CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022231Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	022231		
Applicant Name	Mallinckrodt Pharmaceuticals Ireland Ltd.		
Drug Product Name	TERLIVAZ® (terlipressin)		
Dosage Form.	Injection, powder for reconstitution		
Proposed Strength(s)	0.85 mg		
Route of Administration	Intravenous		
Maximum Daily Dose	3.4 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Indicated to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function.		
Drug Product Description	Terlipressin is a lyophilized powder in a single-dose vial for reconstitution, equivalent to 1 mg terlipressin acetate.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 2°C to 8°C in the original carton to protect from light.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Manufacturing	Vidya Pai OPMA/DPMAIV/PMB12	Sateesh Sathigari OPMA/DPMAIV/PMB12
	Other (specify):	N/A	
	RBPM	Grafton Adams OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver	

		ONDP/DNDPIII/NDPB5
Consults	None.	

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 24 months is granted for the drug product when stored at 2°C to 8°C in the original carton to protect from light.

b. Additional Comments for Action
None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. Background

The Applicant, Mallinckrodt Pharmaceuticals Ireland Ltd., resubmitted the 505(b)(1) NDA for Terlivaz® (terlipressin) for injection, NDA 022231, as a Class 2 Resubmission (Supporting document 119, dated 6/9/2022). This NDA Resubmission 119 is intended to address a facility deficiency identified late in the review cycle for the previous NDA resubmission (see NDA 022231 Resubmission 104 and IQA reviews #1 and #2, dated 2/17/22). Specifically, a withhold recommendation was made for the labeling and secondary packaging facility, [redacted] (b) (4) due to cGMP deficiencies identified in an FDA inspection, resulting in a facility alert issued on [redacted] (b) (4) The Applicant withdrew this facility and then submitted [redacted] (b) (4) as the secondary packaging facility, but the latter facility was not ready for inspection, resulting in a withhold recommendation for this facility and a final Complete Response action for NDA 022231 resubmission 104 on February 18, 2022.

2. Summary of review issues and basis for recommendation

After the Complete Response action for NDA Resubmission 104, the Applicant withdrew the [redacted] (b) (4) and submitted a new labeling/secondary packaging facility, [redacted] (b) (4) which was

[redacted]

subsequently reviewed after receipt of NDA resubmission 119. This facility was approved based on previous history. Since there are no other changes to the other facilities or to the chemistry, manufacturing, and controls information submitted for all other OPQ disciplines, and this information had been previously reviewed and found to be adequate for all OPQ disciplines, the overall recommendation for this NDA from OPQ is Approval.

3. Additional comment regarding drug product stability data

In addition to submitting the new labeling/secondary packaging facility for review, the Applicant submitted documents containing accelerated, excursion, and in-use stability data for the drug product in NDA 022231 Resubmission 119, dated 6/9/2022. These data are not new stability data but rather a consolidation of previously submitted and reviewed stability data in support of the expiry dating and in-use periods of the terlipressin drug product. This update was provided for ease of review in the future, as stated by the Applicant, because these data had been previously removed from the current eCTD view of the application in an amendment to the eCTD file. Therefore, see previous IQAs, and drug product and microbiology reviews, for review of these data.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes, see previous integrated quality assessments for all disciplines.

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comparability Protocols (PACMP): No

Additional Lifecycle Comments: None.

Theodore Carver

Digitally signed by Theodore Carver
Date: 8/14/2022 09:28:09PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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

Theodore Carver

Digitally signed by Theodore Carver
Date: 8/14/2022 09:33:53PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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/

THEODORE E CARVER
08/14/2022 09:47:35 PM

Resubmitted NDA 022231 Terlivaz® (terlipressin) for Injection Integrated Quality Review #2

Recommendation: A Complete Response

Drug Name/Dosage Form	Terlivaz® (terlipressin) for Injection
Strength	Each single-dose vial contains 0.85 mg terlipressin (free base) equivalent to 1 mg terlipressin acetate
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Mallinckrodt Pharmaceuticals Ireland, Ltd., C/O Mallinkrodt Hospital Products, Inc.
Submission(s) Reviewed	Resubmitted NDA 022231, Sequence No. 0104, and all subsequent CMC amendments.

Quality Review Team

Discipline	Reviewer	Branch/division
Drug Substance	Daniel Jansen	OPQ/ONDP/DNDAPI/NDB3
Drug Product, Labeling, and Environmental Assessment	Theodore Carver	OPQ/ONDP/DNDPIII/NDPB5
Microbiology	Eric Adeeku	OPQ/OPMA/DMAI/MAB1
Process/ Facility	Vidya Pai	OPQ/OPMA/DPMAIII/PMB7
Biopharmaceutics	Joan Zhao	OPQ/ONDP/DB/BB3
Regulatory Business Process Manager	Grafton Adams	OPQ/OPRO/DRBPMI/RBPMB2
Application Technical Lead	Theodore Carver	OPQ/ONDP/DNDPIII/NDPB5

Executive Summary

1. Recommendations and Conclusions on Approvability

Although the Office of Pharmaceutical Quality review team has assessed NDA 022231 with respect to the drug substance, drug product, and microbiological quality and has determined that it meets all applicable standards for those disciplines, the manufacturing and facilities assessment has identified unresolved quality issues. The drug product labeling and secondary packaging facility (b) (4) (b) (4) currently has a 'Withhold' recommendation, because this facility was not ready for inspection by FDA. Therefore, from an OPQ perspective, this NDA is not deemed ready for approval until a satisfactory inspection has been completed for this facility. As such, OPQ recommends a Complete Response (CR) action from a product quality perspective.

2. Background Summary

The Applicant, Mallinckrodt Pharmaceuticals Ireland, Ltd. (C/O Mallinkrodt Hospital Products, Inc.), submitted this 505(b)(1) NDA for Terlivaz® (terlipressin) for Injection as a Class 2 Resubmission. The resubmission is intended to address deficiencies listed in the Complete Response Letter issued by the Agency on 11 September 2020. The IQA Review #1 of this resubmission recommended approval from the product quality perspective, including an approval recommendation for all manufacturing facilities. Subsequent to IQA Review #1, facility issues with this NDA were identified and a facility alert was issued. This review (IQA Review #2) is limited to the manufacturing and facilities review only, see previous integrated quality assessments for reviews with respect to other disciplines, as noted below.

3. Summary of Quality Assessments

3.1 Drug Substance (terlipressin acetate)

The drug substance, terlipressin acetate, is a synthetic peptide comprising 12 amino acids, and it contains a disulfide bridge between Cys4 and Cys9. The CMC information for the drug substance was previously reviewed and found adequate, and no new information regarding the drug substance is included in the current resubmission.

3.2 Drug product (Terlipressin Injection)

A) Product Design and Specification: Terlipressin for Injection is a sterile, lyophilized powder for reconstitution supplied in a single-dose glass vial containing 0.85 mg terlipressin (free base) equivalent to 1 mg terlipressin acetate. The CMC information for the drug product was previously reviewed and found adequate, and no new information is included in the current resubmission that is the subject of this review.

B) Drug Product Manufacturing: The CMC information for the manufacturing process was previously reviewed and found adequate, and no new information is included in the current resubmission.

C) Biopharmaceutics Aspects: This NDA resubmission did not include any new biopharmaceutics data or information and, hence, no biopharm evaluation is needed.

D) Container Closure System: Terlipressin drug product is packaged in 6-mL USP (b) (4) (b) (4) glass vials with (b) (4) stoppers, and aluminum flip-off seals. The CMC information for the manufacturing process was previously reviewed and found adequate, and no new information is included in the current resubmission.

4. Assessment of Manufacturing Facilities

In the manufacturing assessment #1 for the resubmitted NDA, the Office of Product Manufacturing Assessment (OPMA) recommended approval of all facilities, including the labeling and secondary packaging facility. After this review was submitted, a facility alert was noted for the contract packaging facility (performing vial labeling and secondary packaging), (b) (4) This alert was a result of a recent FDA inspection at the facility between (b) (4) and (b) (4) Based on these deficiencies, the OPMA review team recommended a 'Withhold' for this facility. On (b) (4) the Applicant submitted an amendment withdrawing the (b) (4) (b) (4) facility and adding a new facility for labeling and secondary packaging, (b) (4) However, in the form 365h submitted in this amendment, the Applicant indicated that this facility is not ready for inspection and will not be ready for inspection until (b) (4). The OPMA team recommended 'Withhold' based on inability of FDA to inspect this facility. Therefore, the final recommendation for this NDA resubmission is Withhold. See the draft facility deficiency below.

5. **Environmental Assessment**: The information to support the environmental assessment has not changed since the previous review. The applicant has claimed categorical exclusion citing 21 CFR§ 25.31(c) and indicated that, to the best of their knowledge, no extraordinary circumstances exist that would warrant preparation of an environmental assessment.

6. **Expiration Dating and Storage Conditions**: No changes to the previous review with respect to supporting stability data or shelf life are indicated. The stability data provided by the Applicant support a shelf-life of 24 months for the product when stored at 2°C to 8°C and a 48-hour hold period when stored at 2°C to 8 °C after reconstitution with 0.9 % sodium chloride.

7. **Quality Labeling**: The container and carton label were reviewed as part of the drug product review. The dosage form description, strength, established name, NDC #, Lot #/Expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Comments regarding the draft USPI were conveyed to the Applicant, and it will be finalized as part of the review. Refer to the labeling review for additional information.

8. **List of CMC Deficiencies:**
   Facilities:

(1) Our field investigator could not complete inspection of the (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.

9. **Life Cycle Knowledge Information:** See the Integrated Quality Assessment dated 18 August 2020 for the final Risk Assessment for this NDA.

OVERALL ASSESSMENT AND SIGNATURES:

From the chemistry, manufacturing and controls (CMC)/quality perspective, the resubmitted NDA 022231, Terlipressin for Injection, is not recommended for approval because the (b) (4) manufacturing facility at (b) (4) is not ready for inspection. A satisfactory inspection of this facility is required before this application may be approved.

Theodore Carver, Ph.D.
Senior Pharmaceutical Quality Assessor
Application Technical Lead

Theodore Carver

Digitally signed by Theodore Carver
Date: 2/17/2022 04:58:49PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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/

THEODORE E CARVER
02/17/2022 05:11:12 PM

Resubmitted NDA 022231 Terlivaz® (terlipressin) for Injection Integrated Quality Review #1

Recommendation: Approval

Drug Name/Dosage Form	Terlivaz® (terlipressin) for Injection
Strength	Each single-dose vial contains 0.85 mg terlipressin (free base) equivalent to 1 mg terlipressin acetate
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Mallinckrodt Pharmaceuticals Ireland Ltd.
Submission(s) Reviewed	Resubmitted NDA 022231, Sequence No. 0104, and all subsequent CMC amendments

Quality Review Team

Discipline	Reviewer/Seconda	Branch/division
Drug Substance	Daniel Jansen	OPQ/ONDP/DNDAPI/NDB3
Drug Product, Labeling, and Environmental Assessment	Theodore Carver	OPQ/ONDP/DNDPIII/NDPB5
Microbiology	Eric Adeeku	OPQ/OPMA/DMAI/MAB1
Process/ Facility	Ying Zhang/ Vidya Pai	OPQ/OPMA/DPMAIII/PMB7
Biopharmaceutics	Joan Zhao	OPQ/ONDP/DB/BB3
Regulatory Business Process Manager	Grafton Adams	OPQ/OPRO/DRBPMI/RBPMB2
Application Technical Lead	Theodore Carver	OPQ/ONDP/DNDPIII/NDPB5

Executive Summary

1. Recommendations and Conclusions on Approvability

The Office of Pharmaceutical Quality Review team has assessed NDA 022231 for Terlivaz® (terlipressin) for Injection with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports to have. As such, OPQ recommends approval of this NDA from a quality perspective.

2. Background Summary

The Applicant, Mallinckrodt Pharmaceuticals Ireland Ltd., submitted 505(b)(1) NDA for Terlivaz® (terlipressin) for injection as a Class 2 Resubmission. The resubmission is intended to address deficiencies listed in the Complete Response Letter issued by the Agency on 11 September 2020. The product quality information in the previous resubmission (02-Feb 2020) was determined to be adequate with a recommendation for approval in the integrated quality assessment filed on 18 August 2020. The current resubmission contains no changes to Module 3; however, additional stability data were submitted during the review cycle, and a facility was withdrawn. Therefore, the review of the current resubmission (Sequence 0104) is limited to specific aspects of the drug product and facilities only, and reference is made to the previous integrated quality assessment for the completed product quality review and approval recommendation.

3. Summary of Quality Assessments

3.1 Drug Substance (terlipressin)

The drug substance, terlipressin acetate, is a synthetic peptide comprising 12 amino acids, and it contains a disulfide bridge between Cys4 and Cys9. The CMC information for the drug substance was previously reviewed and found adequate, and no new information regarding the drug substance is included in the current resubmission.

3.2 Drug product (Terlipressin Injection)

A) Product Design and Specification: Terlipressin for Injection is a sterile, lyophilized powder for reconstitution supplied in a single-dose glass vial containing 0.85 mg terlipressin (free base) equivalent to 1 mg terlipressin acetate. The CMC information for the drug product was previously reviewed and found adequate, and no new information is included in the current resubmission that is the subject of this review.

B) Drug Product Manufacturing: The CMC information for the manufacturing process was previously reviewed and found adequate, and no new information is included in the current resubmission.

C) Biopharmaceutics Aspects: This NDA resubmission did not include any new biopharmaceutics data or information and, hence, no biopharm evaluation is needed.

D) Container Closure System: Terlipressin drug product is packaged in 6-mL USP (b) (4)-glass vials with (b) (4) stoppers, and aluminum flip-off seals. The CMC information for the manufacturing process was previously reviewed and found adequate, and no new information is included in the current resubmission.

4. Assessment of Manufacturing Facilities

The Office of Product Manufacturing Assessment has recommended an overall approval for all the currently listed manufacturing facilities for this NDA resubmission. No new information is included in this resubmission with the exception of withdrawal of a testing facility for the drug substance. See the attached manufacturing assessment for information regarding a testing facility that was withdrawn and has no impact on the approval recommendation.

5. Environmental Assessment: The information to support the environmental assessment has not changed since the previous review. The applicant has claimed categorical exclusion citing 21 CFR§ 25.31(c), because terlipressin is a synthetic peptide consisting of only naturally occurring amino acids and would not significantly alter the amount of natural peptides found in the environment. Additionally, the Applicant confirms that, to the best of their knowledge, no extraordinary circumstances exist that would warrant preparation of an environmental assessment.

6. Expiration Dating and Storage Conditions: A stability update for the primary stability batches of the commercial drug product was requested, because the previously submission did not include enough data to support the requested shelf life, and an additional 12 months of data were available from the supporting stability studies. In an amendment (eCTD Sequence 0107), the Applicant provided 24 months long term stability data, which support a shelf-life of 24 months for the product when stored at 2°C to 8°C in the proposed commercial

container closure system. Based on results of the in-use stability study that was reviewed in the previous product quality review, a 48-hour hold period for Terlipressin for Injection at 2°C to 8 °C after reconstitution with 0.9 % Sodium chloride is acceptable.

7. **Quality Labeling**: The container and carton label were reviewed as part of the drug product review. The dosage form description, strength, established name, NDC #, Lot #/Expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Comments regarding the draft USPI were conveyed to the Applicant, and it will be finalized as part of the review. Refer to the labeling review for additional information.

8. **List of CMC Deficiencies:** None

9. **Life Cycle Knowledge Information:** See the Integrated Quality Assessment dated 18 August 2020 for the final Risk Assessment for this NDA.

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, process, microbiology, manufacturing and facilities, and environmental assessment sections of this NDA. The OPQ overall recommendation for NDA 022231 is *approval.*

Theodore Carver, Ph.D.
Senior Pharmaceutical Quality Assessor
Application Technical Lead

Theodore Carver

Digitally signed by Theodore Carver
Date: 2/17/2022 01:25:57PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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

Theodore Carver

Digitally signed by Theodore Carver
Date: 2/17/2022 01:32:55PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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/

THEODORE E CARVER
02/17/2022 01:37:24 PM

Resubmitted NDA 022231 Terlivaz® (terlipressin) for Injection Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Terlivaz® (terlipressin) for Injection
Strength	Each single-dose vial contains 0.85 mg terlipressin (free base) equivalent to 1 mg terlipressin acetate
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Mallinckrodt Hospital Products IP
Submission(s) Reviewed	Resubmitted NDA 022231, Sequence No. 0104, and all subsequent CMC amendments

Quality Review Team

Discipline	Reviewer	Branch/division
Drug Substance	Daniel Jansen	OPQ/ONDP/DNDAPI/NDB3
Drug Product, Labeling, and Environmental Assessment	Theodore Carver	OPQ/ONDP/DNDPIII/NDPB5
Microbiology	Eric Adeeku	OPQ/OPMA/DMAI/MAB1
Process/ Facility	Ying Zhang/ Vidya Pai	OPQ/OPMA/DPMAIII/PMB7
Biopharmaceutics	Joan Zhao	OPQ/ONDP/DB/BB3
Regulatory Business Process Manager	Grafton Adams	OPQ/OPRO/DRBPMI/RBPMB2
Application Technical Lead	Theodore Carver	OPQ/ONDP/DNDPIII/NDPB5

Executive Summary

1. Recommendations and Conclusions on Approvability

The Office of Pharmaceutical Quality Review team has assessed NDA 022231 for Terlivaz® (terlipressin) for Injection with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports to have. As such, OPQ recommends approval of this NDA from a quality perspective. .

2. Background Summary

The applicant, Mallinkrodt hospital Products, Ltd, submitted 505(b)(1) NDA for Terlivaz® (terlipressin) for injection as a Class 2 Resubmission. The resubmission is intended to address deficiencies listed in the Complete Response Letter issued by the Agency on 11 September 2020. The product quality information in the previous resubmission (02-Feb 2020) was determined to be adequate with a recommendation for approval in the integrated quality assessment filed on 18 August 2020. The current resubmission contains no changes to Module 3; however, additional stability data was submitted during the review cycle, and a facility was withdrawn. Therefore, the review of the current resubmission (Sequence 0104) is limited to specific aspects of the drug product and facilities only, and reference is made to the previous integrated quality assessment for the completed product quality review and approval recommendation.

3. Summary of Quality Assessments

3.1 Drug Substance (b) (4)

The drug substance, terlipressin acetate, is a synthetic peptide comprising 12 amino acids, and it contains a disulfide bridge between Cys4 and Cys9. The CMC information for the drug substance was previously reviewed and found adequate, and no new information regarding the drug substance is included in the current resubmission.

3.2 Drug product (b) (4)

A) Product Design and Specification: Terlipressin for Injection is a sterile, lyophilized powder for reconstitution supplied in a single-dose glass vial containing 0.85 mg terlipressin (free base) equivalent to 1 mg terlipressin acetate. The CMC information for the drug product was previously reviewed and found adequate, and no new information is included in the current resubmission that is the subject of this review.

B) Drug Product Manufacturing: The CMC information for the manufacturing process was previously reviewed and found adequate, and no new information is included in the current resubmission.

C) Biopharmaceutics Aspects: This NDA resubmission did not include any new biopharmaceutics data or information and, hence, no biopharm evaluation is needed.

D) Container Closure System: Terlipressin drug product is packaged in 6-mL USP (b) (4) glass vials with (b) (4) stoppers, and aluminum flip-off seals. The CMC information for the manufacturing process was previously reviewed and found adequate, and no new information is included in the current resubmission.

4. **Assessment of Manufacturing Facilities**

   The Office of Product Manufacturing Assessment has recommended an overall approval for all the currently listed manufacturing facilities for this NDA resubmission. No new information is included in this resubmission with the exception of withdrawal of a testing facility for the drug substance. See the attached manufacturing assessment for information regarding a testing facility that was withdrawn and has no impact on the approval recommendation.

5. **Environmental Assessment**: The information to support the environmental assessment has not changed since the previous review. The applicant has claimed categorical exclusion citing 21 CFR§ 25.31(c), because terlipressin is a synthetic peptide consisting of only naturally occurring amino acids and would not significantly alter the amount of natural peptides found in the environment. Additionally, the Applicant confirms that, to the best of their knowledge, no extraordinary circumstances exist that would warrant preparation of an environmental assessment.

6.

7. **Expiration Dating and Storage Conditions**: A stability update for the primary stability batches of the commercial drug product was requested, because the previously submission did not include enough data to support the requested shelf life, and an additional 12 months of data were available from the supporting stability studies. In an amendment (Sequence 0107), the Applicant provided 24 months long term stability data, which support a shelf-life of 24 months for the product when stored at 2°C to 8°C in the proposed commercial container closure

system. Based on results of the in-use stability study that was reviewed in the previous product quality review, a 48-hour hold period for Terlipressin for Injection at 2°C to 8 °C after reconstitution with 0.9 % Sodium chloride is acceptable.

8. **Quality Labeling**: The container and carton label were reviewed as part of the drug product review. The dosage form description, strength, established name, NDC #, Lot #/Expiry, and storage conditions are adequately described in the carton and container label, which meets relevant regulatory requirements for labeling. Comments regarding the draft USPI were conveyed to the Applicant, and it will be finalized as part of the review. Refer to the labeling review in the IQA dated 18 August 2020 for additional information.

9. **List of CMC Deficiencies:** None

10. **Life Cycle Knowledge Information:** See the Integrated Quality Assessment dated 18 August 2020 for the final Risk Assessment for this NDA.

OVERALL ASSESSMENT AND SIGNATURES:

At present, there are no outstanding deficiencies related to the drug substance, drug product, microbiology, manufacturing, and environmental assessment sections of this NDA. The OPQ overall recommendation for NDA 022231 is *approval*.

Theodore Carver, Ph.D. 12/13/21
Senior Pharmaceutical Quality Assessor
Application Technical Lead

Theodore Carver

Digitally signed by Theodore Carver
Date: 12/13/2021 11:42:27AM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

10 Page(s) 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

THEODORE E CARVER
12/13/2021 12:01:09 PM

Resubmitted NDA 022231 Terlivaz® (terlipressin) for Injection

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Terlivaz® (terlipressin) for Injection
Strength	Each single-dose vial contains 0.85 mg terlipressin (free base) equivalent to 1 mg terlipressin acetate
Route of Administration	Parenteral
Rx/OTC Dispensed	Rx
Applicant	Mallinckrodt Hospital Products IP
Submissions (s) Reviewed	Resubmitted NDA 022231, Sequence No. 0023, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Daniel Jansen	OPQ/ONDP/DNDAPI/NDB3
Drug Product, Labeling, and Environmental Assessment	Ted Carver	OPQ/ONDP/DNDPIII/NDPB5
Microbiology	Eric Adeeku	OPQ/OPMA/DMAI/MAB1
Process and Facility	Ying Zhang	OPQ/OPMA/DPMAIII/PMB7
Biopharmaceutics	Joan Zhao	OPQ/ONDP/DB/BB3
Regulatory Business Process Manager	Grafton Adams	OPQ/OPRO/DRBPMI/RBPMB2
Application Technical Lead	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, the resubmitted NDA 022231 Terlivaz® (terlipressin) for Injection is recommended for approval. A shelf-life of (b) (4) months is approved for the product when stored at 2°C – 8°C in the proposed commercial container closure system.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Quality Assessment Summary

A. Background: The applicant, Mallinkrodt hospital Products, Ltd, submitted 505(b)(1) NDA for Terlivaz® (terlipressin) for injection as a rolling Class 2 Resubmission. The resubmission aimed to address deficiencies listed in the Complete Response Letter issued by the Agency on 04 November 2009. The final portion of the rolling NDA resubmission (Sequence No. 0023) dated March 12, 2020, contained a complete CMC package, including the data to support the new drug product manufacturing site as well as responses to the Quality Deficiencies, identified in the Complete Response Letter.

B. Drug Substance (Terlipressin Acetate)

The drug substance terlipressin acetate, a new molecular entity (NME), is a synthetic peptide comprised of 12 amino acids. All amino acids are of the L-configuration except for glycine which does not have a chiral center. The peptide is (b) (4) no crystalline or polymorphic forms are known. There is a disulfide bridge between Cys4 and Cys9. The applicant has provided sufficient characterization information, including confirmation of the presence of the disulfide linkage in the drug substance. Terlipressin acetate is synthesized by (b) (4) (b) (4) (b) (4) All the critical steps and in-process controls are well controlled. Elemental impurities have been analyzed per ICH Q3D option 2a. Residual solvents in drug substance are controlled via drug substance specification per ICH Q3C. The identity, quality, and purity of each batch of the drug substance are assessed and confirmed as per the specification, which involves testing for the critical quality attributes (CQAs) for the drug substance. Based on

(b) (4) month stability data, the proposed re-test period of (b) (4) months when stored at (b) (4) is acceptable.

C. Drug Product (Terlipressin For Injection)

C.1. Terlipressin for Injection is a sterile, lyophilized powder for reconstitution supplied in a single-dose glass vial containing 0.85 mg terlipressin (free base) equivalent to 1 mg terlipressin acetate. All excipients utilized in the proposed drug product formulation are compendial. Prior to administration, the product is to be reconstituted with 5 mL of 0.9% Sodium Chloride and administered via slow bolus injection. The applicant has satisfactorily addressed the Complete Response deficiency by providing additional details regarding the (b) (4) drug product. All the product critical quality attributes, which include identification, reconstitution time, pH, water content, uniformity of dosage units, assay, impurities, osmolality, particulate matter for injection, bacterial endotoxins, and sterility, are controlled by product specification. All the analytical methods have been adequately validated. Regarding elemental impurities, the product risk assessment has been conducted per ICH Q3D Option 2. The sum of the expected concentrations from each identified potential source have been found to be below the control threshold limits for parenteral route of administration for each target element, thereby complying with ICH Q3D requirements. Therefore, routine elemental impurities testing is not necessary for the drug product. From product quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, sterility, and stability.

C.2. Manufacturing: The manufacturing process is typical for a lyophilized drug product and involves (b) (4) After completion of clinical studies, the manufacturing process has been transferred from (b) (4) to (b) (4) the commercial drug product manufacturer. Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

C.3. Microbiological Aspects: The product release specification includes testing for bacterial endotoxins and sterility per USP <85> and USP <71>, respectively. The endotoxin dose at the proposed endotoxins specification and maximum dose is within the USP <85> recommendation of (b) (4) EU/kg/h. The data for the qualification of the container closure integrity test are adequate. The validated process for (b) (4) are adequate. Regarding labeling instructions, each vial is reconstituted with 5 mL of 0.9 % Sodium chloride, and if not administered immediately, the product is recommended to be stored 2°C – 8 °C (36°F – 46 °F) for up to 48 h. The results of the microbiological in-use study support a 48-hour hold period for Terlipressin for Injection at 2°C – 8 °C after reconstitution with 0.9 % Sodium chloride. In conclusion, the microbiology information provided is adequate.

C.4. Biopharmaceutics Aspects: This NDA did not include any biopharmaceutics data or information and, hence, no biopharm evaluation is needed.

C.5. Container Closure System: Terlipressin drug product is packaged in 6-mL USP (b) (4) (b) (4) glass vials with (b) (4) stoppers, and aluminum flip-off seals. The applicant has demonstrated compatibility with the active ingredient, excipients, container and closure

components, and dosing components. Since the volume of the vials (6 mL) is much larger than the fill volume (b) (4) the risk of (b) (4) is minimized. The product stability data indicate suitability of the proposed container closure system for the intended use. Evidence of adequate functionality of the container closure system is also provided by sterility testing during the stability program.

C.6. Expiration Date & Storage Conditions: The current stability data support a shelf-life of (b) (4) months for the product when stored at 2°C – 8°C in the proposed commercial container closure system. Based on results of the microbiological in-use study, a 48-hour hold period for Terlipressin for Injection at 2°C – 8 °C after reconstitution with 0.9 % Sodium chloride is acceptable.

C.7. Environmental Assessment

The applicant has claimed categorical exclusion citing 21 CFR§ 25.31(c), because terlipressin is a synthetic peptide consisting of only naturally occurring amino acids and would not significantly alter the amount of natural peptides found in the environment. Additionally, the Applicant confirms that, to the best of their knowledge, no extraordinary circumstances exist that would warrant preparation of an environmental assessment.

III. Assessment of Manufacturing Facilities: The Office of Product Manufacturing Assessment has recommended an overall approval for all the currently listed manufacturing facilities concerning this NDA resubmission.

IV. Product Quality Labeling Recommendations: In compliance with USP salt policy and FDA guidance i.e., *Naming of Drug Products Containing Salt Drug Substance, Guidance for Industry, 2015,* the dosage strength needs to be expressed in terms of the active moiety rather than the salt form. All labeling recommendations from quality perspective are reflected in the most recent version of the product labeling.

V. Life Cycle Knowledge Information

A Final Risk Assessment Tabulated on the Next Page

Resubmitted NDA 022231 Terlivaz® (terlipressin) for Injection
Final Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H (High)**	(b) (4)	Acceptable	(b) (4)
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M (Moderate)**		Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels will need to be evaluated based on the maximum total daily dose.
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)		Acceptable	(b) (4)
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low))		Acceptable	

Final Risk Assessment (continued, next page)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	(b) (4)	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	**M (Moderate)**		Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, the resubmitted NDA 022231 Terlivaz® (terlipressin) for Injection is recommended for approval. A shelf-life of (b) (4) months is approved for the product when stored at 2°C – 8°C in the proposed commercial container closure system.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiology and Nephrology Division
CDER/OPQ/ONDP/DNDPIII/NDPB5

Mohan K. Sapru -S

Digitally signed by Mohan K. Sapru -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mohan K. Sapru -S, 0.9.2342.19200300.100.1.1=2000589315
Date: 2020.08.18 16:08:44 -04'00'

43 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The PI assessed in this review was submitted on 21-Feb 2020. Based on the information provided, there are edits required to the statement of dosage strength to consistently express the dosage strength in terms of the active moiety instead of the salt form. These edits are required in both the PI and the vial and carton labels. In addition, several minor changes to the wording of the PI are required. The product quality aspects of the labeling will be adequate after the Applicant's acceptance of the proposed labeling revisions.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TERLIVAZ (terlipressin) for injection, for intravenous use	Adequate.
Established name(s)		Adequate.
Route(s) of administration		Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Remove (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		N/A

APPEARS THIS WAY ON ORIGINAL

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient use). Other package terms include pharmacy bulk package and imaging bulk package.		Adequate

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4)	Inadequate. Remove (b) (4)

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	For injection: 0.85 mg terlipressin (b) (4) a white to off-white lyophilized powder in a single-dose vial for reconstitution. .	(b) (4)
Strength(s) in metric system		Adequate.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		Adequate.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		Adequate.

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TERLIVAZ (terlipressin) (b) (4) vasopressin (b) (4)	Adequate.
Dosage form(s) and route(s of administration		Adequate.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	TERLIVAZ is a sterile, preservative-free, lyophilized powder for intravenous administration. (b) (4) It is a white to off-white powder, (b) (4) Each vial contains 0.85 mg terlipressin equivalent to 1 mg terlipressin acetate, 10.0 mg mannitol. Glacial acetic acid and/or sodium hydroxide may be added to adjust pH at the time of manufacture. (b) (4)	Remove (b) (4) (b) (4) and revise contents to read: Each vial contains the (b) (4) 0.85 mg terlipressin (b) (4) as 1 mg of terlipressin acetate , 10.0 mg mannitol. Glacial acetic acid and/or sodium hydroxide may be added to adjust pH at the time of manufacture.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.		Adequate.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		N/A
Statement of being sterile (if applicable)		Adequate.
Pharmacological/ therapeutic class		Inadequate. Delete (b) (4) (b) (4) (b) (4) and revise to include only the following

		text for pharmacologic class: (b) (4) (b) (4)
Chemical name, structural formula, molecular weight	Terlipressin is a 12-amino acid peptide (b) (4) with the chemical name *N*-[*N*-(*N*-glycylglycyl)glycyl]-8-L-lysinevasopressin. (b) (4) The structure of terlipressin is shown below (as free base): (b) (4)  	Adequate.
If radioactive, statement of important nuclear characteristics.		N/A
Other important chemical or physical properties (such as pKa or pH)	Molecular formula: $C_{52}H_{74}N_{16}O_{15}S_2$ (as free base). (b) (4) Average molecular weight: 1227.38 (as free base). (b) (4)	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None.	N/A

Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	Adequate.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	TERLIVAZ (terlipressin) is supplied as a sterile, preservative-free, lyophilized powder in single-dose vials (b) (4) 0.85 mg of terlipressin (b) (4) Each vial is supplied in a carton (b) (4) (NDC 43825-200-01).	Inadequate (b) (4) Revise to "TERLIVAZ (b) (4) is supplied as a sterile, preservative-free, lyophilized powder in single-dose vials containing (b) (4) 0.85 mg of terlipressin. Each vial is supplied in a carton (b) (4) (NDC 43825-200-01)."
Strength(s) in metric system		Adequate.

APPEARS THIS WAY ON ORIGINAL

Available units (e.g., bottles of 100 tablets)		Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	See above.	Adequate.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store TERLIVAZ vials in the carton under refrigerated conditions at 2°C to 8°C (36°F to 46°F). Protect from light prior to reconstitution. (b) (4)	Adequate. The shelf life and in-use conditions are supported by stability results.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	2°C to 8°C (36°F to 46°F)	Adequate. Supported by in-use stability study to 72 hours.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	No information included.	N/A
Include information about child-resistant packaging	No Information included.	Adequate.

1.2.5 Other Sections of Labeling
N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Mallinckrodt Hospital Products Inc. Bedminster, NJ 07921, USA	Adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):
To be assessed

3.0 CARTON AND CONTAINER LABELING

Assessment of Container and Carton labeling:
Inadequate. (b) (4)

(b) (4)

3.1 Container Label

(b) (4)

3.2 Carton Labeling

(b) (4)

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

The labeling/labels will be adequate from a quality perspective after the recommended changes have been made.

Theodore Carver

Digitally signed by Theodore Carver
Date: 8/09/2020 11:21:47PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

David Claffey

Digitally signed by David Claffey
Date: 8/10/2020 09:13:52AM
GUID: 508da71e00029e20b201195abff380c2

CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	022231
Assessment Cycle Number	02
Drug Product Name/ Strength	Terlivas® (Terlipressin) for Injection / 1 mg
Route of Administration	Intravenous bolus injection
Applicant Name	Mallinckrodt Hospital Products IP Limited
Therapeutic Classification/ OND Division	Type 1 – New Molecular Entity / NA
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Inadequate**

Assessment Summary: The submission is **not recommended** for approval. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

The safety risk due to the microbiology deficiencies is considered minor.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
73 (eCTD 0022)	02/21/2020
74 (eCTD 0023)	03/12/2020
77 (eCTD 0026)	05/28/2020
85 (eCTD 0034)	07/23/2020

List of submissions being reviewed

Submit	Received	Review Request	Assigned to Reviewer
02/21/2020	02/21/2020	N/A	04/06/2020
03/12/2020	03/12/2020	N/A	04/06/2020
05/28/2020	05/28/2020	N/A	05/29/2020
07/23/2020	07/23/2020	N/A	07/24/2020

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks:

This is an electronic submission.
Goal date is 09/12/2020.
The NDA is a Type 1 New Molecular entity.

NDA 022231 was 'Microbiology Recommended' on 09/25/2009 for the manufacture of Terlipressin sterile, lyophilized powder for injection at the [redacted]. The sponsor is proposing the [redacted] facility as the alternate manufacturing facility by rolling NDA submission to the Agency. The rolling submissions are in Part I and Part II dated 2/21/20 and 3/12/20 respectively.

Review also contains responses to the Agency's 05/18/2020 and 07/14/2020 information requests.

Concise Description of Outstanding Issues

Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

Supporting Documents:

N022231R1.doc – Sterility assurance review of the same drug product to be manufactured at the [redacted] site that was found adequate in the 09/25/2009 microbiology review.

[redacted]

[redacted].doc – Sterility assurance review of the depyrogenation of the [redacted] stoppers that was found adequate on 11/10/2005.

[redacted].doc – Sterility assurance review of the depyrogenation of the [redacted] stoppers that was found adequate on 02/03/2017.

The Agency's 05/18/2020 and 07/14/2020 information requests are addressed in the body of the review as comments. The most recent deficiencies are in italics.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product –

(section 3.2.P.1).

Terlipressin drug product is a sterile, lyophilized powder for injection. A single dose glass vial contains 0.85 mg of terlipressin (free-base) equivalent to about 1 mg of terlipressin acetate to be reconstituted prior to administration.

Drug product composition –

(section 3.2.P.1).

Ingredient	Function	mg per vial
Terlipressin (free base), In-House[a]	Drug substance	0.85
Mannitol, USP	[redacted]	10.0
Glacial Acetic Acid, USP	pH adjustment	to adj. pH

Sodium Hydroxide, NF	pH adjustment	to adj. pH
Water for Injection, USP[b]	(b) (4)	
(b) (4)		

[a]0.85 mg of terlipressin (free base) is equivalent to about 1 mg terlipressin acetate

(b) (4)

Description of container closure system –
(section 3.2.P.7).

Component	Description	Manufacturer
Vial	6 mL/20 mm USP (b) (4) glass vials	(b) (4)
Stopper	20 mm (b) (4) rubber stopper	
Seal	20 mm plastic flip-off aluminum caps	

The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

27 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Eric Adeeku

Digitally signed by Eric Adeeku
Date: 8/07/2020 11:53:39AM
GUID: 508da70b00028e3db199467cfbd47cb0

Paul Dexter

Digitally signed by Paul Dexter
Date: 8/07/2020 11:58:34AM
GUID: 508da70c00028f8ef6fc7fb5f60df2ce

CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	022231
Assessment Cycle Number	03
Drug Product Name/ Strength	Terlivas® (Terlipressin) for Injection / 1 mg
Route of Administration	Intravenous bolus injection
Applicant Name	Mallinckrodt Hospital Products IP Limited
Therapeutic Classification/ OND Division	Type 1 – New Molecular Entity / NA
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary: The submission is **recommended** for approval. No outstanding issues remain.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
90 (eCTD 0038)	08/12/2020

List of submissions being reviewed

Submit	Received	Review Request	Assigned to Reviewer
08/12/2020	08/12/2020	N/A	08/12/2020

Date(s) of previous submission(s)	Microbiology Review #	Date(s) of previous Micro Review(s)
02/21/2020	2	07/30/2020
03/12/2020	2	07/30/2020
05/28/2020	2	07/30/2020
07/23/2020	2	07/30/2020

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks:

This is an electronic submission.
Goal date is 09/12/2020.
The NDA is a Type 1 New Molecular entity.

NDA 022231 was 'Microbiology Recommended' on 09/25/2009 for the manufacture of Terlipressin sterile, lyophilized powder for injection at the

[redacted] (b) (4) facility. The sponsor is proposing the [redacted] (b) (4) facility as the alternate manufacturing facility by rolling NDA submission to the Agency. The rolling submissions are in Part I and Part II dated 2/21/20 and 3/12/20 respectively.

Review also contains responses to the Agency's 07/14/2020 information requests.

Concise Description of Outstanding Issues: No outstanding issues remain.

Supporting Documents:

N022231R1.doc – Sterility assurance review of the same drug product to be manufactured at the [redacted] (b) (4) site that was found adequate in the 09/25/2009 microbiology review.

Product Quality Microbiology Assessment

This review contains the response to the Agency's 07/14/2020 information requests. The deficiency statement is in italics.

It is acknowledged that microbial in use data was provided for post-reconstitution hold studies performed in 2018 in response to the Agency's request for a microbial growth promotion study after drug product reconstitution. The studies provided do not address the potential microbial growth at the time periods during or up to the worst-case duration and hold conditions in the proposed package insert (48 h at 2 – 8 °C after reconstituting the drug with 0.9 % Sodium chloride Injection). The Agency's concern is for the risk to a human patient exposed to a reconstituted drug product inadvertently contaminated by medical personnel at drug administration. For additional information on growth promotion study design, please see https://www.americanpharmaceuticalreview.com/Featured-Articles/114491-Microbiological-Quality-of-Drug-Products-after-Penetration-of-the-Container-System-for-Dose-Preparation-Prior-to-Patient-Administration/
Please provide a risk assessment summarizing studies that show adventitious microbial contamination does not grow under the specified storage conditions (i.e. 48 h at 2 – 8 °C after reconstitution with 0.9 % Sodium chloride Injection). Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7.

The assessment should include a description of the test methods and results of studies that are designed using a minimum countable inoculum (≤ 100 CFU/mL) to simulate potential microbial contamination that may occur during product reconstitution. The test should be performed using the storage conditions (temperature [2 – 8 °C] and duration [including at least up to 48 h) and diluents specified in product labeling. Challenge organisms may include strains described in USP <51> plus typical skin flora, species associated with nosocomial infection,

or psychrophilic organisms. The test should include positive control results that demonstrates the viability of the organisms over the duration of the test period.

Response: Confirmatory in-use microbial study was performed using ≤ 100 CFU/mL of compendial organisms and other isolates. A description of test methods used, including positive controls that demonstrates the viability of the organisms over the duration of the test period was also provided.

The following compendial organisms and environmental isolates were used for the studies:

- *Escherichia coli* ATCC 8739
- *Pseudomonas aeruginosa* ATCC 9027
- *Staphylococcus aureus* ATCC 6538
- *Candida albicans* ATCC 10231
- *Aspergillus brasiliensis* ATCC 16404
- *Staphylococcus epidermidis* ATCC 12228
- *Micrococcus luteus* ATCC 10240
- *Corynebacterium jeikeium* ATCC 43734

The following are the sponsor's acceptance criteria:

(b) (4)

The relevant results are provided in the tables below.

Log recovery at each time point using product reconstituted with 0.9 % Sodium chloride and stored at 2 – 8 ºC.

Challenge Organisms	Initial		0 h		24 h		48 h			72 h			96 h	144 h
	CFU	Log_{10}	CFU	Log_{10} Rec.	CFU	Log_{10} Rec.	CFU	Log_{10} Rec.	LRV	CFU	Log_{10} Rec.	LRV	LRV	LRV
E. coli	60	1.78	61	1.79	63	1.80	46	1.66	-0.12	39	1.59	-0.19	-0.24	-0.40
P. aeruginosa	59	1.77	48	1.68	47	1.67	37	1.57	-0.20	31	1.49	-0.28	-0.32	-1.29
S. aureus	74	1.87	58	1.76	42	1.62	37	1.57	-0.30	33	1.52	-0.35	-0.69	-1.57
S. epidermidis	76	1.88	94	1.97	21	1.32	1	0.0	-1.88	0	0.0	-1.88	-1.88	-1.88
M. luteus	67	1.83	66	1.82	49	1.69	27	1.43	-0.40	18	1.26	-0.57	-0.57	-1.53
C. jeikeium	97	1.99	93	1.97	0	0.0	0	0.0	-1.99	0	0.0	-1.99	-1.99	-1.99
C. albicans	81	1.91	87	1.94	88	1.94	94	1.97	+0.06	86	1.93	+0.02	-0.01	+0.02
A. brasiliensis	82	1.91	83	1.92	86	1.93	79	1.90	-0.01	82	1.91	0.00	+0.04	+0.03

LRV: Log_{10} reduction value
Log_{10} Rec.: log recovery

Log recovery at each time point for diluent (0.9 % Sodium chloride) positive controls stored at 2 – 8 °C.

Challenge Organisms	0 h		24 h		48 h			72 h			96 h	144 h
	CFU	Log_{10}	CFU	Log_{10} Rec.	CFU	Log_{10} Rec.	LRV	CFU	Log_{10} Rec.	LRV	LRV	LRV
E. coli	60	1.78	53	1.72	63	1.80	+0.02	49	1.69	-0.09	-0.30	- 1.78
P. aeruginosa	59	1.77	37	1.57	10	1.00	-0.77	2	0.30	-1.47	-1.77	-1.77
S. aureus	74	1.87	62	1.79	43	1.63	-0.24	16	1.20	-0.67	-1.87	-1.87
S. epidermidis	76	1.88	6	0.78	4	0.6	-1.28	0	0.0	-1.88	-1.88	-1.88
M. luteus	67	1.83	38	1.58	24	1.38	-0.45	11	1.04	-0.79	-1.83	-1.83
C. jeikeium	97	1.99	0	0.0	0	0.0	-1.99	0	0.0	-1.99	-1.99	-1.99
C. albicans	81	1.91	65	1.81	73	1.86	-0.05	64	1.81	-0.10	-0.35	-0.46
A. brasiliensis	82	1.91	77	1.89	78	1.89	-0.02	85	1.93	+0.02	+0.05	+0.03

The product does not promote microbial growth for up to 144 h, justifying a hold time of 48 hours at 2 – 8 °C.

Adequate data was also provided for the studies performed at storage temperature of 20 – 25 °C.

The results confirm the acceptability of a 48-hour hold time for Terlipressin for Injection at 2 – 8 °C after reconstitution with 0.9 % Sodium chloride.

Adequate

Post-Approval Commitments

None provided.

MICROBIOLOGY LIST OF DEFICIENCIES: None

Primary Microbiology Assessor Name and Date:

Eric Adeeku, 08/13/2020

Secondary Assessor Name and Date:

Capt. Paul Dexter, 08/13/2020

Eric Adeeku

Digitally signed by Eric Adeeku
Date: 8/13/2020 02:16:21PM
GUID: 508da70b00028e3db199467cfbd47cb0

Paul Dexter

Digitally signed by Paul Dexter
Date: 8/13/2020 12:48:35PM
GUID: 508da70c00028f8ef6fc7fb5f60df2ce

1 Page(s) has been Withheld in FUll as b4 (CCI/TS) immediately following this page

---

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/

MOHAN K SAPRU
08/18/2020 04:21:08 PM

NDA 22-231

LUCASSIN
Terlipressin for Injection

Orphan Therapeutics, LLC

Division of Cardiology and Renal Products, HFD 110

Shastri Bhamidipati, Ph.D.
Division of Pre-Marketing Assessment I,
Office of New Drug Quality Assessment

Receipt Date : 04-MAY-2009
PDUFA Goal Date: 04-NOV-2009

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-231

2. REVIEW #: 3

3. REVIEW DATE: 5-NOV-2009

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Quality Review #1	29-SEPT-2009
Quality Review #2	21-OCT-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-231 Original Submission	01-MAY-2009
NDA 22-231 Supporting Document 0029	15-OCT-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Orphan Therapeutics, LLC

Address: 3 Werner Way, Suite# 210
Lebanon, NJ 08833

Representative: Candice Teuber, Pharm.D.
Sr. Director, Regulatory Affairs
3 Werner Way, Suite# 210
Lebanon, NJ 08833

Telephone: (909) 849-4851

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LUCASSIN
b) Non-Proprietary Name (USAN): Terlipressin for Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(1)

10. PHARMACOL. CATEGORY: Cardiology, Hepatorenal Syndrome (HRS) Type I

11. DOSAGE FORM: Lyophilized Powder for Injection

12. STRENGTH/POTENCY: 0.85 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous, Bolus

14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

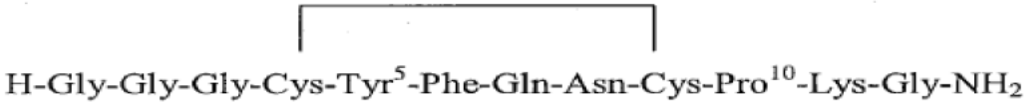
___X___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): N-[N-(N-glycylglycyl)glycyl)-8-L-lysinevasopressin
Glcyl-glycyl-glycyl[8-L-lysine]vasopressin
N-α-glycyl-glycyl-glycyl -vasopressin
1-triglycyl-8-lysine-vasopressin

Molecular Formula: $C_{52}H_{74}N_{16}O_{15}S_2$

Molecular Weight: 1226.5 (free base)
CAS: [14636-12-5]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	Adequate		Last reviewed by Dr. Dong, ONDQA/Div IV in Dec. 2008
	III			4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	IND (b) (4)	Terlipressin (b) (4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	Not applicable		
EES	Withhold	11/03/2009	C. Cruz (HFD-323)
Pharm/Tox	Approvable	08/06/2009	Dr. Gowra Jagadeesh
Clinical Pharmacology	Acceptable pending agreement on labeling contents	08/27/2009	Dr. Divya Menon-Anderson
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Trade name was reviewed and deemed acceptable	08/13/2009	Anne Crandall, Pharm.D.
EA	Claimed categorical exclusion granted		
Microbiology	Approval recommended	10/01/2009	Dr. Vinayak Pawar

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-231

The Office of Compliance has not provided an overall recommendation for the manufacturing sites for this NDA at the time CMC review #2 was finalized in DARRTS. On Nov. 3rd, 2009, the Office of Compliance has made a withhold recommendation for the manufacturing and testing facilities and a summary report was reproduced below. The action letter to the sponsor requires that the deficiencies at [redacted] (b) (4) and [redacted] (b) (4) facilities should be resolved prior to consideration of the application for approval. Please refer to the quality reviews filed in DARRTS (dated 29-SEPT-2009 and 21-OCT-2009) for comprehensive review of the original application.

Chemistry Assessment Section

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22231/000	**Sponsor:**	ORPHAN
Org. Code:	110		3 WERNER DR STE 300
Priority:	1P		LEBANON, NJ 08833
Stamp Date:	04-MAY-2009	**Brand Name:**	LUCASSIN (TERLIPRESSIN)
PDUFA Date:	04-NOV-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	TERLIPRESSIN
District Goal:	05-SEP-2009	**Product Number; Dosage Form; Ingredient; Strengths**	001; POWDER, FOR INJECTION SOLUTION; TERLIPRESSIN; 1MG

FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	S. BHAMIDIPATI	Review Chemist	301-796-2426
	K. SRINIVASACHAR	Team Leader	301-796-1760

Overall Recommendation: WITHHOLD on 03-NOV-2009 by C. CRUZ (HFD-323) 301-796-3254

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 10-SEP-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** (b) (4) **FEI:**

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** POTENTIAL OAI

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-NOV-2009

Decision: WITHHOLD

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-OCT-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 28-OCT-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-JUN-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-NOV-2009

Decision: WITHHOLD

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-JUN-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:**

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 01-OCT-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** (b) (4)	**FEI:** (b) (4)	
	(b) (4)		
DMF No:		**AADA:**	
Responsibilities:			
Profile:		**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	06-AUG-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

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/

SHASTRI P BHAMIDIPATI
11/05/2009

KASTURI SRINIVASACHAR
11/05/2009

Lucassin
(terlipressin) for Injection
NDA 22-231

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Orphan Therapeutics
3 Werner Drive, Suite 300
Lebanon, NJ 08813
USA

Indication: Lucassin (terlipressin) for injection is intended for treating Hepatorenal Syndrome Type I

Presentation: Lucassin (terlipressin) for injection is a preservative-free, lyophilized powder for injection. The drug product is supplied in one strength (0.85 mg of terlipressin free base per vial) in a 6 mL single use, (b) (4) glass vial. The drug product is secondarily packaged in a carton containing (b) (4) units of single use vials.

EER Status: Pending overall recommendation, 28-October-09

Consults: Microbiology- Recommended Approval, Dr. Vinayak Pawar (10/1/09)
Methods Validation – Revalidation by Agency was not requested
EA – Categorical exclusion granted under 21 CFR §25.31(c)

Original Submission: 04-May-2009

Post-Approval Agreements: None

Drug Substance:

Terlipressin, an analogue of vasopressin, is a 12-residue synthetic peptide with the primary sequence of Gly-Gly-Gly-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly with a disulfide bond between two Cysteine residues. The chemical name is N-[N-(N-glycylglycyl)glycyl]-8-L-lysine vasopressin; the molecular formula is $C_{52}H_{74}N_{16}O_{15}S_2$ and the molecular weight of the free base is 1226.5. Terlipressin is freely soluble in water, soluble in methanol, and insoluble in acetonitrile and dicholoromethane. The chemical structure of terlipressin was characterized by physical, chemical and analytical methods to establish the structure including proton and carbon NMR, electrospray MS and MS/MS, amino acid analysis, chiral GC/MS and reverse phase HPLC.

The drug substance is synthesized by (b) (4)
(b) (4)

[redacted] The manufacturing process includes appropriate in-process controls and was adequately described. The analytical procedures for release of drug substance were adequately described and validated. The release tests include: identification (mass spectrometry, reverse phase HPLC, amino acid analysis), assay (reverse phase HPLC), purity (reverse phase HPLC), specified and unspecified impurities (reverse phase HPLC), solvent content, water content, optical rotation, bacterial endotoxin, bioburden, and mass balance. However, the specification for the drug substance is deficient in that it does not include appropriate testing for confirmation of the disulfide bond, heavy metals, or residual solvent testing [redacted]

The final drug substance is a [redacted]

Drug Product:

The drug product is a preservative-free, sterile, lyophilized powder. The formulation contains Terlipressin, the active at 0.85 mg as free base, mannitol USP [redacted], glacial acetic acid USP and/or sodium hydroxide NF (used for pH adjustment), and water for injection USP. The manufacturing process for the bulk drug product is a [redacted] Individual steps in manufacturing process have been evaluated for process variabilities, compatibility and ensuring product quality.

The proposed drug product specification meets the quality requirements for parenteral products. However, it was noted that the [redacted] In addition, stability data provided in support of the use of reconstituted solution for administration was determined to be inadequate [redacted]

The sponsor presented stability data for both 36 months at long term storage conditions (5 °C) and accelerated stability data (25°C) using drug product batches manufactured at [redacted] scale with the commercial manufacturing process. Additionally, they submitted 6 month stability data at long term storage conditions (5°C) and accelerated storage conditions for three registration drug product batches manufactured at the proposed commercial manufacturing site. However, the analytical method employed for terlipressin assay and impurities was changed between these studies and detection of new impurities necessitated further development of the analytical method. A method comparison study was performed employing the three methods and stability samples from development batches and the registration batches. Based on the evaluation of the results from method comparison study and the stability data, it was determined that a shelf life beyond [redacted] months cannot be recommended for the drug product unless the sponsor provides additional information that justify the use of supporting stability data as primary data.

Conclusion:

The application cannot be recommended for approval from CMC perspective in its current form. Please see the reviews in DARRTS for details. The following summarizes the deficiencies related to drug substance specification, drug product characterization, stability, and labeling.

1. The proposed analytical method for disulfide bonds is not adequately justified.

2. The specification for drug substance should include testing for heavy metals.

3. The analytical method intended for quantitation of residual solvents in the drug substance is not adequate.

4. The specification for water content in the product is not suitably justified when considering its potential effect on product stability.

5. The vial label should include drug product composition (excipients and quantities).

6. The carton label should be revised regarding storage temperatures, times and conditions for reconstitution.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Overall Conclusion:

NDA 22-231 for Lucassin (terlipressin) for Injection 0.85 mg/vial **cannot be recommended for approval** in its current form from CMC perspective, pending resolution to the deficiencies listed above and an acceptable recommendation from the Office of Compliance.

Christine M. V. Moore, Ph.D.
Acting Director, DPA I/ONDQA

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/

CHRISTINE M MOORE
10/28/2009

NDA 22-231

LUCASSIN
Terlipressin for Injection

Orphan Therapeutics, LLC

Division of Cardiology and Renal Products, HFD 110

Shastri Bhamidipati, Ph.D.
Division of Pre-Marketing Assessment I,
Office of New Drug Quality Assessment

Receipt Date : 04-MAY-2009
PDUFA Goal Date: 04-NOV-2009

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-231

2. REVIEW #: 2

3. REVIEW DATE: 15-OCT-2009

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Quality Review #1	29-SEPT-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-231 Original Submission	01-MAY-2009
NDA 22-231 Supporting Document 0029	15-OCT-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Orphan Therapeutics, LLC

Address: 3 Werner Way, Suite# 210
Lebanon, NJ 08833

Representative: Candice Teuber, Pharm.D.
Sr. Director, Regulatory Affairs
3 Werner Way, Suite# 210
Lebanon, NJ 08833

Telephone: (909) 849-4851

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: LUCASSIN
b) Non-Proprietary Name (USAN): Terlipressin for Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(1)

10. PHARMACOL. CATEGORY: Cardiology, Hepatorenal Syndrome (HRS) Type I

11. DOSAGE FORM: Lyophilized Powder for Injection

12. STRENGTH/POTENCY: 0.85 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous, Bolus

14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

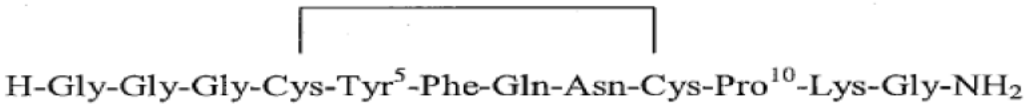
__X___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): N-[N-(N-glycylglycyl)glycyl)-8-L-lysinevasopressin
Glcyl-glycyl-glycyl[8-L-lysine]vasopressin
N-α-glycyl-glycyl-glycyl -vasopressin
1-triglycyl-8-lysine-vasopressin

Molecular Formula: $C_{52}H_{74}N_{16}O_{15}S_2$

Molecular Weight: 1226.5 (free base)
CAS: [14636-12-5]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	Adequate		Last reviewed by Dr. Dong, ONDQA/Div IV in Dec. 2008
	III			4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	IND (b) (4)	Terlipressin (b) (4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	Not applicable		
EES	Overall recommendation from OC is pending		
Pharm/Tox	Approvable	08/06/2009	Dr. Gowra Jagadeesh
Clinical Pharmacology	Acceptable pending agreement on labeling contents	08/27/2009	Dr. Divya Menon-Anderson
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Trade name was reviewed and deemed acceptable	08/13/2009	Anne Crandall, Pharm.D.
EA	Claimed categorical exclusion granted		
Microbiology	Approval recommended	10/01/2009	Dr. Vinayak Pawar

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-231

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application for Terlipressin Lyophilized Powder for Injection, 0.85 mg/vial, can not be recommended for approval from quality perspective pending resolution of the CMC deficiencies identified at the end of this review. Additionally, final recommendation as to the status of manufacturing and testing facilities from the Office of Compliance is pending. The sponsor has submitted the trade name, Lucassin®, for the drug product and Division of Medication Error Prevention and Analysis (DMEPA) has reviewed the trade name and recommended as acceptable.

This review encompasses the evaluation of sponsor provided responses to the IR letter sent on 22-SEPT-2009. Please refer to the quality review filed in DARRTS (dated 29-SEPT-2009) for a comprehensive review of the original application.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None applicable at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The proposed drug product, Lucassin® (Terlipressin) for Injection, is a 12-residue synthetic peptide analogue of vasopressin, a systemic vasoconstrictor, and was developed to treat hepatorenal syndrome (HRS) Type I based on the drug product currently marketed in (b) (4) The drug product is a preservative-free sterile lyophilized powder and the formulation contains Terlipressin, the active at 0.85 mg as free base, mannitol, USP (b) (4) , glacial acetic acid, USP and/or sodium hydroxide, NF (used for pH adjustment) and water for injection USP. Lucassin® (Terlipressin) for Injection is packaged in 6 mL (b) (4) glass vial and will be marketed in only one strength (0.85 mg/vial) for single use. The drug product should be reconstituted with only 0.9% Sodium Chloride solution for injection prior to administration.

The pharmaceutical development of Terlipressin drug product (b) (4) (b) (4) The manufacturing process for the bulk drug product is (b) (4)

(b) (4)

(b) (4) The proposed drug product specification meet the quality requirements for parenteral products. (b) (4) In addition, stability data provided in support of the use of reconstituted solution for administration was determined to be inadequate due to (b) (4)

The sponsor presented 36 month stability data at long term storage conditions of 5°C for three drug product batches (b) (4) and 6 month stability data at long term storage conditions of 5°C for another three registration drug product batches (b) (4) manufactured at the proposed commercial manufacturing site. However, the analytical method employed for terlipressin assay and impurities in drug product was changed to improve resolution of impurities (b) (4) (b) (4) Additionally, after initiating the stability study for the registration batches, detection of new impurities in stability samples necessitated further development of the analytical method. A method comparison study was performed employing the three methods and stability samples (long term and accelerated storage conditions) from development batches and the registration batches. The sponsor compared the similarity of the data profiles for the development batches and the registration batches at long term storage conditions and proposed a 24 month shelf-life for drug product. Based on the evaluation of the results from method comparison study and the stability data, it was determined that a shelf life beyond (b) (4) months can not be recommended for the drug product unless the sponsor provides additional information that justify the use of supporting stability data as primary stability data.

Drug Substance:
Terlipressin, an analogue of vasopressin, is a 12 residue synthetic peptide with the primary sequence of Gly-Gly-Gly-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly with a disulfide bond. The drug substance was synthesized by (b) (4) and characterized by physical, chemical and analytical methods to establish the structure. The manufacturing

process includes appropriate in-process controls and was adequately described. The final drug substance is a [redacted] The analytical procedures for release of drug substance were adequately described and validated. The specification for the drug substance, however, does not include testing for confirmation of the disulfide bond. Additionally, residual solvent testing of the drug substance [redacted]

B. Description of How the Drug Product is Intended to be Used

Lucassin® (terlipressin) for Injection, is provided as preservative-free, sterile lyophilized powder (0.85 mg of Terlipressin free base and 10 mg of mannitol per vial) for single-use in 6 mL [redacted] glass vials and packaged in [redacted] unit carton. Each vial should be reconstituted with 5 mL of 0.9% sodium chloride solution for injection. [redacted] The drug product is stored refrigerated at 2-8°C (36- [redacted] °F). Once reconstituted, the drug product is stored refrigerated at 2-8°C and used within [redacted] hrs.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application for Lucassin (terlipressin) for Injection, 0.85 mg/vial can not be recommended for approval from CMC perspective pending resolution of deficiencies identified at the end of this review. Based on the evaluation of stability data submitted by the sponsor, the recommended shelf-life for the product is limited to [redacted] months. Additionally, an overall recommendation for the manufacturing and testing sites from the Office of Compliance is pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shastri Bhamidipati, Ph.D.
Chemistry Team Leader Name/Date: Kasturi Srinivasachar, Ph.D.

C. CC Block

Original NDA 22-231
DCRP (HFD-110)/NDA Division File
DCRP(HFD-110)/CSO/A. Park
ONDQA/DPAI/Chemist/S. Bhamidipati
ONDQA/DPAI /PAL/K.Srinivasachar
ONDQA/DPAI/ RPM/D.Henry
ONDQA/DPAI /Branch Chief/R. Sood

6 Page(s) 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/

SHASTRI P BHAMIDIPATI
10/20/2009

RAMESH K SOOD
10/21/2009

Product Quality Microbiology Review

September 25, 2009

NDA: 22-231

Drug Product Name
Proprietary: Lucas sin®
Non-proprietary: terlipressin for injection.

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
May 1, 2009	May, 4, 2009	May 21, 2009	May 26, 2009

Applicant/Sponsor
Name: Orphan Therapeutics, Inc
Address: 3 Werner Drive, Lebanon, NJ 08833
Representative: Candice A. Teuber, Senior Director RA
Telephone: 908-849-4851

Name of Reviewer: Vinayak. B. Pawar, Ph.D.

Conclusion: The NDA is recommended for approval from microbiology product quality standpoint.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original NDA

2. SUBMISSION PROVIDES FOR: Use of terlipressin for injection in the treatment of hepatorenal syndrome.

3. MANUFACTURING SITE: (b) (4)

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Lyophilized powder, Intravenous 0.85 mg/vial.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment of Hepatorenal Syndrome.

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: The consult requests microbiology product quality review of Original NDA 22-231 for Lucassin®. The paper submission consisted of 7 volumes. The IQA was filed by Kasturi Srinivasachar on June 4, 2009.

filename: C:\my documents\review\NDA\N022231R1

Executive Summary

I. Recommendations

A. Recommendation on Approvability – Recommended for approval.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – (b) (4) (b) (4)

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

Vinayak B. Pawar, Ph.D.
CDER/OPS/NDMS

B. Endorsement Block _____

Stephen Langille, Ph.D.
CDER/OPS/NDMS

C. CC Block
N/A

Product Quality Microbiology Assessment

1. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

S DRUG SUBSTANCE - N/A

P DRUG PRODUCT

P.1 Description of the Composition of the Drug Product

- Description of drug product – Terlipression for injection is a sterile, lyophilized powder for reconstitution supplied as 0.85 mg terlipression (free base) per vial.
- Drug product composition – See Table 1.

Table 1. Description and Composition of the Drug Product.

Ingredient	Function	Mg per vial
Terlipression (as free base)	Drug substance	0.85
Mannitol USP	(b) (4)	10.0
Glacial Acetic Acid USP	pH adjustment	As required for pH adjustment
Sodium Hydroxide, NF	pH adjustment	As required for pH adjustment
Water for injection USP	(b) (4)	(b) (4)

- Description of container closure system – Terlipressin for injection is packaged in 6-mL USP (b) (4) vials with (b) (4) stoppers and (b) (4) aluminum flip-off caps.

P.2 Pharmaceutical Development

(b) (4)

4 Page(s) 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/

VINAYAK B PAWAR
09/30/2009

STEPHEN E LANGILLE
10/01/2009

NDA 22-231

LUCASSIN
Terlipressin for Injection

Orphan Therapeutics, LLC

Division of Cardiology and Renal Products, HFD 110

Shastri Bhamidipati, Ph.D.
Division of Pre-Marketing Assessment I,
Office of New Drug Quality Assessment

Receipt Date : 04-MAY-2009
PDUFA Goal Date: 04-NOV-2009

Table of Contents

4 Pages(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Chemistry Review Data Sheet

1. NDA 22-231

2. REVIEW #: 1

3. REVIEW DATE: 28-SEPT-2009

4. REVIEWER: Shastri Bhamidipati, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Not applicable	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 22-231 Original Submission	01-MAY-2009
NDA 22-231 Supporting Document 0018	08-JUN-2009
NDA 22-231 Supporting Document 0021	11-JUN-2009
NDA 22-231 Supporting Document 0029	08-SEPT-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Orphan Therapeutics, LLC

Address: 3 Werner Way, Suite# 210
Lebanon, NJ 08833

Representative: Candice Teuber, Pharm.D.
Sr. Director, Regulatory Affairs
3 Werner Way, Suite# 210
Lebanon, NJ 08833

Telephone: (909) 849-4851

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Not provided at this time
b) Non-Proprietary Name (USAN):
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.50, 505(b)(1)

10. PHARMACOL. CATEGORY: Cardiology, Hepatorenal Syndrome (HRS) Type I

11. DOSAGE FORM: Lyophilized Powder for Injection

12. STRENGTH/POTENCY: 0.85 mg/vial

13. ROUTE OF ADMINISTRATION: Intravenous, Bolus

14. Rx/OTC DISPENSED: ___X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

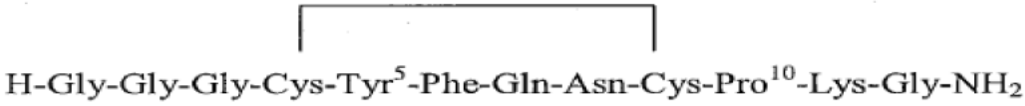
___X___Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name(s): N-[N-(N-glycylglycyl)glycyl)-8-L-lysinevasopressin
Glcyl-glycyl-glycyl[8-L-lysine]vasopressin
N-α-glycyl-glycyl-glycyl -vasopressin
1-triglycyl-8-lysine-vasopressin

Molecular Formula: $C_{52}H_{74}N_{16}O_{15}S_2$

Molecular Weight: 1226.5 (free base)
CAS: [14636-12-5]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		4	Adequate		Last reviewed by Dr. Dong, ONDQA/Div IV in Dec. 2008
	III			4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	IND (b) (4)	Terlipressin (b) (4)

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER(S)
Biometrics	Not applicable		
EES	Overall recommendation from OC is pending		
Pharm/Tox	Approvable	08/06/2009	Dr. Gowra Jagadeesh
Clinical Pharmacology	Acceptable pending agreement on labeling contents	08/27/2009	Dr. Divya Menon-Anderson
Methods Validation	Not requested. The methods are conventional and do not qualify for internal validation by FDA labs		
DMEPA	Trade name was reviewed and deemed acceptable	08/13/2009	Anne Crandall, Pharm.D.
EA	Claimed categorical exclusion granted		
Microbiology	Microbiology review is pending		Dr. Vinayak Pawar

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-231

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application for Terlipressin Lyophilized Powder for Injection, 0.85 mg/vial, can not be recommended for approval from CMC perspective at this juncture due to the CMC issues identified at the end of this review. Additionally, review of microbiology section of the NDA and a final recommendation as to the status of manufacturing and testing facilities from the Office of Compliance are pending. The sponsor has been formally informed of the CMC issues through information request letter and a response is pending from the sponsor. The sponsor has submitted the trade name, Lucassin®, for the drug product and Division of Medication Error Prevention and Analysis (DMEPA) has reviewed the trade name and recommended as acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None applicable at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The proposed drug product, Lucassin® (Terlipressin) for Injection, is a 12-residue synthetic peptide analogue of vasopressin, a systemic vasoconstrictor, and was developed to treat hepatorenal syndrome (HRS) Type I based on the drug product currently marketed in (b) (4) The drug product is a preservative-free sterile lyophilized powder and the formulation contains Terlipressin, the active at 0.85 mg as free base, mannitol, USP (b) (4) , glacial acetic acid, USP and/or sodium hydroxide, NF (used for pH adjustment) and water for injection USP. Lucassin® (Terlipressin) for Injection is packaged in 6 mL (b) (4) glass vial and will be marketed in only one strength (0.85 mg/vial) for single use. The drug product should be reconstituted with only 0.9% Sodium Chloride solution for injection prior to administration.

The pharmaceutical development of Terlipressin drug product (b) (4)

The manufacturing process for the bulk drug product is a (b) (4)

Individual steps in manufacturing process have been evaluated for process

variabilities, compatibility and ensuring product quality. (b) (4) (b) (4) (b) (4) The proposed drug product specification meet the quality requirements for parenteral products. (b) (4) (b) (4). In addition, stability data provided in support of the use of reconstituted solution for administration was determined to be inadequate due to (b) (4)

The sponsor presented 36 month stability data at long term storage conditions of 5°C for three drug product batches (b) (4) and 6 month stability data at long term storage conditions of 5°C for another three registration drug product batches (b) (4) manufactured at the proposed commercial manufacturing site. However, the analytical method employed for terlipressin assay and impurities in drug product was changed to (b) (4) Additionally, after initiating the stability study for the registration batches, detection of new impurities in stability samples necessitated further development of the analytical method. A method comparison study was performed employing the three methods and stability samples (long term and accelerated storage conditions) from development batches and the registration batches. The sponsor compared the similarity of the data profiles for the development batches and the registration batches at long term storage conditions and proposed a 24 month shelf-life for drug product. Based on the evaluation of the results from method comparison study and the stability data, it was determined that a shelf life beyond (b) (4) months can not be recommended for the drug product unless the sponsor provides additional information that justify the use of supporting stability data.

Drug Substance:
Terlipressin, an analogue of vasopressin, is a 12 residue synthetic peptide with the primary sequence of Gly-Gly-Gly-Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly with a disulfide bond. The drug substance was synthesized by (b) (4) and characterized by physical, chemical and analytical methods to establish the structure. The manufacturing process includes appropriate in-process controls and was adequately described. The final drug substance is a (b) (4)

(b) (4) The analytical procedures for release of drug substance were adequately described and validated. The specification for the drug substance, however, does not include testing for confirmation of the disulfide bond. Additionally, residual solvent testing of the drug substance (b) (4)

B. Description of How the Drug Product is Intended to be Used

Lucassin® (terlipressin) for Injection, is provided as preservative-free, sterile lyophilized powder (0.85 mg of Terlipressin free base and 10 mg of mannitol per vial) for single-use in 6 mL (b) (4) glass vials and packaged in (b) (4) unit carton. Each vial should be reconstituted with 5 mL of 0.9% sodium chloride solution for injection. (b) (4) The drug product is stored refrigerated at 2-8°C (36- (b) (4) °F). Once reconstituted, the drug product is stored refrigerated at 2-8°C and used within (b) (4) hrs.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application for Lucassin (terlipressin) for Injection, 0.85 mg/vial can not be recommended for approval from CMC perspective in the present form at this juncture due to pending CMC issues related to drug product characterization and analytical procedures. Based on the evaluation of stability data submitted by the sponsor, the recommended shelf-life for the product is limited to (b) (4) months. Additionally, an overall recommendation for the manufacturing and testing sites from the Office of Compliance is pending.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Shastri Bhamidipati, Ph.D.
Chemistry Team Leader Name/Date: Kasturi Srinivasachar, Ph.D.

C. CC Block

Original NDA 22-231
DCRP (HFD-110)/NDA Division File
DCRP(HFD-110)/CSO/A. Park
ONDQA/DPAI/Chemist/S. Bhamidipati
ONDQA/DPAI /PAL/K.Srinivasachar
ONDQA/DPAI/ RPM/D.Henry
ONDQA/DPAI /Branch Chief/R. Sood

115 Page(s) 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)
NDA-22231	ORIG-1	ORPHAN THERAPEUTICS LLC	LUCASSIN (TERLIPRESSIN)
NDA-22231	ORIG-1	ORPHAN THERAPEUTICS LLC	LUCASSIN (TERLIPRESSIN)
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/

SHASTRI P BHAMIDIPATI
09/29/2009

RAMESH K SOOD
09/29/2009

Date: 15 September, 2009

From: Michael A. Phelan

Through: Michael Norcross, Principle Investigator, and Daniela Verthelyi,
Chief, Laboratory of Immunology, Division of Therapeutic Proteins, FDA

Subject: Consult on product immunogenicity

Product: Terlipressin (tri-glycyl vasopressin) a synthetic vasopressin analogue of 12 amino acids.

Sponsor: Orphan Therapuetics, LLC, 3 Werner Way, Round Valley Executive Center Lebanon, NJ 08833

Submission Reference Number: OT-0401

Submission Application Number: 22-231

Submission Receipt Date: May 1, 2009.

Summary

This package contains the validation report for a screening assay to assess the development of antibodies to Terlipressin, a recombinant human vasopressin as well as the results for the screening of 246 patients from a phase III study. With the current assay, no patients, who did not already have detectable antibodies (4 persons) prior to the trial, developed detectable antibodies after drug administration. Additional information is needed on how the cut of was established. Of the 246 patients, three had antibodies to Terlipressin at base line collection. The 4th barely registered barely above the cut-off at day 14 sampling, but this individual received placebo. The sponsor does not show whether antibodies to the product would bind to endogenous vasopressin or whether they could have a neutralizing effect.

Comments to the File: The information on the screening assay to assess immune responses to the product is incomplete and internally inconsistent hindering the interpretation of the data submitted.

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/

MELINDA J BAUERLIEN
09/16/2009

MICHAEL A PHELAN
09/16/2009

DANIELA I VERTHELYI
09/16/2009

Initial Quality Assessment
Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	22-231
Applicant:	Orphan Therapeutics, LLC
Letter Date:	01 May 2009
Status Date:	04 May 2009
PDUFA Date:	04 May 2010
Tradename:	Lucassin
Established Name:	Terlipressin
Dosage Form:	Sterile lyophilized solid, 1 mg/vial as terlipressin acetate
Route of Administration:	Intravenous bolus
Indication:	Treatment of hepatorenal syndrome, type 1
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes

Summary

This NDA, in paper CTD format, is for a lyophilized formulation of terlipressin acetate for injection. Terlipressin is a vasopressin analog. It is a synthetic 12- amino acid peptide which differs from endogenous human vasopressin by the substitution of lysine for arginine at the 8th position of the endogenous molecule and the addition of three glycyl residues at the amino terminus. Terlipressin is a systemic vasoconstrictor, acting both as a pro-drug for lysine vasopressin and having some pharmacologic activity on its own. Clinical trials for the proposed indication were conducted under IND 68,582 and terlipressin was granted Orphan Drug designation and Fast Track status. The NDA application was accepted as a rolling submission with the CMC section the last to be submitted. There have been no CMC specific meetings with the Applicant and the only meeting with CMC discussion was the pre-IND meeting held on Jan 22, 2004. In this meeting, Orphan Therapeutics was asked to consider a bioassay or provide justification why this would not be necessary.

Drug Substance

Terlipressin is a C-terminal amide peptide containing 12 amino acids which is metabolized to lysine vasopressin by tissue peptidases. All chiral amino acids are present in the naturally occurring L-configuration. There is a disulfide bridge between Cys^4 and Cys^9. The drug substance is [redacted] (b) (4) It is freely soluble in water but insoluble in organic solvents like acetonitrile and dichloromethane. Structure characterization has been carried out by multiple methods including ^{1}H and ^{13}C NMR, ESI MS for molecular weight, MS/MS using Collision Induced Dissociation for primary amino acid sequence, ESI MS of the native peptide and [redacted] (b) (4) to confirm the disulfide bridge. There is an USP monograph for the metabolite, vasopressin.

The drug substance is synthesized by [redacted] (b) (4)

(b) (4)

Only 2 impurities are listed in the specification although numerous others are discussed which seem to fall into the category of (b) (4)%. Based on stability studies, a re-test period of (b) (4) months is proposed for storage at (b) (4)

Drug Product

Terlipressin is formulated as a sterile, lyophilized powder for reconstitution with mannitol as a (b) (4) and glacial acetic acid and sodium hydroxide for pH adjustment. Water for injection is (b) (4) All excipients are of compendial quality. The product is packaged in 6 mL (b) (4) vials with (b) (4) stoppers and (b) (4) aluminum flip-off caps. No preservatives are included since these vials are for single use.

The drug product is manufactured by (b) (4)

(b) (4)

(b) (4) In-use stability studies after reconstitution of the lyophilized product with 0.9% sodium chloride have also been conducted at room temperature and under refrigerated conditions for (b) (4) hours. A 24 month expiration period is proposed for the drug product stored at 5˚C ± 3˚C.

Critical Review Issues

Drug substance

- Has the Applicant shown tha (b) (4)

- The inclusion of an ID test for the presence of a disulfide bridge in the drug substance specification should be considered.
- Are the proposed limits for (b) (4) justified?
- Only (b) (4) is listed in the specification. Is this acceptable?
- Has the Applicant made a convincing argument for not (b) (4)

Drug Product

- Since this is a sterile solid for injection, the major critical issue is sterility assurance of the product after manufacture and maintenance of sterility over the shelf-life. These aspects are expected to be covered by the microbiology reviewer.
- Regarding the specification—
    - Identification by (b) (4) is not considered adequate
    - The proposed pH limits of (b) (4) seem to be too broad
    - Identification of (b) (4) stated to be on-going, should be completed within the review cycle
    - Are the proposed shelf-life acceptance criteria for (b) (4) and total impurities acceptable?
    - For assigning an expiration date, should data from both (b) (4) and (b) (4) batches be considered?
    - Is the method comparison protocol for the 3 different RP-HPLC methods used for assay and impurities during the course of the stability program acceptable**?**

Labeling

The quantitative amounts of all excipients in the drug product vial should be listed in the Description section of the Package Insert in a similar manner to the carton labels.

Comments and Recommendations

The application is fileable. Manufacturing, testing and packaging facilities are being entered into EES and the reviewer should verify the accuracy and completeness of the entries. It should be noted that Section 2.2.1 lists a number of facilities which perform release tests in addition to (b) (4) however, it is not clear whether these testing facilities are going to be used for commercial drug substance since they were not listed in the attachment to form 356h. A microbiology reviewer has been assigned to this NDA. A single CMC reviewer is recommended for this application.

Kasturi Srinivasachar — Jun. 3, 2009
Pharmaceutical Assessment Lead — Date
Ramesh Sood, Ph.D. — Jun. 3, 2009
Branch Chief — Date

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

/s/

Kasturi Srinivasachar
6/3/2009 05:52:46 PM
CHEMIST

Ramesh Sood
6/4/2009 09:58:48 AM
CHEMIST