a critical role in regulating several major physiological processes of the gastrointestinal tract, including secretion, motility, inflammation, and sensation, and is over-secreted in patients with carcinoid syndrome.

Xermelo is the first drug in the tryptophan hydroxylase (TPH) inhibitors drug class. Other treatments for alleviation of carcinoid syndrome (CS) include somatostatin analogs like lanreotide and octreotide for the relief of CS and tumor stasis. Somatostatin analogs inhibit the release of serotonin by NETs and have become first-line therapy for CS.¹

The molecular weight of the free base (telotristat ethyl) is 575.0 Daltons. Each Xermelo tablet contains 250 mg of telotristat ethyl (free base). The apparent half-life of telotristat ethyl in healthy subjects following a single 500 mg oral dose is approximately 0.6 hour and (b) (4) 5 hours. (b) (4)

2

Disease Background

Well-differentiated neuroendocrine tumors (NETs), formerly known as carcinoid tumor, are relatively rare tumor types that arise from cells of the neuroendocrine system.^{3,4} Carcinoid tumors are a type of neuroendocrine tumors often found in the gastrointestinal (GI) tract or in the lungs. Carcinoid tumors are rare and often slow growing, and can lead to various symptoms. These symptoms are called carcinoid syndrome. Carcinoid syndrome (CS) occurs when well-differentiated NETs secrete large amounts of serotonin and other vasoactive products into the systemic circulation. Symptoms associated with CS include cutaneous flushing, diarrhea, wheezing, abdominal pain, and valvular

¹ Modlin IM, Pavel M, Kidd M, et al. Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumors. *Aliment Pharmacol Ther* 2010;31(2):169-88

² Proposed labeling

³ Turaga KK, Kvolis LK. Recent Progress in the Understanding, Diagnosis, and Treatment of Gastroenteropancreatic Neuroendocrine Tumors. *CA Cancer J Clin* 2011;61:113-32.

⁴ Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": Epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008;26:3063-72.

heart disease (shortness of breath, fibrosis (scarring) of heart valves, high blood pressure, heart murmur, and fatigue). The prevalence of carcinoid tumor is approximately 50,000 cases in any 1 year in the United States.⁵ A detailed analysis based on Surveillance, Epidemiology, and End Results Program (SEER Database 2007)⁶ estimates the prevalence of NETs to be 103,312 cases.³ It has been estimated that 10% of all patients with carcinoid tumors will develop carcinoid syndrome.⁷ Therefore, the prevalence estimate of carcinoid syndrome is about 5,166 cases. About 75% of carcinoid syndrome patients will experience diarrhea,^{8,9} which results in an estimated prevalence of 3,874 cases of carcinoid syndrome associated with diarrhea.

Pregnancy and Lactation Labeling Rule (PLLR)

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”¹⁰ also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule¹¹ format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW

Pregnancy

Nonclinical experience

In animal studies, telotristat ethyl was neither carcinogenic nor mutagenic nor clastogenic. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral telotristat etiprate to rats during organogenesis at exposures approximately 11 times the exposure at the maximum recommended human dose (MRHD). Treatment of pregnant rabbits at exposures approximately 19 times the exposure at the MRHD during organogenesis produced maternal toxicity, post-implantation loss, and reduced fetal weight. In a pre-/postnatal development study in rats, there was an increased incidence of mortality in rat offspring observed during postnatal days 0-4 when telotristat etiprate was administered to pregnant rats during organogenesis through lactation at exposures approximately 6 times the exposure at the MRHD. A clear determination cannot be made as to whether the in utero drug exposure or ingestion of drug in milk was causative for the increased mortality in the high dose group. For further details, the reader is referred to the full Pharmacology/Toxicology review by K. Zhang, Ph.D..

Review of Literature

DPMH searched PubMed, Embase, ReproTox and TERIS databases for information regarding telotristat ethyl and use during pregnancy. No published information was identified.

⁵ Vinik, A.I., et al. Neuroendocrine Tumors. A Comprehensive Guide to Diagnosis and Management. Inter Science Institute GI Council 2006, p9. Accessed at: www.carcinoid.org/medpro/docs/WolteringVinikISIbook1.pdf on 15 Jul 2008

⁶ By NIH, National Cancer Institute

⁷ Horton, K.M., et al., Carcinoid tumors of the small bowel: a multi-technique imaging approach. Am J. Roentgenol 2004; 182:559-67.

⁸ Khan, A.N. et al., Carcinoid, Gastrointestinal. February 16, 2007. E-Medicine. Accessed at: www.emedicine.com/RADIO/topic126.htm on 28 Feb 2008.

⁹ Vinik, A. Carcinoid Tumors. Chapter 2. August 2, 2004. Accessed at: <http://www.endotext.org/gluthormones/gluthormone2/gluthormone2.htm> on 31 Aug 2006.

¹⁰ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

¹¹ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

Review of Clinical Trials

As per the applicant, no studies of telotristat ethyl have been conducted in pregnant women. The applicant received only one report of a pregnancy across all telotristat ethyl clinical trials. In Study LX1606-1-105-NR (Thorough QT study), the subject was randomized to receive 400 mg moxifloxacin on Day 1 of Period 1 and 1500 mg (as free base) telotristat ethyl on Day 1 of Period 2. No additional study medication was given. The subject, a 26-year-old African American female, had a positive pregnancy test on study day 22, which was 14 days after a single 1500 mg dose of telotristat ethyl. On that day, she was withdrawn from the trial. Positive pregnancy test was recognized later in the day, when the patient had already been withdrawn from the trial for personal reasons. Approximately 8 months later (39 weeks of gestation), she delivered a normal, healthy female infant. These limited clinical data are insufficient to draw safety conclusions about the effects of telotristat ethyl during pregnancy and lactation.

Summary

Limited available data with telotristat ethyl use in pregnant women are insufficient to inform a drug associated risk. Telotristat ethyl is expected to cross the placenta because of its low molecular weight. In addition, safety data regarding exposure during pregnancy are lacking because pregnant women were excluded during telotristat ethyl's clinical development program, and limited outcome data are available on the women who became pregnant in the clinical trials. Therefore, post-approval studies to assess outcomes following exposure in pregnancy are important to help characterize telotristat ethyl's safety in pregnancy. However, a pregnancy exposure registry would likely be unfeasible because of the low number of patients of reproductive potential who will be treated while pregnant.

Lactation

Nonclinical Experience

The pre-/postnatal development study in rats did not measure the drug in rat milk and there is no separate animal lactation study.

Review of Literature

DPMH conducted a search of Medications and Mother's Milk¹², the Drugs and Lactation Database (LactMed)¹³, Micromedex¹⁴, and of published literature in PubMed using the search terms "telotristat ethyl and lactation" and "telotristat ethyl and breastfeeding." No reports of clinical lactation studies or case reports of telotristat ethyl use in lactating women were found in published literature.

Reviewer Comment:

The physical characteristics of the free base telotristat ethyl and its primary metabolite suggest that, if the drug is present in breastmilk, it would be present in small amounts. This hypothesis relies on the fact that they are both >99% bound to plasma protein, have small molecular weight, and short half-lives (telotristat ethyl MW 575.0 Daltons, half-life ~ 0.6 hour; its primary metabolite half-life 5 hours). However, physicochemical properties alone are not sufficient to predict exposure or potential risks to the breastfed infant. The effects of local gastrointestinal and systemic exposure to Xermelo on the breastfed infant are unknown. Administration of Xermelo to adults can cause elevation in liver enzymes and constipation. Other common adverse reactions reported in clinical trials include nausea, abdominal pain and distention and decreased appetite.

¹² Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing

¹³ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

¹⁴ Truven Health Analytics information, <http://www.micromedexsolutions.com/>.

Summary

The applicant did not provide any data about the presence of telotristat ethyl in human or animal milk and there are no publications available. Xermelo may be present in breast milk. Therefore, DPMH recommends that the breastfeeding risk/benefit statement is included in section 8.2 of labeling, together with advice for a woman to monitor the breastfed infant for symptoms of constipation.

Females and Males of Reproductive Potential

Nonclinical Experience

Animal fertility studies did not demonstrate any effects on fertility and early embryonic development in the rat at 500 mg/day (highest dose tested) which corresponds to 6 times the exposure at the maximum recommended human dose. For further details, the reader is referred to the full Pharmacology/Toxicology review by K. Zhang, Ph.D..

Review of Literature

DPMH performed a search of published literature on telotristat ethyl and infertility and did not identify any publications.

Summary

Animal reproductive studies on administration of telotristat ethyl did not show any adverse effects on fertility. In addition, because there are no human data available on the effect of telotristat ethyl on fertility, Section 8.3, Females and Males of Reproductive Potential, will not be included in Xermelo labeling.

CONCLUSION

The Pregnancy and Lactation, sections of Xermelo labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**
 - The “Pregnancy” section of Xermelo labeling was formatted in the PLLR format to include: “Risk Summary,” and “Data” sections.
- **Lactation, Section 8.2**
 - The “Lactation” section of Xermelo labeling was formatted in the PLLR format to include the “Risk Summary” section.

(b) (4)

RECOMMENDATIONS

DPMH participated in a labeling meeting with DGIEP. DPMH revised sections 8.1, 8.2, (b) (4) of Xermelo labeling for compliance with the PLLR. DPMH refers to the final NDA action for final labeling. DPMH proposed labeling for Xermelo is included in Appendix A.

APPENDIX A: DPMH PROPOSED PREGNANCY AND LACTATION LABELING EDITS FOR XERMELO

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data on XERMELO use in pregnant women to inform a drug associated risk. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral telotristat (b) (4) to rats during organogenesis at doses up to 750 mg/kg/day (approximately (b) (4) times the exposure at the (b) (4)). Treatment of pregnant rabbits with oral (b) (4)

In a pre-/postnatal development study, an increased incidence of mortality in rat offspring was observed during postnatal days 0-4 at the maternal oral dose of 500 mg/kg/day (approximately (b) (4) times the exposure at the (b) (4)), given during organogenesis through lactation [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

An embryo-fetal development study performed in rats with oral telotristat (b) (4) at doses up to 750 mg/kg/day (approximately (b) (4) times the AUC [area under the plasma concentration-time curve] for the active metabolite at the (b) (4)) during organogenesis produced no harm to embryo-fetal development.

In pregnant rabbits treated orally with telotristat (b) (4) during organogenesis, an increased incidence of post-implantation loss at doses of 250 and 500 mg/kg/day (approximately (b) (4) times the AUC for the active metabolite at the (b) (4)) and a decrease in fetal weight at 500 mg/kg/day (approximately (b) (4) times the AUC for the active metabolite at the (b) (4)) was observed. The adverse effects on embryo-fetal development were associated with maternal toxicity (impaired weight gain and mortality) at 250 and 500 mg/kg/day. No adverse effects on embryo-fetal development were observed at 125 mg/kg/day (approximately (b) (4) times the AUC for the active metabolite at the (b) (4)).

A pre-/postnatal development study was conducted in rats using oral administration of 100, 200, and 500 mg/kg/day telotristat (b) (4) during organogenesis through lactation. An increased incidence of pup mortality was observed during postnatal days 0-4 at the maternal dose of 500 mg/kg/day (approximately (b) (4) times the AUC for the active metabolite at the (b) (4)). No developmental abnormalities or effects on growth, learning and memory, or reproductive performance were observed through maturation of offspring at maternal doses of up to (b) (4) mg/kg/day (b) (4).

8.2 Lactation

Risk Summary

There are no data on the presence of telotristat ethyl in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The effects of local gastrointestinal and systemic exposure to telotristat ethyl are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XERMELO and any potential adverse effects on the breastfed infant from XERMELO or from the underlying maternal condition.

Clinical Considerations

Monitor the breastfed infant for symptoms of constipation.

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/s/

CHRISTOS MASTROYANNIS
10/03/2016

TAMARA N JOHNSON
10/04/2016

LYNNE P YAO
10/04/2016

Clinical Inspection Summary

Date	August 11, 2016
From	Susan Leibenhaut, M.D.
To	Wen-Yi Gao, M.D., Medical Officer, DGIEP
NDA/BLA #	NDA 208794
Applicant	Lexicon Pharmaceuticals, Inc.
Drug	telotristat etiprate
NME (Yes/No)	Yes
Therapeutic Classification	Priority
Proposed Indication	(b) (4) treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy
Consultation Request Date	April 22, 2016
Summary Goal Date	August 24, 2016
Action Goal Date	November 30, 2016
PDUFA Date	November 30, 2016

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigator (CI) sites and the sponsor were inspected for this application. One domestic clinical site has a final classification of no action indicated (NAI). One domestic clinical site has a final classification of voluntary action indicated (VAI), and the violations cited are not considered to have an impact on data integrity. The two foreign sites have preliminary classifications of VAI and the violations cited are not considered to have an impact on data integrity. The sponsor inspection has a preliminary classification of NAI. The preliminary classifications are based on e-mail communications from the FDA field investigators. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Reports. The studies appear to have been conducted adequately, and the data generated by the studies appear acceptable in support of the respective indication.

II. BACKGROUND

The sponsor submitted this NDA for telotristat, a tryptophan hydroxylase inhibitor, for the indication of the (b) (4) treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy.

Drug: telotristat etiprate

Studies – Protocol number and title for all studies that were inspected:

1. Protocol LX1606.1-301-CS entitled “A Phase 3, Randomized, Placebo-controlled, Parallel-group, Multicenter, Double-blind Study to Evaluate the Efficacy and Safety of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome Not Adequately Controlled by Somatostatin Analog (SSA) Therapy”

Number of subjects: 136 subjects were randomized

Number of sites: 48

Number of countries where subjects were enrolled: 12

Dates that study was conducted: January 2013 to September 2015

Primary efficacy endpoint: Change in frequency of BMs averaged over the 12-week

Double-blind Treatment (DBT) Period between the telotristat etiprate and placebo groups

2. Protocol LX 1606.1-303-CS entitled “A Multicenter, Long-term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LXI606)”

Number of subjects: 76 subjects

Number of sites: 29

Number of countries where subjects were enrolled: 12

Dates that study was conducted: January 2014 to October 2015

Primary efficacy endpoint: Change in frequency of BMs averaged over the 12-week

Double-blind Treatment (DBT) Period between the telotristat etiprate and placebo groups

Note that at the time of inspection, the studies were still ongoing and the sites were blinded to treatment assignment. FDA was aware that efficacy endpoint diary data with audit trails would not be available for inspection. Emphasis of the inspections was on protocol adherence, subject safety; and data integrity for elements other than primary endpoint verification. At some sites, diary data was available through the on line portal as noted in the write-up for the individual sites. The sponsor has contracted with the CRO to have CDs prepared and sent to the sites at the close-out of the study.

III. RESULTS (by site):

Both domestic study sites were selected for inspection because of a high enrollment of subjects on Study 301 and no history of inspections. Both foreign study sites were selected for inspection because of a high enrollment of subjects and no history of inspections. Site 66 enrolled a relatively high number of subjects in Study 301, and Site 2701 enrolled a relatively high number of subjects in Study 303. The sponsor was inspected because this drug is a new molecular entity.

Type of Inspected Entity/ Site #/Name/Address	Protocol # / # of Subjects	Inspection Date	Classification
CI /Site #108 Lowell Anthony, M.D. 800 Rose Street, 140 Roach Facility Lexington, Kentucky 40536	301/8 Subjects 303/3 Subjects	May 16 to 20, 2016	NAI
CI/ Site #109 Richard Warner, M.D. One Gustave L. Levy Place New York, New York 10029	301/6 Subjects 303/3 Subjects	June 1 to 9, 2016	VAI
CI/Site #66 Dieter Horsch, M.D. Robert-Koch-Allee 9 Bad Berka, Germany 99437	301/11 Subjects 303/3 Subjects	July 11 to 15, 2016	Pending VAI
CI/ Site #2701 Marta Benavent, M.D. Avienda Manuel Siurot s/n Sevilla, Spain 41013	301/2 Subjects 303/8 Subjects	July 11 to 15, 2016	Pending VAI
Sponsor Lexicon Pharmaceuticals, Inc. 8800 Technology Forest Place The Woodlands, TX 77381	301/136 Subjects 303/76 Subjects	July 12 to 21, 2016	Pending NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Lowell Anthony, M.D., Lexington, Kentucky 40536

At this site for Protocol 301, a total of 9 subjects were screened, 8 subjects were enrolled and completed the study. For Protocol 303, a total of 3 subjects were screened, 3 subjects were enrolled and completed the study. Source records were compared with data listings for primary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment. Records for all enrolled subjects were reviewed for informed consent, eligibility, and efficacy listings. There was no evidence of under-reporting of adverse events. No violations were noted and no Form FDA 483 was issued.

At the time of the inspection, there was no CD of diary data available at the site. The sites were still blinded to study treatment. The sponsor has contracted with the CRO to have CDs prepared and sent to the sites at the close-out of the study. During the inspection, the diary data was available through the on-line portal. Data concerning bowel movement frequency for all 8 subjects throughout the 12 week blinded period was compared with the line listings provided in the NDA and sent to the ORA investigator. There were no discrepancies. Also reviewed were flushing data for Subjects 2, 5, and 7 for the 12 week blind period and abdominal pain data for Subjects 3 and 6 for the 12 week blind period, and no discrepancies were noted.

The urinary 5-HIAA results are reported as “blinded” so they could not be verified.

The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indication.

2. Richard Warner, M.D., New York, New York 10029

At this site for Protocol 301, a total of 8 subjects were screened, 6 subjects were enrolled, and 2 subjects completed the study. For Protocol 303, a total of 3 subjects were screened, 3 subjects were enrolled, and 1 subject completed the study. Source records were compared with data listings for primary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment. Records for all enrolled subjects were reviewed for informed consent, eligibility, and efficacy listings. There were two instances of unreported adverse event attributed to test article that were not reported in the initial data submission. Muscle weakness of Subject #0109-004 was not reported to the sponsor and was cited on the Form FDA 483. Subject #0109-502 experienced extensive ST-T changes on 4/28/15. This AE was discovered and reported by the site to the sponsor on 5/22/16 which was after the interim database lock.

A Form FDA 483 was issued for the following:

1. Failure to report promptly to the sponsor adverse effects (AE) that may reasonably be regarded as caused by, or probably caused by, an investigational drug. Specifically, for protocol number LX1606.301, the following adverse events were documented in subject source records, but were not recorded in the subject's electronic data capture (EDC)/electronic case report forms (eCRF):

- a. Subject #0109-004 (randomized to active treatment): muscle weakness (05MAR14), dry hands (24APR14), and dry feet (24APR14) were recorded on this subject's adverse events log, but were not recorded in this subject's electronic case report form (eCRF)
- b. Subject #0109-002 (randomized to active treatment): Right arm ache; limited motion was recorded in this subject's Week 12 visit record dated 02/04/14, but was not recorded in this subject's electronic case report form.

Reviewer note: In his response, Dr. Warner noted that that, for Subject #0109-004, muscle weakness should have been reported and promised corrective action. He noted that dry hands and feet were inadvertently recorded on the AE page, but had been assessed as clinically insignificant. For Subject #0109-002, it was determined that the symptoms were related to infiltrating carcinoma of the right breast.

2. Failure to assure that an IRB was responsible for the initial and continuing review and approval of a clinical study.

Reviewer note: In his response, Dr. Warner clarified that the lapse in IRB approval of 13 days was a result of delayed review by the IRB.

3. An investigation was not conducted in accordance with the investigational plan.
 - a. Specifically, for protocol number LX1606.301, protocol-required procedures were not followed by your site. The following deviations from the protocol were observed during a review of your subject source records:
 - i. Subject #0109-003 did not have the following assessments at the end of study visit: 12-lead ECG, Chromogranin A levels, and quality of life questionnaire.
 - ii. Subject #0109-007 did not have review of 24 hour urine 5-HIAA concentration prior to randomization.

Reviewer note: In his response, Dr. Warner clarified that assessments for Subject #0109-003 were not done because he refused further testing and that HIAA was used by the sponsor for stratification and did not need to be reviewed by the clinical investigator. The line listings reflect the absence of the HIAA determinations and these are not considered significant violations.

- b. Specifically, for protocol number LX1606.303, protocol-required procedures were not followed by your site. Subject #0109-502 did not have the end of Study/ Week 48 visit ECG and clinical laboratory assessments.

Reviewer note: In his response, Dr. Warner stated that the assessments were not completed because the ECG machine had broken and the bloodwork was drawn, but not received by the central laboratory. This is reflected in the line listings and is not considered a significant violation.

4. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.
 - a. Specifically, for protocol number LX1606.301:
 - i. The date your site became aware of Subject #0109-008's Serious Adverse Event (SAE) cannot be determined from this subject's source records. This subject's SAE report notes that they experienced hypokalemia beginning on (b) (6) through (b) (6). This report was signed by the clinical research coordinator (CRC) on 10/29/14 and by the PI on 12/1/14.

Reviewer note: In his response, Dr. Warner admitted that the telephone note of 10/29/14 alerting the site was not in the record. He promised corrective action.

- ii. According to the protocol's Exclusion Criteria, patients with QTcF > 450 ms could not be enrolled in this study. QTcF values were not noted in the following subjects' screening source records: 0109-002, 0109-003, 0109-004, and 0109-005. Screening QTcF values were only noted in the eCRF for these subjects; they were not recorded within the source documentation. Additionally, Subject 0109-005's QTcF was 463 ms on 3/12/14; this subject was randomized and received study drug on 4/8/2014.

Reviewer note: In his response, Dr. Warner noted that the ECG machine used at his site did not make these calculations automatically. When the sponsor became aware of this issue, they provided the site with a calculator. In addition, the deviation for Subject 0109-005 is noted in the line listing for "Major Protocol Deviations".

- b. Specifically, for protocol number LX1606.303, the date your site became aware of Subject #0109-501's SAE cannot be determined from this subject's source records. This subject's SAE report notes that they experienced dehydration beginning on (b) (6) through (b) (6). This report was signed by the CRC on 11/10/15 and by the PI on 11/18/15.

Reviewer note: In his response, Dr. Warner admitted that the telephone note was not in the file.

In addition to the violations cited on the Form FDA 483, there was a discussion of the following adverse events found at the site that occurred after the cut-off date of October 30, 2015 or were entered into the database after the interim data extraction:

Subject 0109-501 was hospitalized for dehydration and the last dose was taken on (b) (6). This was not found in the sponsor's line listings because it was after the cutoff date of 10/30/15, Interim Data Extraction.

Reviewer note: The review division should review the safety update to ensure that this was reported by the sponsor.

Subject 0109-502 experienced extensive ST-T changes on 4/28/15. This event was not found on the sponsor's line listing. The study staff explained that this was discovered on 05/22/16, after the 10/30/15 cutoff date. She stated that it was entered in the subject's EDC post-data lock.

Reviewer note: This was a discussion item, but occurred prior to data cut-off, so is considered an unreported AE and is noted above in the first paragraph. Review division should review the safety update to determine whether this was reported by the sponsor.

The violations cited on the Form FDA 483 are considered minor and do not significantly impact data integrity. Dr. Warner adequately responded to the inspection findings in a letter dated June 14, 2016. The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Dieter Horsch, M.D., Bad Berka, Germany 99437

Note: Observations below for this clinical investigator (CI) inspection are based on review of the Form FDA 483 and communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

At this site for Protocol 301, a total of 13 subjects were screened, 11 subjects were enrolled, 9 subjects completed the double blind portion of the study, and 5 subjects completed the extension study. For Protocol 303, a total of 3 subjects were screened, 3 subjects were enrolled and 2 subjects completed the study. Source records were compared with data listings for primary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment. Records for all enrolled subjects were reviewed for informed consent, eligibility, and efficacy listings.

There was no evidence of under-reporting of adverse events. At the time of the inspection, there was no CD of diary data available at the site. The sites were still blinded to study treatment. The sponsor has contracted with the CRO to have CDs prepared sent to the sites at the close-out of the study. Data was not available through the on-line portal at this site. The urinary 5-HIAA results are reported as “blinded” so they could not be verified. A Form FDA 483 was issued for the following:

1. An investigation was not conducted in accordance with the investigational plan. Specifically, Subjects 606-007 and 606-009 were enrolled with EKG showing QTcF>450ms, even though this was an exclusion criterion.

Reviewer note: These protocol violations were reported by the sponsor in the line listings to the NDA.

2. Investigational drug disposition records were not adequate with respect to dates, quantity, and use by subjects. Specifically:
 - a. A review of the drug accountability records for both studies found that receipt and dispensation of the study drug cannot always be traced. There was no master inventory record established to trace the receipt and dispense of the study drug. Also, the dates the bottles containing the investigational drug were opened by the study subjects, the amount of the study drug consumed daily and the dates the study drug bottles were finished by the subjects were not always documented.

Reviewer note: In his response, the CI stated that the master record for drug allocated to the sites was available in the “Trial Line and Balance Systems” which was not provided the FDA investigator during the inspection. According to communication with the FDA investigator, the site did perform drug accountability during the study so that drug was accounted for over the course of the studies. In addition, documentation of daily compliance was not required by the protocol, so this not a violation.

- b. According to study records, Subject #0606-004 was randomized on August 14, 2013, but appears to have received a study drug kit on August 13, 2013. This discrepancy in dates is not explained in the records.
 - c. On October 2, 2013, study drug bottle #20015 was dispensed to study subject #0606-002 (randomized to LX1606 500mg) instead of study subject #0606-003 (placebo). The

study drug bottle was returned by subject #0606-002 on October 16, 2013 and re-dispensed to study subject #0606-003 on October 21, 2013. However, dispensation, receipt and examination of the returned product were not documented in study subject #0606-002 Drug Accountability Records.

Reviewer note: This violation was not reported in the line listings to the NDA. It appears that a subject on active treatment received a bottle intended for a subject randomized to placebo and that the error was discovered two weeks later. This finding was communicated to the review team in an e-mail on August 11, 2016. It does not appear significant to this reviewer, however, the final determination of significance is deferred to the review team.

- d. Investigational drug bottle #20017 was labelled with the expiration date 02/2014 (February 2014). On December 16, 2013, Week 20 Visit, open label bottle #20017 was dispensed to study subject #0606-003 and used by the study subject until March 9, 2014.

As anticipated prior to initiation of the inspection, the efficacy data could not be verified at this site. Otherwise, it appears that the studies were conducted adequately, and the data generated by these studies appear acceptable in support of the respective indication.

4. Marta Benavent, M.D., Sevilla, Spain 41013

Note: Observations below for this CI inspection are based on review of the Form FDA 483 and communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

At this site, for Protocol 301, a total of 2 subjects were screened and enrolled, and 1 subject completed the study. For Protocol 303, a total of 9 subjects were screened, 8 subjects were enrolled, and 6 subjects completed the study. For all enrolled subjects, source records were compared with data listings for primary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment. There was no evidence of underreporting of adverse events. During the inspection, the diary data was available through the on-line portal for all subjects except Subject 2701-501 (see explanation below). The FDA investigator was able to review the bowel movement frequency, flushing, abdominal pain eligibility data for the 8 subjects enrolled for Protocol 303 and 2 subjects enrolled for Protocol 301. There were no discrepancies between the on-line data and the subject line listings that had been provided to the FDA investigator.

A Form FDA 483, Inspectional Observations form, was issued for the following:

1. An investigation was not conducted in accordance with the investigational plan. Specifically, Subject 2701-505 enrolled into Protocol 303 failed to meet the inclusion criterion "If currently receiving Long Acting Release/Depot/infusion somatostatin therapy for the treatment of carcinoid syndrome, must be currently receiving a stable-dose, averaging <4 BMs per day, and must have ≥ 1 of the following sign/symptoms of CS." Subject 2701-505 according to the EPX eligibility report was averaging 4 BMs per day. No sponsor waiver was issued.

Reviewer note: In a response on August 1, 2016, the CI explained that the subject had >4 BMs/day due to antibiotic therapy. The CI provided documentation that the sponsor agreed to

an extended screening period, after the antibiotic was discontinued, the BMs became within eligible range and the subject could be enrolled.

2. Failure to maintain adequate and accurate case histories. Specifically, the data (e.g. bowel movement, abdominal pain and flushing) from the patient's daily diary entered into the EPX for subject 2701-501, enrolled into the study protocol Number LX1606.1-303-CS were missing and not available. The only verifiable data entered as completed from the daily diary were for the following dates: July 11, 2014, July 12, 2014 and July 13, 2014.

Reviewer note: In a response on August 1, 2016, the CI explained that the failure to access the report on the web was a result of an error at the site in the diary set-up for the subject in which the subject number was mistakenly entered as 001. When the site realized the error, they recalled the patient and ended the diary collection under the Patient's 2701-001 ID by identifying this subject number as a Screen Failure. They reissued the diary to the patient with the correct ID (2701-501) on 14-Jul-2014. The patient continued to enter data into the diary from July 15 to August 3, 2014, the period reviewed to determine subject eligibility for randomization.

At the site's request in December 2015, the sponsor processed a Data Clarification Form to relocate the 11-13Jul-2014 data from patient ID -001 to patient ID -501. This added the 3 additional days of diary data to the 20 days of data collection already in the database for the screening period. However, as a result of this relocation of data, the eligibility report was inadvertently reset (without impact to the database), and since then, the report displayed only the data from the 11-13 Jul-2014 period and not the full 24 day period as had been intended by the site. In the response, the site attached a copy of the daily summary report showing the results from the 24 day Screening period and the Data Clarification Form which documented the request to relocate the 3 days collected under the 2701-001 patient ID.

The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. Lexicon Pharmaceuticals, Inc., The Woodlands, TX 77381

Note: Observations below for this sponsor inspection are based on review of the Form FDA 483 and communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

This inspection evaluated compliance with sponsor responsibilities for Protocols 301 and 303 including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data. The inspection included review of general correspondence and study master files, site monitoring for the clinical sites, and handling of adverse events and other sponsor/monitor related activities.

Review of the sponsor documents did not note any significant deficiencies. Monitoring practices at the sites inspected above and an additional site in the Netherlands were reviewed in detail. Results of the inspection indicated that, in general, monitoring of investigators was adequate and the sponsor maintained adequate oversight of the trials.

The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

{See appended electronic signature page}

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OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague

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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/

SUSAN LEIBENHAUT
08/12/2016

SUSAN D THOMPSON
08/12/2016

KASSA AYALEW
08/12/2016

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA208794
Brand Name	Xemelo
Generic Name	Telotristat Eliprate (LX1606)
Sponsor	Lexicon Pharmaceuticals, Inc.
Indication	Treatment of gastrointestinal symptoms associated with carcinoid syndrome
Dosage Form	(b) (4) Tablets
Drug Class	Inhibitor of L-tryptophan hydroxylase (TPH)
Therapeutic Dosing Regimen	Maximum proposed clinical dosing regimen is 500 mg t.i.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	1500 mg single dose clinically
Submission Number and Date	001 and 3/30/2016
Review Division	DGIEP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of 1500 mg telotristat etiprate (LX1606) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between 1500 mg telotristat etiprate and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for $\Delta\Delta\text{QTcF}$ moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 2, indicating that assay sensitivity was established.

In this randomized, a Phase 1, partially double-blind, single-center, single-dose, placebo-controlled, 6-sequence, crossover study, 48 healthy subjects received 1500 mg telotristat etiprate, placebo and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for 1500 mg Telotristat Etiprate and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta QTcF$ (ms)	90% CI (ms)
1500 mg Telotristat Etiprate	60	1.2	(-1.2, 3.7)
400 mg Moxifloxacin	4	10.2	(8.3, 12.1)

Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 7.6 ms.

The supratherapeutic dose (1500 mg single dose) produces mean C_{max} 3.3-fold the mean steady state C_{max} for the therapeutic dose (500 mg TID). These concentrations are above those for the predicted worst case scenario (severe renal impairment) and show that at these concentrations there are no detectable prolongations of the QT-interval.

2 PROPOSED LABEL

The following is the sponsor's proposed labeling language related to QT.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a (b) (4) mg, Xermelo (b) (4) not prolong the QT interval to any clinically relevant extent.

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2. Pharmacodynamics

Cardiac Electrophysiology

(b) (4)
 (b) (4) XERMELO (u) (4) not
 prolong QTc to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Telotristat etiprate (LX1606) is an orally administered small molecule inhibitor of L-tryptophan hydroxylase (TPH), which has been shown in animal studies to reduce 5-HT levels in the blood and GI tissues without affecting 5-HT levels in the brain.

3.2 MARKET APPROVAL STATUS

Telotristat is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

The in vitro effect of telotristat etiprate and its primary metabolite (LP-778902) on the human ether-a-go-go related gene (hERG) potassium channel current (the rapidly activating, delayed rectifier cardiac potassium current) was evaluated using concentrations of telotristat etiprate up to 1 μ M and LP-778902 up to 10 μ M. The half maximal inhibitory concentration of LP-778902 on hERG potassium current is >10 μ M; the corresponding value for telotristat etiprate is 0.3 μ M.

The effect of telotristat etiprate on cardiovascular function was investigated in the telemeterized dog. A total of 4 telemeterized male Beagle dogs received single oral doses of telotristat etiprate once every 7 days in doses up to 200 mg/kg. Results from this study showed that telotristat etiprate had no effects on the cardiovascular system of the dog.

3.4 PREVIOUS CLINICAL EXPERIENCE

The sponsor has conducted nine phase 1 studies, and three phase 2 studies. No AEs related to ECGs were reported. The sponsor is currently conducting three phase 3 studies of these studies the 12-week double blind period has been completed in two studies. No AEs related to the ECG parameter has been identified.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of telotristat etiprate's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 78749. The sponsor submitted the study report LX1606-1-105-NRM for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Randomized, Double-blind, Placebo-controlled, Positive-controlled, 3-period, 6-sequence, Crossover Study to Define the Electrocardiogram Effects of a Single Dose of Telotristat Etiprate (LX1606 Hippurate), 1500 mg, Compared with Placebo and Open-label Moxifloxacin in Healthy Subjects: A Thorough QT Study

4.2.2 Protocol Number

LX1606-1-105-NRM

4.2.3 Study Dates

First subject consented: 28 May, 2014

Last subject visited: 14 August, 2014

4.2.4 Objectives

The primary objective of this study is to demonstrate that 1500 mg (as free base) of telotristat etiprate does not differ from placebo in the mean time-matched change from Baseline QT interval corrected for heart rate (HR; ΔQT_c), by showing that the upper bound of the 2-sided 90% confidence interval (CI) for the greatest placebo-corrected change from Baseline QT interval corrected for HR ($\Delta \Delta QT_c$) was <10 msec

Secondary Objectives

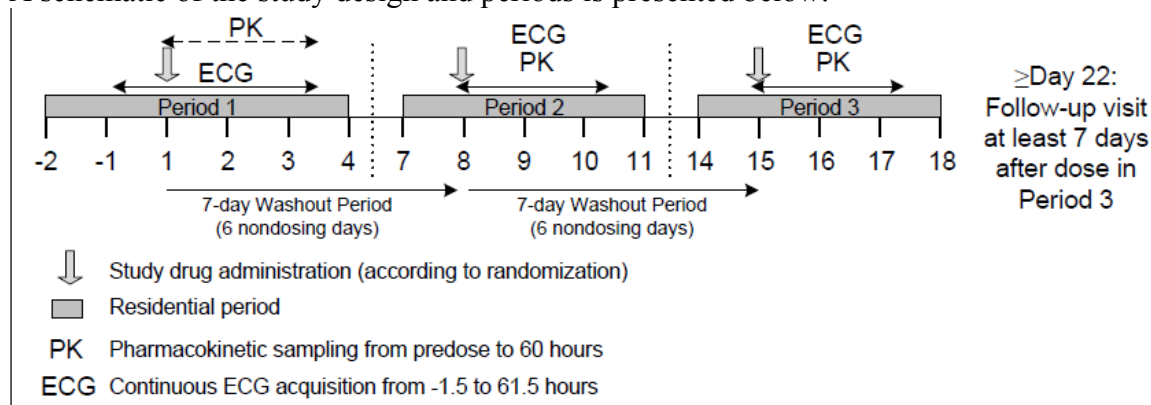
- To establish assay sensitivity by demonstrating that 400 mg moxifloxacin differs from placebo in the time-matched mean ΔQT_c at selected time points, by showing that the lower bound of 2-sided multiple comparison corrected CIs was >5 msec for at least 1 time point
- To assess the safety and tolerability of a single oral dose of 1500 mg (as free base) telotristat etiprate in healthy subjects
- To assess the pharmacokinetics (PK) of telotristat ethyl and its major metabolite LP-778902
- To explore a potential relationship between telotristat ethyl and its major metabolite LP-778902 plasma concentrations and time-matched $\Delta \Delta QT_c$ following a dose of 1500 mg (as free base) telotristat etiprate
- To evaluate the effect of telotristat etiprate on other electrocardiogram (ECG) parameters including HR, PR, QRS, T-wave morphology including presence or absence of U-waves, and outlier assessments

4.2.5 Study Description

4.2.5.1 Design

This was conducted as a Phase 1, randomized, partially double-blind, single-center, single-dose, placebo-controlled, 6-sequence, crossover study evaluating the acute effects of a single dose of 1500 mg (as free base) telotristat etiprate on cardiac repolarization intervals in healthy male and female subjects.

A schematic of the study design and periods is presented below:



4.2.5.2 Controls

The sponsor used both moxifloxacin and placebo controls.

4.2.5.3 Blinding

Moxifloxacin group conducted as an open-label.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

The 3 study drugs were administered as single oral doses as below:

- 1500 mg (as free base) telotristat etiprate
- telotristat etiprate-matching placebo
- 400 mg moxifloxacin

4.2.6.2 Sponsor's Justification for Doses

The intended therapeutic dosage of telotristat etiprate in patients with CS is 500 mg (as free base) tid (1500 mg [as free base] total daily dose). Regulatory guidance (ICH E14) recommends testing doses at substantial multiples of the anticipated maximum therapeutic exposure, if not prohibited by considerations of safety or tolerability due to adverse effects. In the Phase 1 study LX1606.1-101-NRM1, a single dose of 1500 mg (as free base) was tolerated; however, subjects experienced a notable increase in incidence and severity of GI side effects, leading to the decision to stop further dose escalation. Therefore, Phase 1 study results did not support an increase in single doses of telotristat etiprate above 1500 mg (as free base). It was not anticipated that an excessive accumulation would occur (ie, renal, hepatic, or cytochrome P450 interactions); therefore, it was proposed to evaluate a single dose of 1500 mg (as free base) telotristat etiprate in this study. In addition, the tablet formulation was to be used, as it is the intended formulation for use in the clinical setting. Doses were to be administered with food to represent the intended administration in the clinical setting in order to maximize bioavailability of drug and minimize GI AEs.

Reviewer's Comment: The doses selected for this study are acceptable as they cover the high clinical exposure scenario. Data from the population PK analysis suggest minimal to no change in exposure for both renal and hepatic impairment. The supratherapeutic dose (1500 mg single dose) produces mean C_{max} values 3.3-fold and 1.7-fold the mean steady state C_{max} values with the therapeutic dose (500 mg TID) for the parent drug and the metabolite respectively.

4.2.6.3 Instructions with Regard to Meals

Doses were to be taken with food (ie, within 1 hour following a standard [non high-fat] meal) and to be followed by a fast from food (not including water) for at least 4 hours postdose. Except as part of dosing and fluid provided with the meal, subjects were to restrict their consumption of water for 1 hour prior to dose and for 2 hours postdose; at all other times during the study, subjects were to be allowed to consume water on an ad libitum basis.

Reviewer's Comment: The sponsor's dosing with food is acceptable as this timing of drug with food gives the highest bioavailability.

4.2.6.4 ECG and PK Assessments

The 15-minute ECG extraction window (10 minutes supine + 5 minute extraction) was to precede blood draws to avoid changes in autonomic tone from blood sampling. On Day - of Period 1 only, continuous monitoring was to occur from approximately 1.5 hours before until 24 hours after the intended dose administration time (eg, if dosing was scheduled for 08:00 on Day 1, monitoring was to begin at 06:30 on Day -1) with ECG extraction times: -1.0, -0.75, -0.5, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the intended dosing time. In each dosing period, continuous monitoring was to occur from approximately 1.5 hours before to 61.5 hours after dosing with ECG extraction times: -1.0, -0.75, -0.5, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 60 hours.

Pharmacokinetic blood samples were to be collected at predose (within 20 minutes before dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 60 hours postdose.

Reviewer's Comment: The sponsor's timing of the ECGs and PK collection is acceptable to capture the timecourse of ECGs and PK concentrations over the duration of drug exposure.

4.2.6.5 Baseline

The average of 3 predose timepoints QTc values in each period as baselines.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

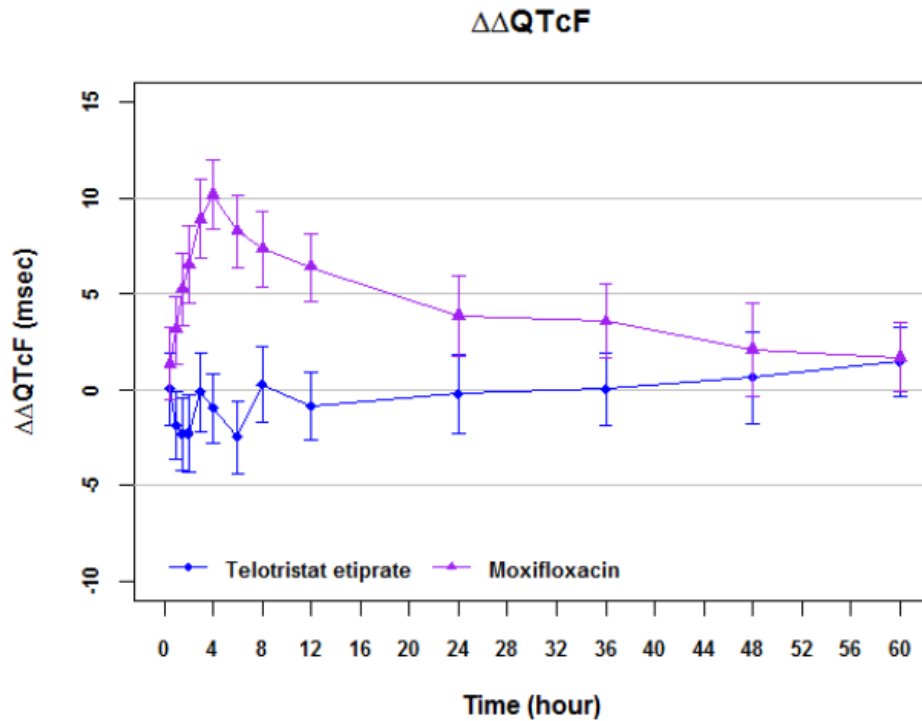
A total of 48 healthy subjects enrolled and 44 completed the study.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoint was baseline-adjusted mean differences between 1500 mg telotristat etiprate and placebo in Δ QTcF. The sponsor used a mixed effect model and the results are presented in Figure 1. The model included period, treatment, time, treatment by time interaction, and gender as fixed effects; subject as a random effect; and the predose baseline QTcF as covariate. The sponsor concluded that telotristat etiprate has no QTcF prolongation effect, as the upper bound of the 2-sided 90% CIs for the mean difference between 1500 mg telotristat etiprate and placebo was below 10 ms.

Figure 1: Sponsor's Placebo-corrected Change from Baseline QTcF



(Source: Applicant's Clinical Study Report LX1606-105, Figure 11.4.1.)

Reviewer's Comments: We will provide our independent analysis result in Section 5.2. Our $\Delta\Delta\text{QTcF}$ results are similar as those reported by the sponsor.

4.2.8.2.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the $\Delta\Delta\text{QTcF}$ effect for moxifloxacin. The results are presented in Figure 1. The lower bound of the 2-sided 90% CI for the mean difference between moxifloxacin and placebo was greater than 5 ms, therefore, the assay sensitivity was established.

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our results are similar to the sponsor's QTcF effect for moxifloxacin.

4.2.8.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of $\text{QTc} \leq 450$ ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline $\text{QTc} \leq 30$ ms, between 30 and 60 ms, and >60 ms. No subject $\text{QTc} > 480$ ms and no subjects $\Delta\text{QTcF} > 60$ ms.

4.2.8.3 Safety Analysis

The incidence of TEAEs was higher following administration of 1500 mg (as free base) telotristat etiprate (13 subjects [27.7%]) compared to placebo (2 subjects [4.4%]). All TEAEs were mild in severity and resolved by the end of the study. One subject with a

previous history of gout (undisclosed at Screening) was discontinued due to an AE of gout exacerbation after having received telotristat etiprate in Period 1; however, the onset of this AE was 3 days prior to dosing. One subject had a positive pregnancy test at the Follow-up visit and this subject will be followed until birth or termination. No SAEs were reported in the study.

Overall, 29 TEAEs were considered to be possibly, probably, or definitely related to study drug, of which 20 were reported following administration of 1500 mg (as free base) telotristat etiprate, 2 were reported following administration of placebo, and 7 were reported following administration of 400 mg moxifloxacin. The most common TEAEs (all causalities) following administration of 1500 mg (as free base) telotristat etiprate were gastrointestinal (GI) disorders (nausea and diarrhea).

There were no clinically significant findings in clinical laboratory evaluations (chemistry, hematology, and UA), vital sign measurements, ECGs, physical examinations, or weight measurements in this study.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results after administration of the 1500 mg suprathreshold dose are presented for the parent in Table 2 and Figure 2 and for the metabolite in Table 3 and Figure 3. Results for the therapeutic dose (500 mg TID) are shown in Appendix 6.1. The suprathreshold dose (1500 mg single dose) produces mean C_{max} values 3.3-fold and 1.7-fold the mean steady state C_{max} values with the therapeutic dose (500 mg TID) for the parent drug and the metabolite respectively.

Table 2. Summary of Pharmacokinetic Parameters of Telotristat Ethyl (Analysis Population: PK Population)

Treatment	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-last} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	λ_z (h ⁻¹)	$t_{1/2}$ (h)
1500 mg (as free base) telotristat etiprate	16.0 (56.9)	2.13 (0.63 – 8.13) ^a	65.0 (50.6)	74.4 (43.8)	0.246 (31.1)	2.81 (31.1)
N	46	46	46	36	36	36

Source: Table 14.2.2-1

Note: AUC_{0-last} = area under the concentration-time curve from time 0 to the time of the last time point with a measurable concentration; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; C_{max} = maximum plasma concentration; CV% = coefficient of variation; λ_z = apparent terminal phase elimination rate constant; max = maximum; min = minimum; N = number of subjects; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time to maximum plasma concentration

Geometric mean (geometric CV%) presented

^a Median (min – max) presented for t_{max}

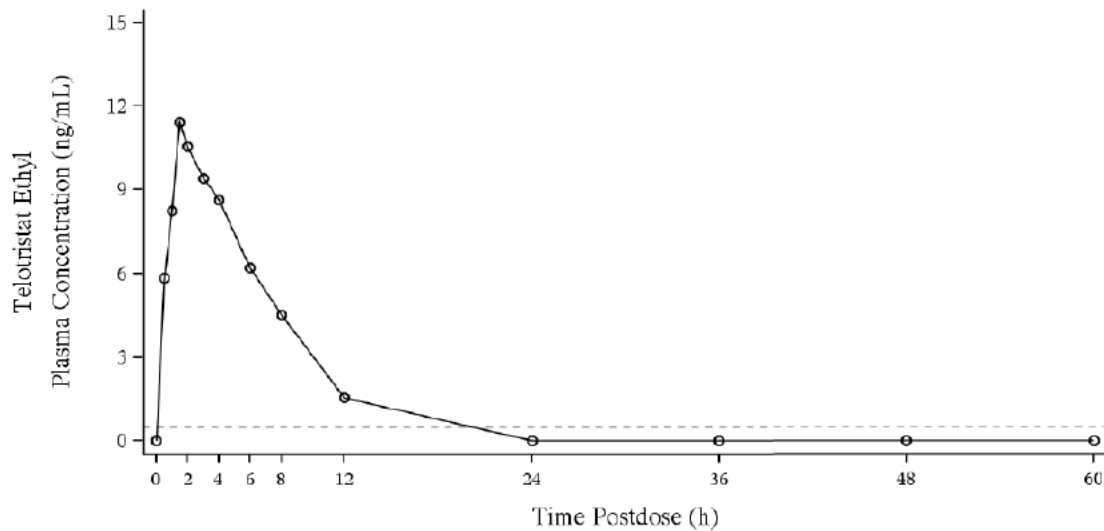
Subject No. 109 was excluded from the descriptive statistics since the subject experienced vomiting at <2 times the median t_{max} and the PK profile appeared to be affected by the AE.

For Subject Nos. 103, 112, 119, 127, 130, 132, 133, 135, and 143, λ_z could not be determined due to poor fit; subsequently $AUC_{0-\infty}$ and $t_{1/2}$ could not be calculated.

For Subject No. 126, λ_z was not determined as it would have included C_{max} ; subsequently $AUC_{0-\infty}$ and $t_{1/2}$ could not be calculated.

(Source: Applicant's Clinical Study Report LX1606-105, Table 11.4.2.1-1)

Figure 2. Arithmetic Mean Plasma Concentration Profiles for Telotristat Ethyl (Analysis Population: PK Population)



(Source: Applicant's Clinical Study Report LX1606-105, Figure 11.4.2.1-1)

Table 3. Summary of Pharmacokinetic Parameters of LP-778902 (Analysis Population: PK Population)

Treatment	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-last} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	λ_z (h ⁻¹)	$t_{1/2}$ (h)
1500 mg (as free base) telotristat etiprate	1756 (27.2)	4.13 (2.13 – 8.13) ^a	11874 (35.2)	11920 (35.1)	0.0762 (19.4)	9.10 (19.4)
N	46	46	46	46	46	46

Source: [Table 14.2.2-2](#)

Note: AUC_{0-last} = area under the concentration-time curve from time 0 to the time of the last time point with a measurable concentration; $AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity; C_{max} = maximum plasma concentration; CV% = coefficient of variation; λ_z = apparent terminal phase elimination rate constant; max = maximum; min = minimum; N = number of subjects; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time to maximum plasma concentration

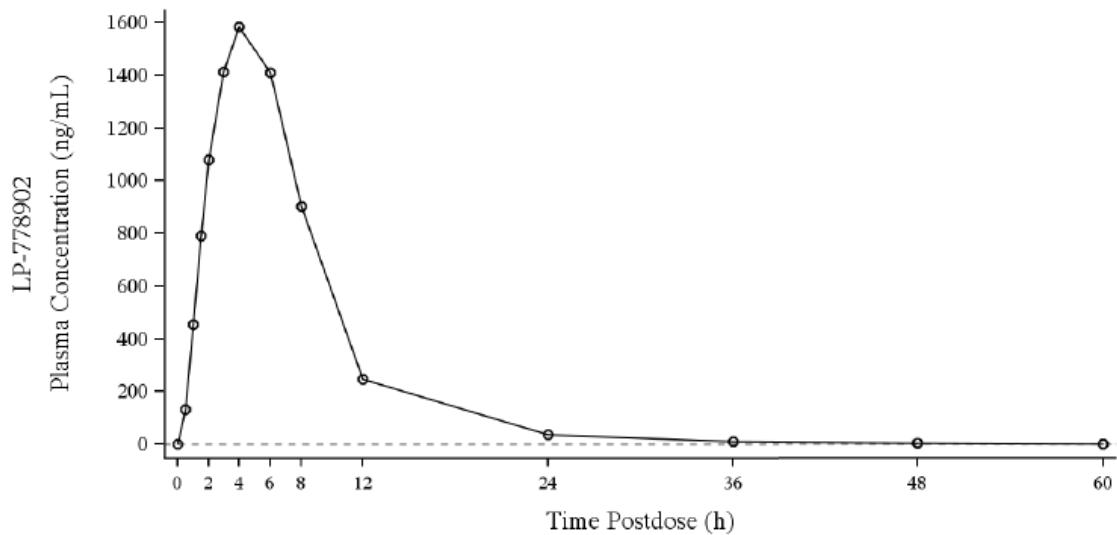
Geometric mean (geometric CV%) presented

^a Median (min – max) presented for t_{max}

Subject No. 109 was excluded from the descriptive statistics since the subject experienced vomiting at <2 times the median t_{max} and the PK profile appeared to be affected by the AE.

(Source: Applicant's Clinical Study Report LX1606-105, Table 11.4.2.2-1)

Figure 3. Arithmetic Mean Plasma Concentration Profiles for LP-778902 (Analysis Population: PK Population)

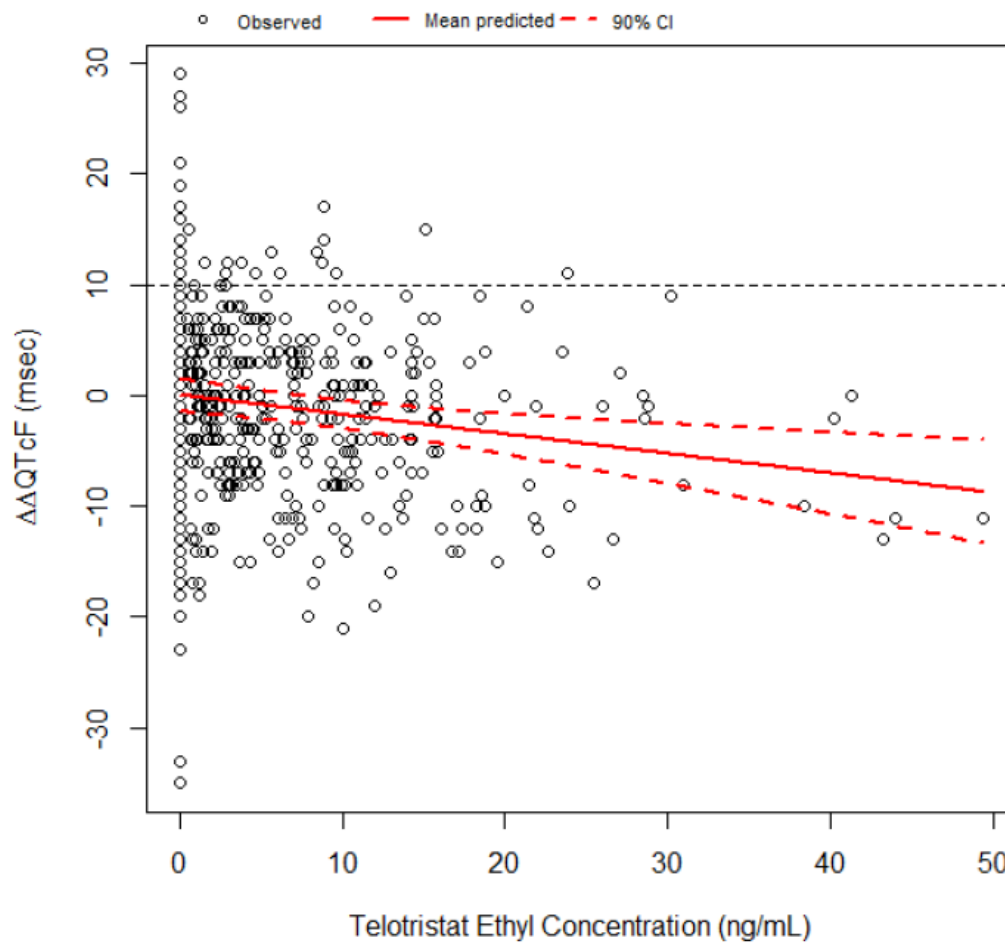


(Source: Applicant's Clinical Study Report LX1606-105, Figure 11.4.2.2-1)

4.2.8.4.2 Exposure-Response Analysis

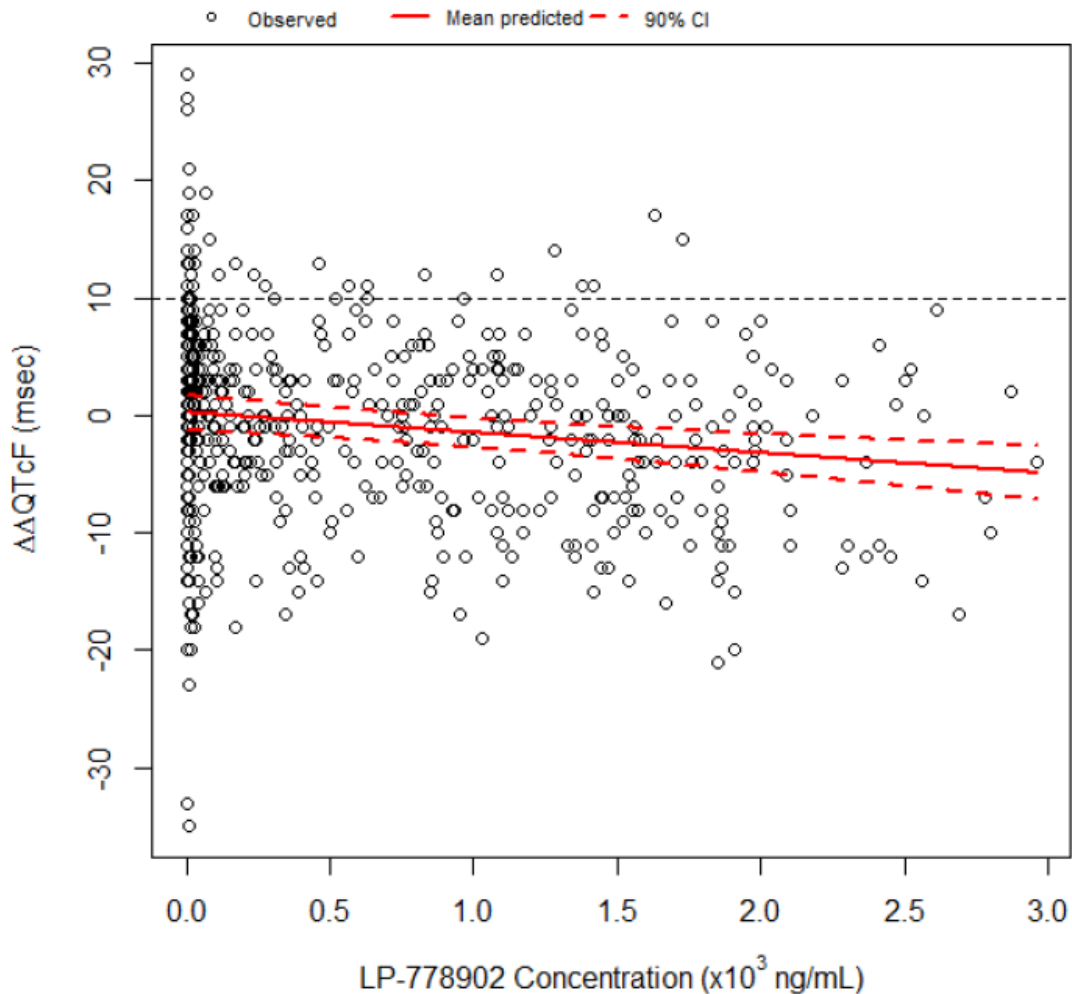
The relationships between the individually observed telotristat ethyl concentrations and $\Delta\Delta\text{QTcF}$ and the observed metabolite concentrations and $\Delta\Delta\text{QTcF}$ are presented in Figure 4 and Figure 5.

Figure 4. Relationship Between Telotristat Ethyl Plasma Concentrations and $\Delta\Delta QTcF$ with 90% Confidence Interval (PK/QTc Population)



(Source: Applicant's Clinical Study Report LX1606-105, Figure 11.4.8.1-1)

Figure 5. Relationship Between LP-778902 Plasma Concentrations and $\Delta\Delta QTcF$ with 90% Confidence Interval (PK/QTc Population)



(Source: Applicant's Clinical Study Report LX1606-105, Figure 11.4.8.1-1)

Reviewer's Analysis: The reviewer's independent analysis with the single delta $QTcF$ as the dependent variable reached similar conclusions (see Section 5.3).

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

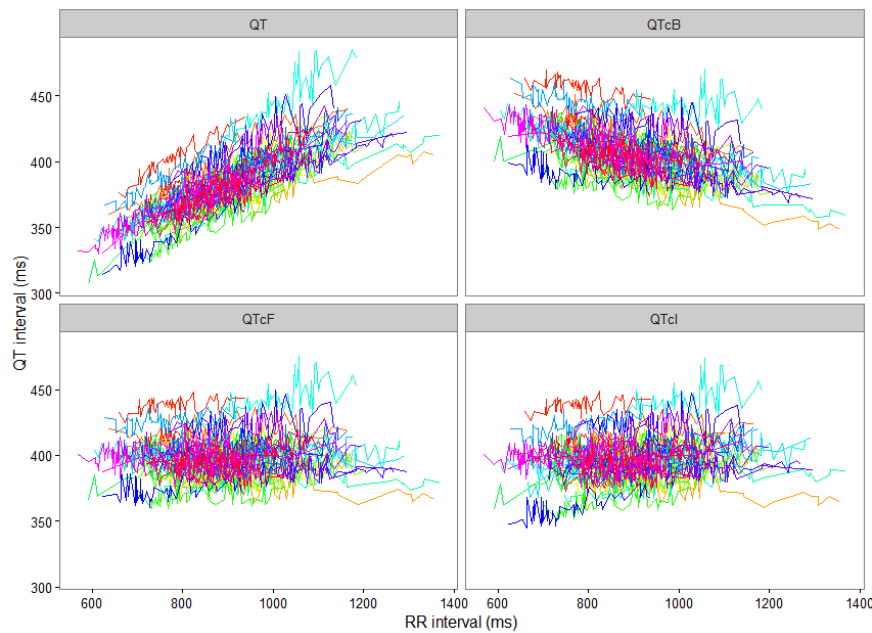
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR . The smaller this value is, the better the correction. Based on the results listed in Table 4, it appears that $QTcF$ and $QTcI$ are equally better than $QTcB$. To be consistent with the sponsor's analyses, this reviewer used $QTcF$ as primary statistical analysis.

Table 4: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
Placebo	45	0.00775	45	0.00146	45	0.00139
Moxifloxacin 400 mg	46	0.00441	46	0.00244	46	0.00311
1500 mg Telotristat Etiprate	47	0.00746	47	0.00128	47	0.00144
All	48	0.00478	48	0.00107	48	0.00201

The relationship between different correction methods and RR is presented in Figure 6.

Figure 6: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used mixed model to analyze the Δ QTcF effect. The model includes treatment as fixed effects and baselines as covariate. The analysis results are listed in Table 5. The largest upper bounds of the 2-sided 90% CI for the mean differences between 1500 mg Telotristat Etiprate and placebo is 3.7 ms.

Table 5: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for 1500 mg Telotristat Etiprate and 400 mg Moxifloxacin

		Treatment Group								
		1500 mg Telotristat Etiprate				400 mg Moxifloxacin				
		Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
0.5	-3.7	47	-3.7	0.0	(-2.3, 2.3)	46	-2.6	1.1	(-1.2, 3.4)	(-2.0, 4.3)
1	-5.4	47	-7.3	-1.8	(-4.2, 0.5)	46	-2.5	2.9	(0.5, 5.3)	(-0.3, 6.2)
1.5	-6.7	47	-9.0	-2.3	(-4.5, -0.1)	46	-1.7	5.0	(2.8, 7.3)	(2.0, 8.1)
2	-7.8	46	-9.8	-2.0	(-4.2, 0.2)	45	-1.2	6.6	(4.4, 8.8)	(3.6, 9.7)
3	-9.2	46	-9.6	-0.4	(-2.6, 1.8)	46	-0.5	8.7	(6.5, 10.9)	(5.7, 11.7)
4	-7.6	46	-8.4	-0.8	(-2.7, 1.1)	46	2.6	10.2	(8.3, 12.1)	(7.6, 12.8)
6	-4.6	47	-7.1	-2.5	(-4.9, -0.2)	45	3.4	8.0	(5.6, 10.5)	(4.8, 11.3)
8	-6.6	47	-6.3	0.3	(-1.8, 2.5)	44	0.8	7.4	(5.2, 9.6)	(4.4, 10.4)
12	-7.8	47	-8.7	-0.9	(-3.2, 1.4)	45	-1.6	6.1	(3.8, 8.5)	(2.9, 9.3)
24	-7.5	47	-7.8	-0.3	(-2.8, 2.2)	46	-3.9	3.6	(1.1, 6.1)	(0.2, 7.1)
36	-9.9	47	-10.0	-0.1	(-2.5, 2.3)	46	-6.6	3.3	(0.9, 5.7)	(-0.0, 6.6)
48	-7.3	47	-6.8	0.5	(-2.3, 3.3)	46	-5.5	1.8	(-1.0, 4.6)	(-2.1, 5.6)
60	-10.6	45	-9.4	1.2	(-1.2, 3.7)	46	-9.1	1.5	(-0.9, 3.9)	(-1.8, 4.8)

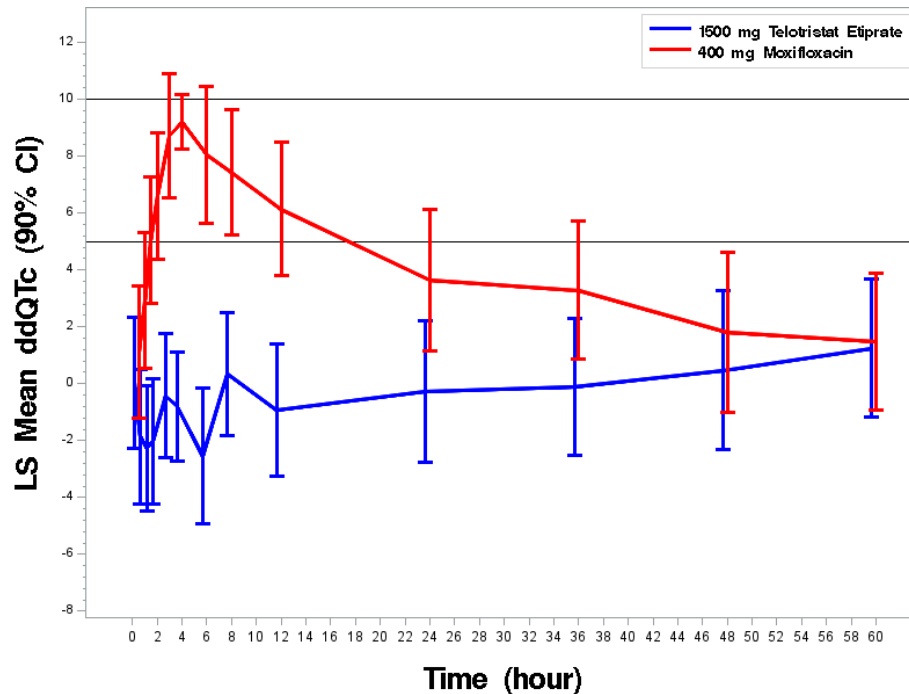
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 5. The largest unadjusted 90% lower confidence interval is 8.3 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 7.6 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of $\Delta\Delta\text{QTcF}$ Over Time

The following figure displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups.

Figure 7: Mean and 90% CI $\Delta\Delta\text{QTcF}$ Time Course



5.2.1.4 Categorical Analysis

Table 6 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 450 ms and 480 ms, and >500 ms. No subject's QTcF is above 480 ms.

Table 6: Categorical Analysis for QTcF

Treatment Group	Total N	Value $\leq$ 450 ms	450 ms<Value $\leq$ 480 ms	480 ms<Value $\leq$ 500 ms	Value $>$ 500
1500 mg Telotristat Etiprate	47	47 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
400 mg Moxifloxacin	46	45 (97.8%)	1 (2.2%)	0 (0.0%)	0 (0.0%)
Placebo	45	45 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 7 lists the categorical analysis results for ΔQTcF . No subject's change from baseline is above 60 ms.

Table 7: Categorical Analysis of Δ QTcF

Treatment Group	Total N	Value $\leq$ 30 ms	30 ms<Value $\leq$ 60 ms	60 ms<Value $\leq$ 90 ms	Value>90 ms
1500 mg Telotristat Etiprate	47	47 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
400 mg Moxifloxacin	46	45 (97.8%)	1 (2.2%)	0 (0.0%)	0 (0.0%)
Placebo	45	45 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the Δ HR effect. The model includes treatment as fixed effects and baseline as covariate. The analysis results are listed in Table 8. The largest upper bounds of the 2-sided 90% CI for the mean different between 1500 mg Telotristat Etiprate and placebo is 3.4 bpm, respectively. Table 9 presents the categorical analysis of HR. Two subjects who experienced HR interval greater than 100 bpm are in telotristat etiprate 1500 mg group.

Table 8: Analysis Results of Δ HR and $\Delta\Delta$ HR for 1500 mg Telotristat Etiprate and 400 mg Moxifloxacin

		Treatment Group							
	Placebo	1500 mg Telotristat Etiprate				400 mg Moxifloxacin			
	ΔHR	ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	10.8	47	10.4	-0.4	(-2.4, 1.5)	46	8.9	-1.9	(-3.9, 0.0)
1	10.4	47	9.8	-0.6	(-2.5, 1.3)	46	8.9	-1.6	(-3.5, 0.4)
1.5	9.6	47	8.9	-0.7	(-2.7, 1.3)	46	9.2	-0.5	(-2.5, 1.6)
2	9.0	46	6.9	-2.1	(-4.1, -0.1)	45	8.4	-0.5	(-2.5, 1.4)
3	5.7	46	5.3	-0.4	(-2.5, 1.7)	46	7.2	1.5	(-0.6, 3.6)
4	4.5	46	5.4	0.9	(-1.2, 3.1)	46	4.8	0.3	(-1.9, 2.4)
6	10.0	47	10.2	0.2	(-2.1, 2.4)	45	10.3	0.3	(-2.0, 2.5)
8	5.1	47	8.0	2.9	(0.8, 5.0)	44	7.5	2.4	(0.3, 4.6)
12	10.9	47	12.0	1.2	(-0.8, 3.1)	45	12.6	1.7	(-0.3, 3.7)
24	9.8	47	11.3	1.5	(-0.4, 3.4)	46	8.6	-1.2	(-3.1, 0.7)
36	12.5	47	12.0	-0.5	(-2.9, 2.0)	46	12.0	-0.5	(-2.9, 2.0)
48	10.5	47	10.5	0.0	(-2.3, 2.4)	46	10.9	0.4	(-1.9, 2.8)
60	13.7	45	13.6	-0.2	(-2.6, 2.3)	46	13.8	0.1	(-2.4, 2.5)

Table 9: Categorical Analysis for HR

Treatment Group	Total N	HR ≤ 100 bpm	HR >100 bpm
1500 mg Telotristat Etiprate	47	45 (95.7%)	2 (4.3%)
400 mg Moxifloxacin	46	45 (97.8%)	1 (2.2%)
Placebo	45	44 (97.8%)	1 (2.2%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean different between 1500 mg Telotristat Etiprate and placebo is 4.2 ms. Table 11 presents the categorical analysis of PR. One subject who experienced PR interval greater than 200 ms is in telotristat etiprate 1500-mg group.

Table 10: Analysis Results of Δ PR and $\Delta\Delta$ PR for 1500 mg Telotristat Etiprate and 400 mg Moxifloxacin

		Treatment Group							
	Placebo	1500 mg Telotristat Etiprate				400 mg Moxifloxacin			
	ΔPR	ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	-1.2	47	-2.4	-1.2	(-3.7, 1.3)	46	-0.2	1.1	(-1.5, 3.6)
1	-3.1	47	-3.2	-0.1	(-2.5, 2.4)	46	-3.2	-0.1	(-2.6, 2.4)
1.5	-5.4	47	-3.5	1.9	(-0.8, 4.6)	46	-5.2	0.2	(-2.6, 2.9)
2	-5.0	46	-4.4	0.6	(-2.0, 3.3)	45	-5.9	-0.9	(-3.6, 1.8)
3	-5.0	46	-4.8	0.3	(-2.2, 2.7)	46	-6.7	-1.7	(-4.1, 0.8)
4	-3.8	46	-4.4	-0.6	(-2.9, 1.7)	46	-6.8	-3.0	(-5.3, -0.7)
6	-7.1	47	-7.4	-0.3	(-3.0, 2.4)	45	-9.5	-2.4	(-5.1, 0.4)
8	-4.5	47	-7.0	-2.5	(-5.0, -0.1)	44	-7.8	-3.3	(-5.8, -0.8)
12	-5.5	47	-8.1	-2.6	(-5.8, 0.6)	45	-7.4	-1.9	(-5.1, 1.3)
24	-4.1	47	-6.1	-2.1	(-4.9, 0.8)	46	-5.7	-1.6	(-4.5, 1.2)
36	-6.1	47	-5.7	0.3	(-3.0, 3.7)	46	-5.3	0.8	(-2.6, 4.1)
48	-4.1	47	-2.9	1.2	(-1.8, 4.2)	46	-3.1	1.0	(-2.0, 4.0)
60	-7.5	45	-7.2	0.2	(-3.3, 3.8)	46	-5.8	1.6	(-1.9, 5.2)

Table 11: Categorical Analysis for PR

Treatment Group	Total N	PR ≤ 200 ms	PR >200 ms
1500 mg Telotristat Etiprate	47	46 (97.9%)	1 (2.1%)
400 mg Moxifloxacin	46	45 (97.8%)	1 (2.2%)
Placebo	45	45 (100%)	0 (0.0%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effects and baseline values as a covariate. The analysis results are listed in Table 12. The largest upper bounds of the 2-sided 90% CI for the mean different between 1500 mg Telotristat Etiprate and placebo is 1.1 ms. Table 13 presents the categorical analysis of QRS. Eight subjects who experienced QRS interval greater than 110 ms are in telotristat etiprate 1500-mg group.

Table 12: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for 1500 mg Telotristat Etiprate and 400 mg Moxifloxacin

		Treatment Group							
	Placebo	1500 mg Telotristat Etiprate				400 mg Moxifloxacin			
	ΔQRS	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.5	0.4	47	0.2	-0.2	(-0.9, 0.4)	46	0.1	-0.3	(-0.9, 0.3)
1	-0.0	47	-0.2	-0.2	(-0.7, 0.3)	46	-0.2	-0.1	(-0.6, 0.4)
1.5	-0.4	47	-0.6	-0.2	(-0.7, 0.3)	46	-0.5	-0.0	(-0.5, 0.5)
2	-0.4	46	-0.5	-0.1	(-0.5, 0.4)	45	-0.3	0.1	(-0.4, 0.6)
3	-0.3	46	-0.5	-0.1	(-0.6, 0.3)	46	-0.3	0.0	(-0.4, 0.4)
4	-0.1	46	-0.4	-0.3	(-0.7, 0.2)	46	-0.2	-0.0	(-0.4, 0.4)
6	-0.3	47	-0.2	0.1	(-0.4, 0.6)	45	-0.5	-0.2	(-0.7, 0.3)
8	-0.2	47	-0.4	-0.2	(-0.7, 0.4)	44	-0.3	-0.1	(-0.7, 0.5)
12	-0.4	47	-0.3	0.1	(-0.5, 0.6)	45	-0.5	-0.2	(-0.7, 0.4)
24	-0.3	47	-0.7	-0.4	(-1.1, 0.3)	46	-0.5	-0.2	(-0.9, 0.5)
36	-0.1	47	0.2	0.3	(-0.6, 1.2)	46	-0.3	-0.2	(-1.1, 0.7)
48	0.2	47	0.3	0.2	(-0.7, 1.1)	46	0.1	-0.0	(-0.9, 0.9)
60	-0.0	45	0.2	0.2	(-0.7, 1.1)	46	-0.1	-0.0	(-0.9, 0.9)

Table 13: Categorical Analysis for QRS

Treatment Group	Total N	QRS ≤ 110 ms	QRS > 110 ms
1500 mg Telotristat Etiprate	47	39 (83.0%)	8 (17.0%)
400 mg Moxifloxacin	46	40 (87.0%)	6 (13.0%)
Placebo	45	37 (82.2%)	8 (17.8%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between ΔQT_c and telotristat eliprate and ΔQT_c and the metabolite LP-778902 was investigated separately by linear mixed-effects modeling. The model used QT_cF change from baseline (ΔQT_cF) as the dependent variable and observed drug concentrations as the continuous variable (0 for the placebo treatment), treatment (active (IND=1) or placebo (IND=0)), day and nominal time postdose as categorical factors, and random effects on intercept and slope. The general model formula is shown below.

$$\Delta QT_{c\ l,k,d,t} = \mu_l + p_t + qC_{l,k,d,t} + V_k C_{l,k,d,t} + W_k + \varepsilon_{l,k,d,t}$$

μ_l = Fixed effect, treatment specific (l) intercept (active ($l=1$), placebo ($l=0$))

p_t = Fixed effect, Study Time (t) specific intercept (as factor)

q = Fixed effect, slope parameter

$C_{l,,}$ = Independent variable, Concentration for time point(t), treatment(l), Study Day (d), and subject (k)

V_k = Random effect, random subject level (k) effect on slope (q)

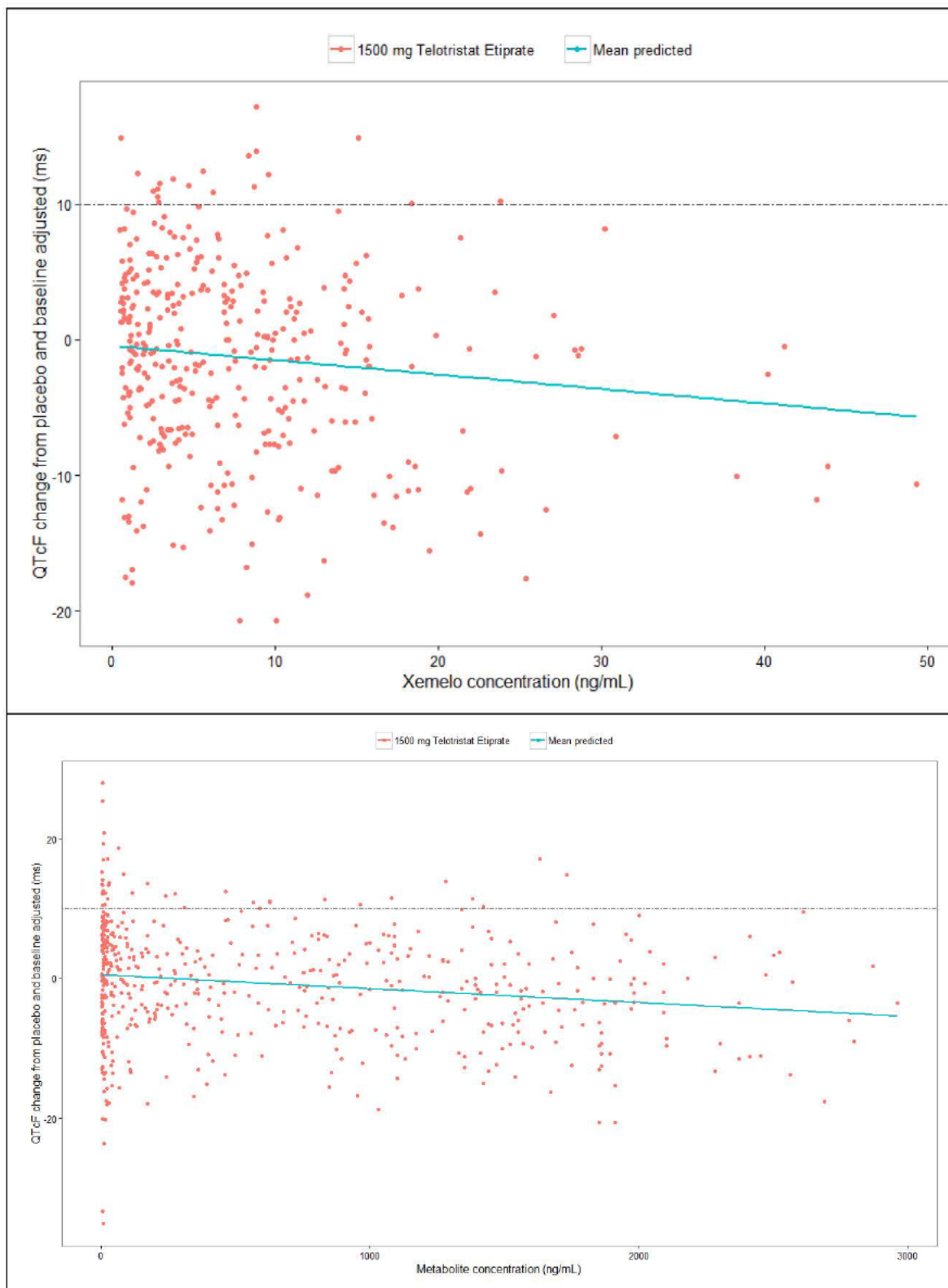
W_k = Random effect, random subject level (k) effect on intercept (μ)

$\varepsilon_{l,,}$ = Random effect, residual error for time point(t), treatment(l), Study Day (d), and subject (k)

Placebo-adjusted change from baseline in QT_cF ($\Delta\Delta QT_cF$) was estimated from the concentration- ΔQT_cF model by contrasting active-placebo treatment at the clinically relevant concentration.

The relationships between $\Delta\Delta QT_cF$ and telotristat concentrations and metabolite concentrations are visualized in Figure 8 with a shallow but statistically significant negative exposure-response relationships (slope = -0.106 with 95% CI: -0.179, -0.0331 ms per ng/mL and slope= -0.00198 with 95% CI: -0.00274, -0.00122 ms per ng/mL for telotristat and metabolite LP-778902 respectively).

Figure 8: $\Delta\Delta\text{QTcF}$ vs. telotristat eliprate concentration (top panel) and $\Delta\Delta\text{QTcF}$ vs. Metabolite (LP-778902) concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

Subject No. 137 reported palpitations approximately 1 hour and 28 minutes after the dose of telotristat etiprate that lasted for less than 1 minute and were considered to be probably related to the study drug. A HR of 71 bpm was observed at the nearest corresponding time point (1.5 hour) at which cardiac monitoring was performed, which was an increase of 14 bpm compared to baseline (57 bpm); however, similar increases in HR were seen for this subject at the 1.5 hour timepoint following placebo administration.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Maximum proposed clinical dosing regimen = 500 mg TID	
Maximum tolerated dose	1500 mg single dose clinically NOAEL for LX1606 administered as a single dose by oral gavage to rats is 2000 mg/kg	
Principal adverse events	GI-related adverse events are the most common (nausea, diarrhea, and abdominal pain)	
Maximum dose tested	Single Dose	1500 mg
	Multiple Dose	500 mg TID for 14 days
Exposures Achieved at Maximum Tested Dose	Single Dose	1500mg : Mean (%CV) C _{max} = 10.48 ng/mL (%CV 47.2) and AUC _{0-last} = 37.14 ng*hr/mL (%CV 50.9) for telotristat etiprate (LX1606) Mean (%CV) C _{max} = 1187.0 ng/mL (%CV 23.4) and AUC _{0-last} = 7289.2 ng*hr/mL (%CV 24.3) for active moiety (LX1033)
	Multiple Dose	500 mg TID (Day 14) Mean (%CV) C _{max} = 4.89 ng/mL (%CV 29.2) and AUC _{0-24hr} = 20.97ng*hr/mL (%CV 29.5) at Day 14 for telotristat etiprate (LX1606) Mean (%CV) C _{max} = 1028.0 ng/mL (%CV 33.5) and AUC _{0-24hr} = 4237.5 ng*hr/mL (%CV 34.0) at Day 14 for active moiety (LX1033)
Range of linear PK	Single dose PK studies have been conducted up to 1500 mg. Exposure was approximately linear for the major metabolite LX1033. Levels of parent LX1606 were substantially lower than for the major metabolite (~400X lower) and also approximately linear with dose.	
Accumulation at steady state	There was no significant accumulation following 14 days of dosing at 500 mg TID.	
Metabolites	A human AME study has been conducted with ¹⁴ C-telotristat etiprate (LX1606) following oral administration at 500mg. LX1606 levels were very low with an AUC _{0-last} of 7.4 ng*hr/mL). The major metabolite was found to be the acid metabolite of LX1606, i.e. LX1033. All other metabolites were at levels <10% of the total plasma AUC, with the exception of an acid metabolite of oxidative deaminated decarboxylated LX1033. All metabolites were at low levels with LX1033 having an AUC _{0-last} of 2.74 ug equiv*h/mL.	
Absorption	Absolute/Relative Bioavailability	LX1606 is rapidly absorbed (median T _{max} 1 hour) and rapidly eliminated with all plasma levels BLOQ by 4 hrs. The major route of elimination was the feces at approximately 92.8% of the dose; < 1% of the dose was eliminated in the urine. While a precise %F cannot be calculated, clearly it is very low.
	T _{max}	LX1606 T_{max} in fasted = mean 1.8 hr (range 0.5-2.0 hr; in fed = mean 3.5 hr (range 1.5-6 hr)

		• LX1033 T_{max} in fasted = mean 2.0 hr (range 1-4 hr); fed = mean 3.5 hr (2.0-6.0 hr)
Distribution	Vd/F or Vd	No Vd/F available. No IV study conducted.
	% bound	Human plasma protein binding is >99% for both LX1606 and LX1033.
Elimination	Route	• Feces 92.8% of the dose • Urine <1% of the dose.
	Terminal $t_{1/2}$	LX1606 $t_{1/2}$ cannot be accurately determined due to rapid conversion. LX1033 $t_{1/2}$ for fasted = mean 6.2 hr (range 4.6-7.6 hr); fed = mean 7.2 hr (range 6.3–10.2 hr)
	CL/F or CL	CL/F for fasted = 304 L/hr; fed = 152 L/hr
Intrinsic Factors	Age	Population PK planned for 3 rd Q 2014
	Sex	Population PK planned for 3 rd Q 2014
	Race	Population PK planned for 3 rd Q 2014
	Hepatic & Renal Impairment	Population PK planned for 3 rd Q 2014
Extrinsic Factors	Drug interactions	In vitro studies suggest LX1606 may be a P-gp and Cyp 3A4 inhibitor. DDI studies are planned with midazolam (Cyp3A4 substrate) and fexofenadine (P-gp substrate).
	Food Effects	LX1606 $t_{1/2}$ cannot be accurately determined due to rapid conversion. LX1033 $t_{1/2}$ for fasted = mean 6.2 hr (range 4.6-7.6 hr); fed = mean 7.2 hr (range 6.3–10.2 hr) AUC_{0-last} for LX1606 for fasted 7.0 ng*hr/mL; for fed 33.2 ng*hr/mL. For 1033 AUC_{0-last} for fasted 2923.5 ng*hr/mL; for fed 3383.3 ng*hr/mL. A food effect study with the final market image formulation is planned.
Expected High Clinical Exposure Scenario	We believe any changes that might occur are well covered by supra therapeutic dose given its linear pharmacokinetics.	

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

/s/

MOH JEE NG
08/11/2016

QIANYU DANG
08/11/2016

JUSTIN C EARP
08/11/2016

JIANG LIU
08/11/2016

MICHAEL Y LI
08/11/2016

CHRISTINE E GARNETT
08/11/2016

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208794 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Xermelo Established/Proper Name: telotristat etiprate Dosage Form: oral tablets Strengths: 250 mg		
Date of Application: March 30, 2016 Date of Receipt: March 30, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: November 30, 2016		Action Goal Date (if different): November 30, 2016
Filing Date: May 29, 2016		Date of Filing Meeting: May 17, 2016
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): Telotristat Etiprate is a tryptophan hydroxylase inhibitor indicated for the (b) (4) treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumors who are receiving somatostatin analogue therapy.		

Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☒ 505(b)(1) ☐ 505(b)(2)
<i>If 505(b)(2) NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 .	☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	☐ 351(a) ☐ 351(k)
Review Classification: <i>The application will be a priority review if:</i> <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> <i>The product is a Qualified Infectious Disease Product (QIDP)</i> <i>A Tropical Disease Priority Review Voucher was submitted</i> <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i>	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☒ Fast Track Designation ☐ Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 078749	

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	☒	☐		
Are the established/proper and applicant names correct in electronic archive? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.</i>	☒	☐		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	☒	☐	☐	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	☐	☒		
If yes , explain in comment column.			N/A	
If affected by AIP , has OC been notified of the submission? If yes , date notified:	☐	☐	N/A	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov:</i>): ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required			

<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</i>	Payment of other user fees: ☒ Not in arrears ☐ In arrears			
User Fee Bundling Policy <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> ☒ Yes ☐ No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). If yes , answer the bulleted questions below:	☐	☒		
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].	☐	☐		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>	☐	☐		

Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm		☐	☒		
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm	☐	☒			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	☐	☐	☒		
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☒	☐		
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	☐	☐	☒		

BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	☐	☐	☒	
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Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes, BLA #	☐	☐	☒	

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included.</i> <i>Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	☒	☐		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	☒	☐		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	☒	☐		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				

Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	☐	☒	☐	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	☐	☐	N/A	Not required because of orphan designation
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☐	
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	☐	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³)</i>	☐	☐		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	☒	☐	☐	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	☐	☒	☐	

2

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm>

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm>

Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	☒	☐		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in Physician Labeling Rule (PLR) format? ⁴	☒	☐		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format?	☒	☐	☐	
Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒	☐	☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	☐	☐	☒	
<i>If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.</i>				
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☐	☒	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (send WORD version if available)	☐	☒	☐	

Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☐	☒	☐	
OTC Labeling	☒ Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	☒	☐	☐	QT Consult and DPMH Consults requested
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s):	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 2/24/2015	☒	☐		
Any Special Protocol Assessments (SPAs)? Date(s): 11/20/14	☒			Carcinogenicity SPA

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 17, 2016

BACKGROUND: Lexicon developed 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 was held February 24, 2015.

Stamp Date: March 30, 2016

Filing Date: May 29, 2016

Day 74 Letter Date: June 12, 2016

Review Completion Goal Date according to GRMP: November 9, 2016

PDUFA Goal Date: November 30, 2016

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Brian Strongin	Y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Stephanie Omokaro		Y
Division Director/Deputy	Donna Griebel		Y
Office Director/Deputy	Julie Beitz and Amy Egan		y
Clinical	Reviewer:	Wen-Yi Gao	Y
	TL:	Stephanie Omokaro	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		

OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Insook Lim	Y
	TL:	Sue Chih Lee	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Shen Li	Y
Biostatistics	Reviewer:	George Kordzakhia	Y
	TL:	Yeh-Fong Chen	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ke Zhang	Y
	TL:	David Joseph	Y
Statistics (carcinogenicity)	Reviewer:	Feng Zhou	N
	TL:	Karl Lin	N
Product Quality (CMC) Review Team:	ATL:	Donuta Gromek-Woods	Y
	RBPM:	Troung Quach	y
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:	Zenfang Ge	Y
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Mishale Mistry	Y
	TL:	Sherly Abraham	Y
OSE/DRISK (REMS)	Reviewer:	Jamie Wilkins-Parker	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	Y
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
Discipline *For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"	Reviewer:		
	TL:		
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL 505 b)(2) filing issues: - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? - Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):		☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO	
Electronic Submission comments List comments:	☐ Not Applicable ☒ No comments	

CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain:	☒ YES ☐ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an NME NDA or original BLA, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? Comments:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF Abuse Liability/Potential Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> Is the product an NME?	☒ YES ☐ NO
<u>Environmental Assessment</u> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	☒ YES ☐ NO ☐ YES ☐ NO
<u>Facility Inspection</u> Establishment(s) ready for inspection? Comments:	☐ Not Applicable ☒ YES ☐ NO

<u>Facility/Microbiology Review (BLAs only)</u> Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs only)</u> Comments:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☐ YES ☒ NO ☐ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	None
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Julie Beitz, M.D. Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): July 8, 2016 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. <u>Review Classification:</u> ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☐	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAAs completed: April 2016

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
07/12/2016

REGULATORY PROJECT MANAGER PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 208794

Application Type: New NDA

Drug Name(s)/Dosage Form(s): Xermelo (telotristat etiprate) Tablets

Applicant: Lexicon Pharmaceuticals, Inc.

Receipt Date: March 30, 2016

Goal Date: November 30, 2016

1. Regulatory History and Applicant's Main Proposals

Lexicon developed LX1606 (telotristat etiprate) 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 was held February 24, 2015.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 1, 2016. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- NO** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment: *HL is not in two-column format and the margin is not 1/2 inch.*

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- NO** 3. A horizontal line must separate:
- HL from the Table of Contents (TOC), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment: *There weren't any horizontal lines separating HL and the TOC and the TOC and FPI.*

- NO** 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment: *There weren't horizontal lines presenting headings from HL.*

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

- NO** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Several references were missing.*

- YES** 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
---------	-------------------

Selected Requirements of Prescribing Information

• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading, "**HIGHLIGHTS OF PRESCRIBING INFORMATION**" must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- N/A** 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

Selected Requirements of Prescribing Information

13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement “*See full prescribing information for complete boxed warning.*”)

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

- N/A** 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

- YES** 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

- N/A** 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 8/2015**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

- NO** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- NO** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: Subsections 5.1 and 5.2 should be added. Subsection 6.1 should be changed to Clinical Trials Experience and Subsection 12.6 should be added.
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- NO** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, "[see *Warnings and Precautions (5.2)*]."

Comment: *Brackets must be italicized.*

Selected Requirements of Prescribing Information

- N/A** 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 34. The following heading “**FULL PRESCRIBING INFORMATION**” must be **bolded**, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 35. All text in the BW should be **bolded**.

Comment:

- N/A** 36. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used.) For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

N/A 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **PROPRIETARY NAME** safely and effectively. See full prescribing information for **PROPRIETARY NAME**.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are text (6.x)

To report **SUSPECTED ADVERSE REACTIONS**, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

See 17 for **PATIENT COUNSELING INFORMATION** and FDA-approved patient labeling **OR** and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 Subsection Title

14.2 Subsection Title

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

BRIAN K STRONGIN
05/18/2016