CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022231Orig1s000

OTHER ACTION LETTERS

NDA 022231

COMPLETE RESPONSE

Mallinckrodt Pharmaceuticals Ireland Ltd
c/o Mallinckrodt Hospital Products Inc.
Attention: Sheryl Raukete, B.Pharm (Hons)
Executive Director, Global Regulatory Affairs Strategy
90 Washington Valley Road
Bedminster, NJ 07921

Dear Ms. Raukete:

Please refer to your new drug application (NDA) dated May 1, 2009, received May 4, 2009, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for terlipressin injection.

We acknowledge receipt of your amendment dated August 18, 2021, which constituted a complete response to our September 11, 2020, action letter.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

(1) Our field investigator could not complete inspection of the (b) (4) (b) (4) manufacturing facility at (b) (4) because the facility was not ready for inspection. Satisfactory inspection is required before this NDA may be approved. Please notify us in writing when this facility is ready for inspection.

PRESCRIBING INFORMATION

We acknowledge receipt of your draft labeling received on February 15, 2022. We reserve further comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

CARTON AND CONTAINER LABELING

We acknowledge receipt of your draft Carton and Container labeling on February 15, 2022. We reserve further comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to our correspondence dated, November 5, 2021, which addresses the proposed proprietary name, TERLIVAZ. This name was found to be acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiency, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, M.D.
Deputy Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
02/18/2022 11:01:02 AM

NDA 22231

COMPLETE RESPONSE

Mallinckrodt Hospital Products IP Limited
Attention: James Burgess
Associate Director, Regulatory Affairs
1425 US Route 206
Bedminster, NJ 07921

Dear Mr. Burgess:

Please refer to your new drug application (NDA) originally submitted May 1, 2009, received May 4, 2009, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Terlivaz (terlipressin) 1 mg injection.

We acknowledge receipt of your resubmission dated March 12, 2020, which constituted a complete response to our November 4, 2009, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

In our 2009 Complete Response letter, we stated that "[y]ou will need to conduct at least one additional adequate and well-controlled study to demonstrate the efficacy and safety of intravenous terlipressin for the treatment of HRS type I. This study will need to be successful, using pre-specified endpoint(s) and analytic plan, at $p<0.05$."

To address this requirement and support a claim for the treatment of adults with hepatorenal syndrome (HRS) type 1, you submitted the results of a randomized, double-blind, placebo-controlled trial comparing intravenous (IV) terlipressin to placebo in adult patients with HRS type I (CONFIRM). The prespecified primary endpoint in CONFIRM was the incidence of verified HRS reversal, defined as 2 consecutive serum creatinine values ≤1.5 mg/dL at least 2 hours apart, while on treatment, by Day 14 or discharge (on treatment defined as up to 24 hours after the final dose of study drug). In order to be counted in the primary endpoint, patients also needed to be alive without renal replacement therapy for at least 10 days after achieving verified HRS reversal.

We agree that CONFIRM met its primary endpoint; however, safety findings in CONFIRM, and in particular, the greater incidence of serious adverse events of respiratory failure in the terlipressin (14%) as compared to the placebo arm (5%) raise concern that the risks of terlipressin may outweigh its benefits, particularly given

unresolved questions about the clinical significance of the primary endpoint. We acknowledge your proposed risk mitigation strategy; however, the strategy has not been prospectively tested, and it is unclear whether its implementation would adversely impact terlipressin's efficacy for its proposed use.

To address this issue, you will need to conduct an adequate and well-controlled study that demonstrates an acceptable risk-benefit profile, perhaps utilizing the proposed risk mitigation strategy. The primary endpoint and analytic plan should be discussed with and agreed upon by the FDA prior to initiation. Given the data proffered thus far, we believe a two-sided p-value of 0.1 could provide sufficient reassurance that the risk mitigation strategy does not adversely impact the product's efficacy.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

PROPRIETARY NAME

Please refer to correspondence dated, April 28, 2020 which addresses the proposed proprietary name, Terlivaz. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

---

[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.

- Present tabulations of the new safety data combined with the original application data.

- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider

this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301)796-1129.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELLIS F UNGER
09/11/2020 05:07:53 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022231 **COMPLETE RESPONSE**

Orphan Therapeutics, LLC
Attention: Candice Teuber, PharmD.
3 Werner Drive Suite 210
Lebanon, NJ 08833

Dear Dr. Teuber:

Please refer to your new drug application (NDA) dated May 4, 2009, received May 4, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Lucassin (terlipressin) injection, 1 mg.

We also refer to your submissions dated May 27, June 30, July 1 and 25, August 1, 8, 13, 20, September 5 and 8, October 3, 9, 29, 2008 and January 29, April 30, May 1 and 21, June 8, 9, 10, 11, 29, July 8, 28, 30, September 2, 8, 22, 30, October 12, 13,15 and 16, 2009.

We have completed our review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address the issues.

CLINICAL/STATISTICAL

To support a claim for the treatment of patients with hepatorenal syndrome (HRS) type I, you submitted two studies, OT-0401 (a double-blind, placebo-controlled study in HRS type I patients) and TAHRS (a smaller, open-label, cross-over study in HRS type I and II patients). In OT-0401, terlipressin, compared to placebo, appeared to show a modest reduction in serum creatinine, but the study failed to show durability of effect. Using the prespecified primary endpoint and the original analytic plan, the results of OT-401 were not statistically significant. Your most favorable analysis, using an endpoint developed post-hoc with a generally unacceptable redefinition of treatment success, reaches statistical significance, but comes nowhere close to the p-value necessary to support approval based upon a single study. The smaller, open-label TAHRS also failed on its pre-specified primary endpoint and failed to show a sustained effect on serum creatinine. In terms of support for the safety of the 14-day terlipressin regimen proposed in labeling, your application includes experience in only 11 subjects in study OT-0401 and 9 subjects in TAHRS with exposure for 14 days. The extent of exposure is clearly insufficient to support the safety of terlipressin for its intended use. Moreover, although the numbers of adverse events were small, many important serious adverse events tended to occur more frequently, or earlier (i.e., death), in terlipressin-treated subjects, compared to subjects in the respective control groups.

You will need to conduct at least one additional adequate and well-controlled study to demonstrate the efficacy and safety of intravenous terlipressin for the treatment of HRS type I. This study will need to be successful, using pre-specified endpoint(s) and analytic plan, at $p<0.05$. The Division is willing to meet with you to discuss possible trial designs and endpoints that you might wish to consider as alternatives to the endpoint pre-specified in OT-0401, as well as the extent of safety data that should be collected.

Vital Signs: We note that the OT-0401 protocol directed assessment of vital signs at baseline and then two hours after each dose; in the TAHRS study, vital signs were obtained once each day, and the time of assessment relative to administration of study drug was not recorded. Given the brief half-life of terlipressin, it appears that there was no assessment of vitals signs during the peak drug effect. In future trial(s), we suggest you obtain vital sign data at peak drug effect, to better characterize the pharmacodynamic effects of terlipressin.

Laboratory Data: We note that the OT-0401 protocol did not include collection of complete blood counts in the monitoring scheme; TAHRS required a complete blood count at baseline, Day 7 and Day 15. For completeness, we suggest you obtain complete blood counts with leukocyte differential counts and platelet counts should you decide to undertake an additional trial.

PRODUCT QUALITY

1. In response to our recommendation for the confirmation of (b) (4) you have stated that (b) (4)

   Provide data in support of this statement (b) (4) and include an acceptance limit in drug substance specification, if necessary.

2. The specification for drug substance should include testing for heavy metals to ensure that every batch meets the USP <231> requirement. Please provide a revised drug substance specification.

3. The analytical method intended for quantitation of residual solvents in the drug substance is considered inferior to USP method based on limit of detection (LOD) and limit of quantification (LOQ) values in the validation report. Additionally, data provided in Attachment 2 in response (dated 09-SEP-09) to the information request letter are inconsistent with the LOD and LOQ values per the validated method. For example, the LOD for the residual solvent, (b) (4) is (b) (4) ppm per the validation data, whereas the results reported in Attachment 2 were (b) (4) ppm. Please provide an explanation and justification for the use of the validated method instead of the USP method.

4. Based on the results provided for three drug substance lots (S.3.2.2.3 Table 14), we recommend that you incorporate testing for (b) (4) in the specification for drug substance.

5. Characterize the (b) (4) (b) (4)

LABELING

We have provided draft recommendations to several sections of the labeling, but reserve comment on the remaining sections until the application is otherwise adequate. Please submit draft labeling that incorporates revisions to the attached labeling.

Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

Please submit draft carton and container labeling revised as follows:

- Vial Label: Include drug product composition (excipients and quantities) as required for parenteral dosage forms.
- Carton Label: Revise the statement from:

(b) (4)

To:

"Once reconstituted, store refrigerated (2-8°C) and use within (b) (4) hours. Do not freeze."

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) and (b) (4) manufacturing facilities for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's *Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants*, May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301) 796-1129.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Draft labeling text

11 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22231	ORIG-1	ORPHAN THERAPEUTICS LLC	LUCASSIN (TERLIPRESSIN)

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

/s/

ELLIS F UNGER
11/04/2009