CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022231Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: September 9, 2022

To: Rekha Kambhampati, M.D., Medical Officer
Division of Cardiology and Nephrology (DCN)

Anna Park, Regulatory Project Manager (DCN)

From: Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for TERLIVAZ (terlipressin) for injection, for intravenous use

NDA: 022231

In response to DCN's consult request dated September 9, 2022, OPDP has reviewed the proposed product labeling (PI) and Carton/Container (C/C) for TERLIVAZ (terlipressin) for injection, for intravenous use. This is a resubmitted application.

PI, C/C: OPDP's comments on the proposed labeling are based on the draft version received by electronic mail from DCN on September 6, 2022, and are provided below.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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CHARUNI P SHAH
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 26, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 022231
Product Name, Dosage Form, and Strength:	Terlivaz (terlipressin) For Injection, 0.85 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mallinckrodt Pharmaceuticals
FDA Received Date:	June 9, 2022
OSE TTT ID #:	2022-17
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Mallinckrodt Hospital Products Inc. submitted a class 2 resubmission for Terlivaz (terlipressin) for injection on June 9, 2022. Terlivaz is a vasopressin receptor agonist proposed to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function. This review evaluates the proposed prescribing information (PI), container label and carton labeling for Terlivaz (terlipressin) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND INFORMATION

NDA 022231 was originally submitted on May 1, 2009. The application received a Complete Response (CR) Letter on November 4, 2009 for product quality issues, facility inspection issues, and the requirement of an additional clinical trial for safety and efficacy. A Class 2 resubmission was submitted on March 12, 2020 and the application received a second CR on September 11, 2020 due to clinical issues. We previously completed a label and labeling review[a]. Another Class 2 resubmission was submitted on August 18, 2021. We completed several label and labeling reviews as part of this resubmission and all of our recommendations were implemented.[bc] The NDA received a third CR on February 18, 2022 for facility inspection issues.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

[a] Straka, M. Label and Labeling Review for Terlivaz (NDA 022231). Silver Spring, MD: FDA, CDER, OSE, DMEPA (US); 2020 AUG 11. RCM No.: 2020-528.
[b] Aidoo, M. Label and Labeling Review for Terlivaz (NDA 022231). Silver Spring, MD: FDA, CDER, OSE, DMEPA (US); 2021 OCT 22. RCM No.: 2020-528-1.
[c] Mehta, H. Label and Labeling Review for Terlivaz (NDA 022231). Silver Spring, MD: FDA, CDER, OSE, DMEPA (US); 2022 JAN 19. RCM No.: 2020-528-2

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and PI for Terlivaz (terlipressin) to identify deficiencies that may lead to medication errors and other areas of improvement. We note all of our previous recommendations were implemented in the previous review cycle. We find the proposed container label, carton labeling, and PI for Terlivaz (terlipressin) acceptable from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

We find the proposed container label, carton labeling, and PI for Terlivaz (terlipressin) acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Terlivaz received on June 9, 2022 from Mallinckrodt Pharmaceuticals.

Table 2. Relevant Product Information for Terlivaz	
Initial Approval Date	N/A
Active Ingredient	terlipressin
Indication	Vasopressin receptor agonist indicated to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function.
Route of Administration	Intravenous
Dosage Form	For Injection
Strength	0.85 mg/vial
Dose and Frequency	Days 1 to 3 administer TERLIVAZ 0.85 mg (1 vial) intravenously every 6 hours. Day 4: Assess serum creatinine (SCr) versus baseline. • If SCr has decreased by at least 30% from baseline, continue TERLIVAZ 0.85 mg (1 vial) intravenously every 6 hours. • If SCr has decreased by less than 30% from baseline, dose may be increased to TERLIVAZ 1.7 mg (2 vials) intravenously every 6 hours. • If SCr is at or above baseline value, discontinue TERLIVAZ. Continue TERLIVAZ until 24 hours after two consecutive SCr ≤1.5 mg/dL values at least 2 hours apart or a maximum of 14 days.
How Supplied	A sterile, preservative-free, white to off-white lyophilized powder in single-dose vials containing 0.85 mg of terlipressin. Each vial is supplied in a carton (NDC 43825-200-01).
Storage	Store TERLIVAZ vials in the carton under refrigerated conditions at 2°C to 8°C (36°F to 46°F). Store in the original carton to protect from light prior to reconstitution.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 14, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Terlivaz'. Our search identified three previous reviews[d,e,f], and we considered our previous recommendations to see if they are applicable for this current review.

[d] Straka, M. Label and Labeling Review for Terlivaz (NDA 022231). Silver Spring, MD: FDA, CDER, OSE, DMEPA (US); 2020 AUG 11. RCM No.: 2020-528.

[e] Aidoo, M. Label and Labeling Review for Terlivaz (NDA 022231). Silver Spring, MD: FDA, CDER, OSE, DMEPA (US); 2021 OCT 22. RCM No.: 2020-528-1.

[f] Mehta, H. Label and Labeling Review for Terlivaz (NDA 022231). Silver Spring, MD: FDA, CDER, OSE, DMEPA (US); 2022 JAN 19. RCM No.: 2020-528-2.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Terlivaz labels and labeling submitted by Mallinckrodt Pharmaceuticals.

- Container label received on June 9, 2022
- Carton labeling received on June 9, 2022
- Prescribing Information (Image not shown) received on June 9, 2022, available from \\CDSESUB1\evsprod\nda022231\0068\m1\us\114-labeling\draft-labeling\draft-label-text\terlivaz-pi-clean.pdf

G.2 Label and Labeling Images

Container Label

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[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: February 14, 2022

To: Rekha Kambhampati, M.D.
Division of Cardiology and Nephrology (DCN)

Anna Park, Regulatory Project Manager, (DCN)

Michael Monteleone, Associate Director for Labeling, (DCN)

From: Melissa Khashei, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for Terlivaz (terlipressin) for injection, for intravenous use

NDA: 22231

In response to DCN's consult request dated August 30, 2021, OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for the original NDA submission for Terlivaz (terlipressin) for injection, for intravenous use (Terlivaz).

Labeling: OPDP has reviewed the draft PI received by electronic mail from DCN (Anna Park) on February 7, 2022, and we have no comments at this time.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on January 11, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Melissa Khashei at (301) 796-7818 or melissa.khashei@fda.hhs.gov.

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MELISSA KHASHEI
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 19, 2022
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 022231
Product Name and Strength:	Terlivaz (terlipressin) for injection, 0.85 mg/vial
Applicant/Sponsor Name:	Mallinckrodt Pharmaceuticals Ireland, Ltd.
OSE RCM #:	2020-528-2
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on January 11, 2022 for Terlivaz (terlipressin) for injection. We reviewed the revised container labels and carton labeling for Terlivaz (terlipressin) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

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[a] Aidoo, M. Label and Labeling Review for Terlivaz (terlipressin) (NDA 022231). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 OCT 22. RCM No.: 2020-528-1.

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HINA S MEHTA
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Memorandum

Division of Pharmacology/Toxicology
Office of Cardiology, Hematology, Endocrinology, & Nephrology
Center for Drug Evaluation and Research

NDA EPC REVIEW

Date:	14 Dec 2021
NDA #	022231
Applicant:	Mallinckrodt Hospital Products, Inc.
Drug:	Terlipressin
Primary Reviewer:	Gowra Jagadeesh, Ph.D.
Secondary Reviewer:	Xuan Chi, Ph.D.

Background

Terlipressin is a synthetic 12 amino acid peptide. It differs from endogenous arginine vasopressin (AVP) by the substitution of lysine for arginine at the 8th position of the arginine vasopressin molecule and the addition of three glycyl residues at the amino terminus. Terlipressin is converted to lysine vasopressin in the circulation after the N-triglycyl residue is cleaved by endothelial peptidases. This results in a slow release of the vasoactive lysine vasopressin, which exerts its effects via the same receptors V1R (vasoconstriction) and V2R (antidiuresis) as with vasopressin. The half-life of terlipressin is longer than that of AVP. Terlipressin is also a full agonist of vasopressin V1B (also known as V3) receptors, present in the central nervous system modulating ACTH release.

The EPC for terlipressin proposed by the applicant is “vasopressin receptor agonist.” This term is scientifically valid as demonstrated by in vitro pharmacology studies with terlipressin (PH Colson, 2016). Furthermore, terlipressin has been shown to be a nonselective vasopressin receptor agonist, exerting its pharmacological activities through activation of V1 receptors (splanchnic vasoconstriction and increased renal blood flow), V2 receptors (increased water reabsorption and antidiuresis), and possibly V3 receptors, which could contribute to the overall safety profile of terlipressin for hepatorenal syndrome patients with cirrhosis.

There is an existing EPC, vasopressin analog, that describes the same mechanism of action. Comparatively, vasopressin receptor agonist is more molecular in nature, with better clarity on the pharmacologic action at the receptor level and would provide more meaningful information to the prescribers.

Recommendation

Based on the existing literature on terlipressin, the reviewing pharmacologists recommend the use of “vasopressin receptor agonist” as the EPC for terlipressin.

Reference

Colson PH, Virsolvy A, Gaudard P, Charrabi A, Corbani M, Manière MJ, Richard S, Guillon G. Terlipressin, a vasoactive prodrug recommended in hepatorenal syndrome, is an agonist of human V1, V2 and V1B receptors: Implications for its safety profile. Pharmacol Res. 2016 Nov;113(Pt A):257-264.

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/s/

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XUAN CHI
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Concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memorandum

Date: 12/3/21 **Date Consulted:** 8/30/21

From: Jane Liedtka, M.D., Medical Officer, Maternal Health Team (MHT)
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, MHT, DPMH

Lynne P. Yao, MD, Director, DPMH

To: Anna Park, Regulatory Project Manager (RPM)
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Division of Cardiology and Nephrology (DCN)

Drug: Terlipressin

NDA: 22231

Indication: the treatment of hepatorenal syndrome Type 1 (HRS-1)

Applicant: Mallinckrodt Pharmaceuticals

Subject: Pregnancy and Lactation Labeling [Class 2 resubmission of 505b(1) New Drug Application (NDA) after Complete Response (CR)]

Materials Reviewed:

- Applicant's submission dated 8/18/21

Consult Question: Please provide labeling recommendations.

INTRODUCTION AND BACKGROUND

- The initial NDA submission for terlipressin under NDA 22231 for the treatment of HRS-1 by Orphan Therapeutics was reviewed in 2009 and received a CR on 11/4/09. Ikaria resubmitted in 2015 and again received a CR.
- It was resubmitted in 2020 by the current applicant, Mallinckrodt Pharmaceuticals and subsequently received a third CR on 9/11/20.
- Mallinckrodt Pharmaceuticals submitted again on 8/18/21 and on 8/30/21, DCN consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of terlipressin labeling to be in compliance with the Pregnancy and Lactation Labeling Rule (PLLR).

Hepatorenal Syndrome Type 1 and Pregnancy

Hepatorenal syndrome (HRS) is a form of impaired kidney function that occurs in individuals with advanced liver disease. Hepatorenal syndrome is classified into 2 types: HRS-1 shows a rapid and progressive decline in renal function with a very poor prognosis (median survival of about 2 weeks); HRS-2 has a more stable kidney failure, with a median survival of 6 months; its main clinical manifestation is refractory ascites. At present, there is no available pharmacological therapy (i.e., approved or proven standard) in the United States for HRS-1[1]. The estimated annual incidence of HRS-1 is 35,000 patients in the US[2].

This reviewer was unable to locate any publications of any kind that mentioned pregnancy in association with HRS. The Applicant provided some literature regarding vasopressin and its analogues and the adverse effects seen on pregnancy from the 1970s and early 1980s. These publications are summarized in Table 1 in Attachment A of this review and demonstrate that vasopressin and its analogues induce an increase in uterine activity and decrease in endometrial blood flow.

Terlipressin Drug Characteristics[3]

Terlipressin is a synthetic vasopressin analog with selectivity for vasopressin V1 receptors. Terlipressin acts as both a prodrug for lysine-vasopressin, as well as having pharmacologic activity on its own. According to the Applicant, in HRS-1 patients, the V1 receptor-mediated vasoconstrictor activity of terlipressin, particularly in the splanchnic circulation, results in an increase in effective arterial volume, an increase in mean arterial pressure, normalization of endogenous vasoconstrictor systems (renin-angiotensin-aldosterone and sympathetic nervous system) resulting in increased renal blood flow leading to restoration of renal function in hypo-perfused kidneys.

Terlipressin is a first-in-class new molecular entity (NME) in the US. However, the active ingredient is approved by other drug manufacturers in many countries outside the US for the

[1]Runyon BA; AASLD. Introduction to the Revised American Association for the Study of Liver Diseases Practice Guideline Management of Adult Patients with Ascites due to Cirrhosis 2012. Hepatology. 2013;57(4):1651-3.

[2]Pant C, Jani BS, Desai M, Deshpande A, Pandya P, Taylor R, Gilroy R, Olyaee M. Hepatorenal syndrome in hospitalized patients with chronic liver disease: results from the Nationwide Inpatient Sample 2002–2012. J Investig Med 2016;64:33–38.

[3] Proposed labeling for terlipressin-confirmed by clinical pharmacology team.

treatment of HRS. According to the Applicant, in countries where terlipressin is available, it is the current standard of care.

- Average molecular weight (as free base) is 1227 Daltons.
- Derived terminal half-life of terlipressin is 0.9 hours (54 minutes)
- Dosing regimen:
    - Days 1 to 3 administer 1 mg TERLIVAZ intravenously every 6 hours
    - Assess serum creatinine and adjust according to schedule (see HPI)
    - Continue TERLIVAZ until 24 hours after two consecutive SCr ≤1.5 mg/dL values at least 2 hours apart or a maximum of 14 days

Reviewer's Comments
According to the pharmacology/toxicology team leader,

> *Terlipressin is basically a prodrug of vasopressin and differs from arginine vasopressin (Vasostrict, NDA 204485) by the substitution of lysine for arginine at the 8th position of the arginine vasopressin molecule and the addition of three glycyl residues at the amino terminus. Terlipressin is converted to lysine vasopressin in the circulation after the N-triglycyl residue is cleaved by endothelial peptidases. This results in a slow release of the vasoactive lysine vasopressin, which exerts its effects via the same receptors V1R (vasoconstriction) and V2R (antidiuresis) as with vasopressin, but with longer half-life.*

REVIEW

Pregnancy

Nonclinical Experience
In published animal reproductive toxicity studies, administration of terlipressin to pregnant guinea pigs at doses of 3 to 10 mcg/kg (about 33 to 103 times less than the maximum recommended human dose (MRHD) of 4 mg terlipressin/day on a body surface area basis) caused a marked decrease in blood flow to the uterus and placenta. In rabbits, terlipressin is both embryotoxic and teratogenic (increased resorptions, increased implantation loss, fetal anomalies and fetal deformities).

Applicant's Review of Literature
The Applicant provided several publications from the 1970s and 1980s describing subjects treated with terlipressin and other vasopressin analogues during pregnancy. See Table 1 below for details.

Table 1: Table for Published Cases of Vasopressin Analogues and Effects Seen in Pregnancy

Compound	# of Doses Used	Population	Effects	Source	Reason for Study
Terlipressin (TGLVP[4]) IV- 0.5 mg (n=7) or 1 mg (n=9)	-LVP: 2-4 intravenous (IV) injections -TGLVP: a single IV injection	Pregnant women in 1st trimester (8-12 weeks)	Increase in uterine activity: increase in uterine tone within 1 minute of injection with maximum between 5-15 minutes. In 1-mg group, the uterine activity remained significantly increased for 4-7 hours	Laudański[5] 1980b	Preliminary study examining different vasopressin analogues as possible agents for induction of abortion in early pregnancy
Terlipressin (TGLVP) IV- 300 µg (n=14)	an IV injection of 300 ug of TGLVP given over 2 minutes	Pregnant women in 1st trimester (6-9 weeks)	Uterine tone and the amplitude and duration of uterine contractions increased in all women receiving the drug, uterine tone usually rising first, with a change in contractions as a secondary effect which lasted for the duration of the 4-6 hour observation period	Akerlund[6] 1978	Preliminary study examining different vasopressin analogues as possible agents for induction of abortion in early pregnancy
Terlipressin (TGLVP) IV- 100-400 µg Intranasal- 1.25-5.0 mg Lysine-	-TGLVP: IV over 2 minutes or intranasally by a pipette in a dose of 1.25-5.0 mg.	Non-pregnant women (n=19)	Increase in uterine activity and decrease in endometrial blood flow; more gradual onset and longer duration observed for terlipressin as compared to lysine- vasopressin	Akerlund[7] 1976	Not discussed in the publication.

[4] TGLVP = N-a-triglycyl-(8-lysine)-vasopressin = terlipressin

[5] Laudański T, Akerlund M. Uterine effects of N-alpha-triglycyl-(8-lysine)-vasopressin and 8-lysine-vasopressin in the first trimester of pregnancy. Contraception. 1980b Aug;22(2):199-208.

[6] Akerlund M, Laudański T. Myometrial response to a long-acting vasopressin analogue in early pregnancy. Br J Obstet Gynaecol. 1978 Jul;85(7):525-9.

[7] Akerlund M, Andersson KE. Vasopressin response and terbutaline inhibition of the uterus. Obstet Gynecol. 1976 Nov;48(5):528-36.

Lysine-vasopressin (LVP) IV- 0.1-0.5 IU (n=9)		Pregnant women in 1st trimester	A dose of 0.3 IU of LVP caused a rise in uterine tone of 17.7 mm Hg; individual contractions were also seen in most recordings and the increase in uterine activity lasted between 5 and 40 minutes	Laudański[8], 1980a	Not discussed in the publication.
Arginine-vasopressin (AVP) IV- 1 unit	Single injection of 0.25, 0.5 or 1 unit	Non-pregnant women and pregnant women (early, mid and late)	AVP induced an increase in uterine activity; AVP effects were compared with oxytocin; AVP effects were greater than oxytocin in the early stage of pregnancy	Embrey[9], 1967	Not discussed in the publication.

Source: Applicant's Clinical Information Amendment, submitted 11/15/21,modified, pages 2-3.

[8] Laudański T, Akerlund M. Interaction of vasopressin and prostaglandin on myometrial activity in vivo in the first trimester of human pregnancy. Br J Obstet Gynaecol. 1980a Feb;87(2):132-38.
[9] Embrey MP, Moir JC. A comparison of the oxytocic effects of synthetic vasopressin and oxytocin. J Obstet Gynaecol Br Commonw. 1967 Oct;74(5):648-52.

DPMH's Review of Literature
DPMH conducted a search of published literature in PubMed using the search terms "terlipressin AND pregnancy," "terlipressin and pregnancy and birth defects," "terlipressin and pregnancy and congenital malformations," "terlipressin and pregnancy and stillbirth," "terlipressin and spontaneous abortion" terlipressin AND teratogenicity" and "terlipressin and pregnancy and miscarriage." No reports of adequate and well-controlled studies of terlipressin use in pregnant women were identified beyond what was provided by the applicant (see Table 1). No observational studies or case reports of terlipressin use in lactating women were found.

Terlipressin is not referenced in Micromedex[10].

Lactation

Nonclinical Experience
There is no nonclinical information regarding the presence of terlipressin in animal milk.

Applicant's Review of Literature
The Applicant did not conduct a review of the literature.

DPMH Review of Literature
DPMH conducted a search of *Medications and Mother's Milk*[11], the Drugs and Lactation Database (LactMed),[12] Micromedex[11], and of published literature in PubMed using the search terms "terlipressin and lactation" and "terlipressin and breastfeeding." No reports of adequate and well-controlled studies of terlipressin use in pregnant women were identified. No observational studies or case reports of terlipressin use in lactating women were found.

Terlipressin is not referenced in *Medications and Mother's* Milk[7] or in LactMed[8].

Females and Males of Reproductive Potential

Nonclinical Experience
Carcinogenesis studies in animals have not been performed. Terlipressin was not mutagenic or clastogenic in the following tests: in vitro bacterial reverse mutation assay, in vivo mouse micronucleus assay, and in vitro mammalian cell (CHO) chromosome aberration assay.

Applicant's Review of Literature
The Applicant did not conduct a review of the literature regarding terlipressin and its effects on fertility.

[10] https://www.micromedexsolutions.com/micromedex2/librarian/ssl/true. Accessed Nov 9, 2021
[11] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing, pg. 422-423.
[12] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed regarding terlipressin and its effects on fertility and found no relevant articles.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are no human pregnancy outcome data for terlipressin that were found in the published English language literature. There were a few case reports from the 1970s and early 1980s of use during pregnancy in women planning a termination, found by the applicant, demonstrating vasopressin and its analogues, including terlipressin, induce an increase in uterine activity and decrease in endometrial blood flow. This drug effect, especially with repeated dosing for up to 14 days, would compromise continuation of pregnancy and have the potential to cause fetal harm. Animal studies demonstrated increased resorptions, increased implantation loss, fetal anomalies, and fetal deformities. Therefore, a Warnings and Precautions for fetal harm is recommended. See DPMH proposed labeling for recommendations. Given the rarity of use predicted by the applicant and confirmed by the lack of any reports in the literature of pregnancies associated with HRS-1, a PMR for a pregnancy registry or single arm pregnancy study is not warranted.

Lactation

There are no data on the presence of terlipressin in human or animal milk. DPMH recommends using the standard risk-benefit statement in labeling. See DPMH proposed labeling for details. Given the rarity of use in the pregnant population predicted by the applicant, a PMR for a lactation study does not seem warranted.

Females and Males of Reproductive Potential

There were no studies of the adverse effects of terlipressin on fertility. Given the acute life-threatening nature of the indication for which terlipressin is prescribed, recommendations for pregnancy testing or recommendations for contraception while taking terlipressin would not be appropriate. Therefore, DPMH recommends that section 8.3 be omitted from the labeling.

LABELING RECOMMENDATIONS

DPMH revised sections 5.6, 8.1and 8.2 of terlipressin labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Terlipressin Pregnancy and Lactation Labeling

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	October 22, 2021
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 022231
Product Name, Dosage Form, and Strength:	Terlivaz (terlipressin) for injection, 0.85 mg/vial (equivalent to 1 mg of terlipressin acetate)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mallinckrodt Pharmaceuticals Ireland, Ltd.
FDA Received Date:	August 18, 2021 and September 3, 2021
OSE RCM #:	2020-528-1
DMEPA 2 Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Mallinckrodt Hospital Products Inc. submitted a response to complete response (CR) for Terlivaz (terlipressin) for injection on August 18, 2021. Terlivaz is being proposed for the treatment of adults with hepatorenal syndrome Type 1 (HRS-1). This review evaluates the proposed prescribing information (PI), container label and carton labeling for Terlivaz (terlipressin) for areas of vulnerability that may lead to medication errors.

REGULATORY HISTORY

The original application was a rolling NDA with the complete submission on May 1, 2009. The application received a Complete Response (CR) Letter on November 4, 2009 for product quality issues, facility inspection issues, and the requirement of an additional clinical trial for safety and efficacy. A Class 2 resubmission was submitted on March 12, 2020 and the application received a second CR on September 11, 2020 due to clinical issues.[a]

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and PI for Terlivaz (terlipressin) to identify deficiencies that may lead to medication errors and other areas

[a] Straka, M. Label and Labeling Review for Terlivaz (NDA 022231). Silver Spring, MD: FDA, CDER, OSE, DMEPA (US); 2020 AUG 07. RCM No.: 2020-528

of improvement. We note throughout the carton label and container labeling that the product strength presentation is denoted as [redacted] We consulted with Office of Pharmaceutical Quality (OPQ) to obtain some clarity regarding whether the product should be presented as terlipressin for injection with a product strength denoted as 0.85 mg/vial or as currently presented as [redacted] OPQ responded by indicating that the product should be expressed as "0.85 mg/vial" since [redacted]

We identified areas of the proposed container label, carton labeling, and PI that could be revised to improve clarity and readability of important information. For the Division, we recommend the removal of abbreviations for the route of administration, replacement of symbols with the intended meaning, and clarity on the description of the product. For the Applicant we recommend changes to the container label and carton labeling to improve readability and prominence of important information. Specifically, we recommend revisions to the product strength presentation, storage information, package type term, net quantity, Rx only statement, and format of the expiration date.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Terlivaz PI, container label and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information – General Comments

1. We note the strength of Terlivaz is 0.85 mg/vial. As such, we recommend revising the dose to "0.85 mg" wherever the dose is described for consistency with the product strength.
2. The route of administration should be presented as a non-abbreviation. We recommend removing the error prone abbreviation "IV" throughout the prescribing information.
3. We note the use of the [redacted] in order to represent the word "to" for the recommended dosage ranges. We recommend removing the [redacted] and replacing it with its intended meaning of "to".

B. Highlights of Prescribing Information

1. As currently presented the dosage information as presented may cause confusion. We recommend revising the first bullet to read "Days 1 to 3 administer 0.85 mg intravenously every 6 hours".

2. The instructions included in the [redacted] (b) (4) section of the "Highlights of Prescribing Information" is redundant. We recommend replacing the instructions with the statement: "See Full prescribing information for instructions on preparation and administration (2.2).".

C. Full Prescribing Information
   1. Section 2.2 Recommend Dosage
      a. As currently presented the length of therapy is not stated in the first sentence under this section. We recommend including the length of therapy to prevent any confusion. Revise to "The recommended dosage of TERLIVAZ is 0.85 mg every 6 hours by slow intravenous bolus injection (over 2 minutes) on days 1 through 3.".
   2. Section 16 How Supplied/Storage and Handling Section
      a. Include the product description "white to off-white", before the descriptor "lyophilized powder" in the statement: "TERLIVAZ (terlipressin) is supplied as a sterile, preservative-free, lyophilized powder in single-dose vials containing 0.85 mg of terlipressin.".

4.2 RECOMMENDATIONS FOR MALLINCKRODT PHARMACEUTICALS IRELAND, LTD.

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

A. General Comments (Container labels & Carton Labeling)
   1. We recommend revising the strength presentation as it should be expressed as the active moiety with the equivalency statement where appropriate for consistency with the prescribing information. Revise as follows:

      Terlivaz
      terlipressin for injection
      0.85 mg/vial

   2. We recommend changing the statement [redacted] (b) (4) to "For Intravenous Use Only" [redacted] (b) (4)
   3. We recommend removing the statement "Sterile Lyophilized Powder" as this information is not needed.
   4. We recommend revising the statement "Single-Dose Only" to "Single-Dose Vial" as this is the appropriate package-type term. In addition, we recommend adding "Discard Unused Portion" right after the single-dose vial statement to prevent confusion.
   5. We recommend debolding the 'Rx Only" statement as currently presented it is more prominent than other information.

B. Carton Labeling

1. We recommend adding “Reconstitute with 5 mL of 0.9% Sodium Chloride Injection, USP before use” on the principal display panel to ensure this important information is not missed.
2. Change the statement: (b) (4) to “Store refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.” for clarity. We recommend bolding this statement to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
3. To ensure consistency with the Prescribing Information, revise the statement (b) (4) to read “Recommended Dosage: See prescribing information.”
4. Replace the term (b) (4) on the side panel with appropriate terminology as “0.9% Sodium Chloride Injection, USP”.
5. As currently presented, the format for the expiration date is defined as MMYYY. To minimize confusion and reduce the risk for deteriorated drug medication errors FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
6. As currently presented, the net quantity is not noted on the principle display panel. Revise to include the statement “1 Single-Dose Vial” to clarify the net quantity in the carton.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Terlivaz received on August 18, 2021 from Mallinckrodt Pharmaceuticals Ireland, Ltd.

Table 2. Relevant Product Information for Terlivaz	
Initial Approval Date	N/A
Active Ingredient	terlipressin
Indication	TERLIVAZ is a vasopressin receptor agonist indicated for the treatment of adults with hepatorenal syndrome Type 1 (HRS-1).
Route of Administration	Intravenous bolus
Dosage Form	for injection
Strength	0.85 mg per vial (0.85 mg of terlipressin free base equivalent to 1 mg of terlipressin acetate)
Dose and Frequency	- Days 1-3: 0.85 mg every 6 hours - Day 4: Assess serum creatinine versus baseline o If serum creatinine (SCr) has decreased by at least 30% from baseline, continue 0.85 mg TERLIVAZ every 6 hours. o If SCr has decreased by less than 30% from baseline, dose may be increased to 1.7 mg TERLIVAZ every 6 hours. o If SCr is at or above baseline value, discontinue Terlivaz. - Continue TERLIVAZ until 24 hours after two consecutive SCr ≤1.5 mg/dL values at least 2 hours apart or a maximum of 14 days.
How Supplied	TERLIVAZ (terlipressin) is supplied as a sterile, preservative-free, lyophilized powder in single-dose vials containing 1 mg terlipressin acetate equivalent to 0.85 mg of terlipressin free base. Each vial is supplied in a carton (NDC 43825-200-01).
Storage	Refrigerate at 2°C to 8°C (36°F to 46°F). Protect from light prior to reconstitution.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 10, 2021, we searched for previous DMEPA reviews relevant to this current review using the terms, 'terlivaz' and 'terlipressin'. Our search identified one previous review [a], and we considered our previous recommendations to see if they are applicable for this current review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Terlivaz labels and labeling submitted by Mallinckrodt Pharmaceuticals Ireland, Ltd.

- Container label received on September 3, 2021
- Carton labeling received on August 18, 2021
- Prescribing Information (Image not shown) received on August 18, 2021, available from \\CDSESUB1\evsprod\nda022231\0053\m1\us\terlivaz-pi-annotated.pdf

G.2 Label and Labeling Images

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: September 21, 2020

To: Anna Park, Regulatory Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Michael Monteleone, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)

From: Puja Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for Terlivaz (terlipressin) 1mg injection

NDA: 22231

This memo is in response to DCN's labeling consult request dated May 19, 2020. Reference is made to a Complete Response letter that was issued on September 11, 2020. Therefore, OPDP defers comment on the proposed labeling at this time, and requests that DCN submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Puja Shah at (240) 402-5040 or puja.shah@fda.hhs.gov.

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/s/

PUJA J SHAH
09/21/2020 12:18:03 PM

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

DIVISION OF HEPATOLOGY AND NUTRITION (DHN)

Medical Officer Consult Responses

NDA	22231
Cross Reference	IND 068582
Sponsor	Mallinckrodt Pharmaceuticals
Drug	Terlipressin, synthetic vasopressin analog
Proposed Indication	Hepatorenal Syndrome Type 1 (HRS-1)
Consulting Division	DCN (Anna Park)
Consult Received Date	8/19/20
Requested Due Date	8/28/20
Date review Completed	8/28/20
Clinical Reviewer	Toru Matsubayashi, MD, MPH, DrPH
Team Leader	Frank Anania, MD, FACP, AGAF, FAASLD
Associate Division Director	Joseph Toerner, MD, MPH
Project Manager	Ayanna Augustus

Materials Reviewed for this Consult:
1. Consult Request on August 17 2020 by Division of Cardiology and Nephrology (DCN)
2. Clinical Study Report MNK19013058 Synopsis
3. MNK19013058 Report Body 1
4. MNK19013058 Protocol Amend 3

Executive Summary

This is a DHN response to a consultation request from DCN – Division of Cardiology and Nephrology for terlipressin that has been developed for the indication of hepatorenal syndrome type 1 (HRS1). Terlipressin is a synthetic, 12-amino-acid peptide analog of vasopressin that acts through vasopressin Type 1 (V1) receptors. Supporting evidence has demonstrated terlipressin can improve renal function in HRS1 patients as a result of splanchnic vasoconstriction. In support of the marketing application of terlipressin for this indication, the applicant conducted a phase 3 study – a randomized, double-blind, placebo-controlled trial – to compare terlipressin to placebo in patients with HRS1. The primary endpoint was the incidence of verified HRS reversal, defined as 2 consecutive serum creatinine values ≤1.5 mg/dL at least 2 hours apart, while on treatment by Day 14 or discharge, whichever came first. To meet the primary endpoint, subjects also needed to be alive without renal replacement therapy (RRT) for at least 10 days after achieving verified HRS reversal. The trial met its primary endpoint with 58/199 patients in the terlipressin arm (29%) achieving verified HRS reversal compared to 16/101 patients in the placebo arm (16%) achieving a response (p=0.012).

DHN was asked to evaluate the result of exploratory subgroup analyses that examined the efficacy and safety of terlipressin in subjects with alcoholic hepatitis (AH) at baseline. In subjects with AH at enrollment baseline, 25/81 patients in the terlipressin arm (31%) achieved verified HRS1 reversal compared to 3/39 patients in the placebo arm (8%) who achieved verified HRS1 reversal (p=0.005). In contrast, those subjects without AH at baseline had a lower treatment response, 33/118 (28%) compared to the placebo arm 13/62 (21%), respectively (p=0.31). Because of significant limitations with *post-hoc* subgroup analyses, DHN's response is based on published literature which could account for the small, but statistically significant higher response rate for cirrhotic patients who had HRS1 with baseline AH as obtained by these analyses. The DHN response is based on what is currently known about the pathophysiology of AH and derangements that have been reported in the peripheral circulation in patients with AH. DHN cautions, however, that limitations of *post-hoc* analysis as well as the small increase in HRS1 resolution reported in subjects with AH as a result may not entirely be accounted for by what we conclude. Nonetheless, pro-inflammatory mechanisms play a significant role in the pathogenesis of AH. The presence of AH sets off a significant release of pro-inflammatory cytokines that trigger additional immune-related and other responses that result in vasodilation of the peripheral vasculature that is known to reduce renal perfusion pressure. AH patients may have substantial pathophysiological overlap with patients who have systemic inflammatory response syndrome (SIRS). We hypothesize terlipressin in AH patients in this study exerted an anti-inflammatory effect by reduction of portal venous pressure, prevention of gut bacterial translocation, and increased peripheral vascular tone. The net result of the actions of terlipressin could have resulted in the slightly improved outcome of cirrhotic patients who had AH at baseline compared to those who did not.

Background of Hepatorenal Syndrome and Terlipressin

HRS is a serious condition characterized as kidney dysfunction which may develop in patients with underlying cirrhosis and clinically significant portal hypertension. Primary etiologies of decompensated liver disease include non-alcoholic steatohepatitis (NASH), alcoholic liver disease, and hepatitis C viral (HCV) infection. HRS is often classified as either rapidly developing acute kidney injury, HRS Type 1 (HRS1), or slowly progressive chronic kidney disease, HRS Type 2 (HRS2). HRS represents the end-stage of a sequence of reduced renal function induced by severe decompensated hepatic injury that has resulted in portal hypertension, splanchnic vasodilation and compensatory renal vasoconstriction. In general, HRS1 and HRS2 have a very poor prognosis with the median survival of 1 month for HRS1 and 3 to 11 months for HRS2 depending on MELD score, respectively[1].

In patients with advanced liver disease, administration of vasopressin and its analogues (e.g. ornipressin, terlipressin) can reduce splanchnic vasodilation, resulting in elevation in mean arterial pressure, reduction in plasma renin activity, and increase in renal blood

[1] Alessandria, C., Ozdogan, O., Guevara, M., Restuccia, T., Jimenez, W., Arroyo, V., Gines, P. (2005). MELD score and clinical type predict prognosis in hepatorenal syndrome: relevance to liver transplantation. *Hepatology,* 41(6), 1282-1289.

flow. Because of these favorable effects, vasopressin analogues have been studied as a potential treatment modality for HRS1. Although the use of ornipressin was abandoned because of its association with high rates of complications such as intestinal infarctions and arrhythmias, terlipressin has been developed and examined as a potentially safe treatment for HRS1. In fact, terlipressin has been already been approved and is used in many countries, although it is not an approved drug in the USA for any indication.

Regulatory History

An initial NDA was submitted in May 2009 relying primarily on the results of study OT-0401 (a randomized, placebo-controlled trial in which 112 subjects with HRS1 were enrolled between Sep 2004 and Aug 2006). Since this study did not meet its pre-specified primary endpoint (i.e. survival with HRS1 reversal at Day 14), the Agency issued a complete response letter (CRL) in November 2009. The CRL indicated that the applicant would need to conduct at least one additional adequate and well-controlled study to demonstrate the efficacy and safety of intravenous terlipressin for the treatment of HRS1. This study would need to be successful, using pre-specified endpoint(s) and analytic plan, with clinically significant results (i.e., $p<0.05$).

To address the CRL, the applicant conducted the REVERSE trial (a randomized, double-blind, placebo-controlled trial that enrolled 196 subjects with HRS1 between October 2010 and May 2013). This study also failed to meet its primary endpoint (i.e. confirmed reversal of HRS1). Nevertheless, the applicant resubmitted an NDA application in April 2015. In May 2015, the Agency issued an Acknowledge Incomplete Response letter, noting that the applicant had failed to address the deficiencies cited in the original CRL. As a result, the sponsor proposed to conduct another study for the same indication. The new trial design, particularly the primary endpoint and statistical analysis plan, was discussed at a Type A meeting on September 11, 2015 with a teleconference on October 1, 2015. Although neither OT-0401 nor REVERSE met their pre-specified primary endpoints, the rate of success was numerically higher in subjects randomized to terlipressin than placebo in both studies. The Agency previously indicated that these studies might provide supportive evidence of efficacy. A Special Protocol Assessment (SPA) for protocol MNK 19013058 titled “A multi-center, randomized, placebo-controlled, double-blind study to confirm efficacy and safety of terlipressin in subjects with HRS1 (The CONFIRM Study)” was requested and the Agency issued a SPA agreement letter on April 20, 2016.

The CONFIRM Study was conducted between July 2016 and July 2019. The Agency received the resubmission to NDA (Class 2 Resubmission) on March 12, 2020, and an Advisory Committee meeting took place on July 15, 2020, when the committee voted 8-7 in favor of approval of terlipressin recommending the Agency grant approval of terlipressin for HRS1. [The Prescription Drug User Fee Act (PDUFA) target date is September 12, 2020.]

Results of the CONFIRM Study and Reason for DHN Consultation

The CONFIRM study was a multi-center, randomized, double-blind, placebo-controlled phase 3 study in patients with HRS1 that was conducted in 60 medical centers in the USA and Canada between July 2016 and July 2019. The objective of the study was to prove the efficacy and safety of intravenous terlipressin vs placebo as a treatment for HRS1 in adults. Table 1 summarizes the study design and key findings of this trial.

Table 1: Summary of the CONFIRM study and trial results and study outcomes

Study Design Features	Protocol	Results
Study design	A randomized, multi-center, double-blind, placebo-controlled, multiple-dose, pivotal study in subjects with HRS-1.	
Study population	Adults ≥ age 18	• Enrolled subjects were between age 23 and 81 (mean age 53.8 with standard deviation 11.5)
Inclusion criteria	• Subjects with cirrhosis and ascites and rapidly progressive worsening in renal function to a serum creatinine (SCr) at least 2.25 mg/dL and meeting a trajectory for SCr to double over 2 weeks. • No sustained improvement in renal function (<20% decrease in SCr and SCr at least 2.25 mg/dL) at least 48 hours after diuretic withdrawal and the beginning of plasma volume expansion with albumin.	• Baseline mean MELD (Model for End-Stage Liver Disease) score 32.8, mean baseline SCr 3.5 mg/dL • Child-Pugh Class A 1.7%, Class B 33.3% and Class C 61.3% of subjects
Exclusion criteria	• SCr level >7.0 mg/dL • At least 1 event of large volume paracentesis within 2 days of randomization • Sepsis and/or uncontrolled bacterial infection • <2 days of anti-infective therapy for documented or suspected infection • Shock • Estimated life expectancy of <3 days • Proteinuria >500 mg/day	
Sample size	Planned: 300 enrolled subjects	Analyzed for efficacy (Intent-to-treat [ITT] population): 300 (199 subjects in the terlipressin group and 101 subjects in the placebo group)
Doses	2:1 randomization to terlipressin acetate 1 mg I.V. every 6 hours vs placebo.	
Treatment duration	Up to 14 days	The mean duration of treatment was 6.2 days in the terlipressin group and 6.0 days in the placebo group.
Dose-escalation criteria	If SCr decreased, but by <30% from the baseline value on Day 4, after a minimum of 10 doses of study drug, the dose of study drug was increased to 2 mg every 6 hours (± 30 minutes; 8 mg/day).	
Key endpoint(s)	**Primary:** Incidence of verified HRS reversal, defined as the percentage of subjects with two consecutive SCr values of no more than 1.5 mg/dL obtained at least 2 hours apart, while receiving treatment by Day 14 or discharge (receiving treatment was defined as up to 24 hours after the final dose of study drug). Subjects had to be alive without renal replacement therapy (RRT) for at least 10 days after achieving verified HRS reversal. Serum creatinine values obtained after RRT, TIPS, liver transplant, or open-label	**Primary** • Terlipressin 29.1% vs Placebo 15.8% (p=0.012)

Study Design Features	Protocol	Results
	vasopressor use was excluded from the primary endpoint analysis. **Secondary:** 1) Incidence of subjects with HRS reversal, defined as the percentage of subjects with a SCr value of no more than 1.5 mg/dL while receiving treatment by Day 14 or discharge (SCr values obtained after RRT, TIPS, liver transplant, or open-label vasopressor use were excluded). 2) Durability of HRS reversal, defined as the percentage of subjects with HRS reversal without RRT to Day 30. 3) Incidence of HRS reversal in the systemic inflammatory response syndrome (SIRS) subgroup, defined as the percentage of SIRS subjects with HRS reversal. 4) Incidence of verified HRS reversal without HRS recurrence by Day 30.	**Secondary** 1) Terlipressin 36.2% vs Placebo 16.8% (p<0.001) 2) Terlipressin 31.7% vs Placebo 15.8% (p=0.003) 3) Terlipressin 33.3% vs Placebo 6.3% (p<0.001) 4) Terlipressin 24.1% vs Placebo 15.8% (p=0.09)

Source: Adopted from MNK19013058 Report Body 1.

Consult Question:

We conducted exploratory subgroup analyses based on alcoholic hepatitis (AH) status at baseline on the primary endpoint (i.e., verified HRS reversal), RRT-free survival (a clinical outcome thought to be predicted by treatment effects on HRS reversal), and the SAE profile. ***Our question to you is: Is there a biological basis to explain the discrepancies in the attached analyses between patients with and without alcoholic hepatitis?***

Table 2: Verified HRS Reversal Within Alcoholic Hepatitis Subgroups, ITT Population

Verified HRS Reversal	Terlipressin n/N (%)	Placebo n/N (%)	Risk Difference (%) (95% CI)	p-value
Alcoholic hepatitis present at baseline	25/81 (31%)	3/39 (8%)	23% (7.0, 39.3)	0.005
Alcoholic hepatitis not present at baseline	33/118 (28%)	13/62 (21%)	7% (-6.4, 20.4)	0.31

Source: Request for Consultation by DCN

Table 3: Serious Adverse Event by Alcoholic Hepatitis Status at Baseline

	Not Present		Present	
	Placebo (N=60)	Terlipressin (N=119)	Placebo (N=39)	Terlipressin (N=81)
Respiratory failure SAEs	4 (6.7)	15 (12.6)	1 (2.6)	13 (16.0)
Sepsis/septic shock SAEs	0	11 (9.2)	0	3 (3.7)
Abdominal pain SAEs	0	7 (5.9)	1 (2.6)	6 (7.4)
Edema/fluid overload SAEs	2 (3.3)	6 (5.0)	0	4 (4.9)
Ischemia-related SAEs	0	2 (1.7)	0	0

Source: Request for Consultation by DCN

DHN Response: -
An inherent issue in this type of *post-hoc* subgroup analysis is that even though randomization ensures that overall characteristics in the intervention and placebo groups are similar at baseline, this cannot be assumed in the subgroups because randomization was not stratified by the history of alcoholic hepatitis at enrollment. This is also true of the subgroup of patients with systemic inflammatory response syndrome (SIRS). Therefore, selection bias is possible in the subgroup analysis and this may not be easily detectable since such bias may have occurred as a result of variables that were not measured or collected in the study.

Also, it is unclear how the diagnosis of AH was made in the study. In patients with underlying cirrhosis, making a diagnosis of AH can be difficult and misclassification of the disease status can easily occur, which may introduce additional bias for the analyses conducted.

Despite the limitations described, DHN assumes all the subgroup analyses conducted are valid. There are several factors that could explain the potential heterogeneity of treatment effect in the patients with underlying AH compared to those patients who did not. As the Table 4 shows, this trial included patients who developed HRS1 from a diverse etiology for cirrhosis.

Table 4: ***Summary of hepatic history (Source: MNK19013058 Report Body Table 18)***

	Terlipressin (N = 199)	Placebo (N = 101)	Total (N = 300)
Etiology of Cirrhosis (n,%)			
Alcohol	134 (67.3)	67 (66.3)	201 (67.0)
Hepatitis B	4 (2.0)	1 (1.0)	5 (1.7)
Hepatitis C	31 (15.6)	7 (6.9)	38 (12.7)
Non-alcoholic steatohepatitis (NASH)	42 (21.1)	24 (23.8)	66 (22.0)
Autoimmune hepatitis (AIH)	10 (5.0)	5 (5.0)	15 (5.0)
Primary biliary cirrhosis	5 (2.5)	3 (3.0)	8 (2.7)
Cryptogenic	6 (3.0)	3 (3.0)	9 (3.0)
Other	9 (4.5)	5 (5.0)	14 (4.7)
Ascites Grade (n,%)			
1	51 (25.6)	19 (18.8)	70 (23.3)
2	81 (40.7)	35 (34.7)	116 (38.7)
3	66 (33.2)	46 (45.5)	112 (37.3)
Alcoholic Hepatitis (n,%)	81 (40.7)	39 (38.6)	120 (40.0)
Hepatocellular Carcinoma (n,%)	13 (6.5)	5 (5.0)	18 (6.0)
Milan Criteria (n,%)			
No	4 (2.0)	3 (3.0)	7 (2.3)
Single lesion ≤2 cm	1 (0.5)	1 (1.0)	2 (0.7)
Single lesion >2 cm and ≤5 cm	6 (3.0)	1 (1.0)	7 (2.3)
≤3 Lesions; None >3 cm	2 (1.0)	0 (0.0)	2 (0.7)
Esophageal Varices (n,%)			
Prior history of esophageal variceal hemorrhage	30 (15.1)	21 (20.8)	51 (17.0)
Received esophageal banding treatment	48 (24.1)	29 (28.7)	77 (25.7)
Received tips (transjugular intrahepatic portosystemic shunt)	7 (3.5)	2 (2.0)	9 (3.0)

N = number of subjects in the treatment group; n = number of subjects in the category of subjects in the treatment group.

First, there may be differences in baseline characteristics between patients with and without AH that can affect a patient's response to terlipressin. For example, patients with underlying AH were more likely to be younger (mean age 48.6 vs 57.3 years) and male (proportion of male 67% vs 55%) compared to non-AH patients. Intrinsic differences between the two populations might have played a role with respect to the response to the intervention and the placebo.

Second there is likely a pathophysiological difference between patients with and without AH that causes a discrepancy in their response to terlipressin. Proinflammatory mechanisms seem to play a significant role in the pathogenesis of AH[2]. It is possible that terlipressin can indirectly exert an anti-inflammatory effect through reduction in portal venous pressure and prevention of gut bacterial translocation. An *in vitro* study result suggests that terlipressin has a direct anti-inflammatory effect on intestinal epithelial cells in the setting of intestinal ischemia [3]. In fact, the translocation of gut bacteria, as a result of comprised intestinal integrity, is likely to be the principle reason patients with AH or acute-on-chronic liver failure (ACLF) develop sepsis[4] and ultimately promotes marked proinflammatory cytokine production which is very likely to contribute to development of HRS1. Yet, in this scenario the patients with baseline AH are more responsive to the treatment that results in a higher trend toward reversal of HRS1[5]. In other words, DHN would state that the subgroup of alcoholic cirrhosis patients in this trial with acute AH are physiologically, a different cohort of patients. This pathophysiological characteristic in the subjects with baseline AH also could explain the much lower incidence of sepsis/septic shock SAEs of terlipressin in this subgroup as shown in **Table 3**.

This working hypothesis is substantiated by the sponsor's data shown in **Table 1**. When subgroup analysis in the trial was conducted in patients with systemic inflammatory response syndrome (SIRS) as one of the secondary endpoints, the results are very similar to what DCN found for the *post-hoc* analysis of the baseline AH patients. That is, HRS1 was reversed with a frequency of 33.3% in the terlipressin group compared to 6.3 % in the placebo group ($p<0.001$). As DHN indicates, AH shares some key pathophysiologic features with SIRS. Both the response rates for either the SIRS or AH cohort compared to their respective placebo groups are very similar.

The sponsor concluded that terlipressin appeared to be particularly effective in the subgroups of patients with AH and SIRS, stating "terlipressin attenuates splanchnic portal hypertension/splanchnic vasodilation-related inflammatory response". It is entirely

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[2] Gao, B., Ahmad, M. F., Nagy, L. E., & Tsukamoto, H. (2019). Inflammatory pathways in alcoholic steatohepatitis. *J Hepatol*, 70(2), 249-259. 3

[3] Liu, Z. M., Zhang, X. Y., Chen, J., Shen, J. T., Jiang, Z. Y., & Guan, X. D. (2017). Terlipressin protects intestinal epithelial cells against oxygen-glucose deprivation/re-oxygenation injury via the phosphatidylinositol 3-kinase pathway. *Exp Ther Med,* 14(1), 260-266. 2

[4] Gustot, T., Fernandez, J., Szabo, G., Albillos, A., Louvet, A., Jalan, R., Moreno, C, et.al. (2017). Sepsis in alcohol-related liver disease. *J Hepatol*, 67(5), 1031-1050.

[5] Mindikoglu, A. L., & Pappas, S. C. (2018). New Developments in Hepatorenal Syndrome. *Clin Gastroenterol Hepatol*, 16(2), 162-177 e161.

possible that these two entities (SIRS and AH) share common pathophysiology (e.g., acute inflammatory state) and retain a margin of reversibility as a result thereby affording these subgroups more favorable response rates to terlipressin.

Summary

Provided that the subgroup analyses are valid, there is a biologically plausible explanation that accounts for the discrepancies in the therapeutic response to terlipressin between patients with and without AH. Baseline characteristics such as age and gender tend to be different in the subgroup of AH compared to the rest of the study population. Such baseline differences may be one potential cause for the discrepancy since the analysis was being conducted in two distinct population which may not be comparable. DHN thinks it's more likely, however, that the pathophysiologic derangements observed in patients with AH, and similar to patients affected by SIRS renders this subgroup more responsive to terlipressin which ultimately increases renal perfusion pressure with reduction in splanchnic vascular tone. This is also borne out by data presented in Table 3 of SAEs in which cirrhotic patients with baseline AH receiving terlipressin had substantially fewer episodes of sepsis/septic shock than patients who were receiving terlipressin who did not have AH at baseline.

We conclude that in addition to its known vasoactive properties, terlipressin is likely to have anti-inflammatory properties that along with peripheral vasoconstriction are synergistic in promoting effective blood flow to the renal glomerulus. Our explanation would account for the data revealed by post-hoc subgroup analyses for both AH patients as well as patients affected by SIRS.

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TORU MATSUBAYASHI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

Date:	August 24, 2020
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Product Name:	Terlipressin
Application Type/Number:	22231
Applicant:	Mallinckrodt Hospital Products IP Limited
OSE RCM #:	2020-809

TABLE OF CONTENTS

1 INTRODUCTION

The purpose of this Pharmacovigilance Review is for the Division of Pharmacovigilance I (DPV-I) to provide to the Division of Cardiology and Nephrology (DCN) a safety summary and analysis of postmarket safety data from case reports or case series for terlipressin from the FDA Adverse Event Reporting System (FAERS) database, VigiBase,[a] and medical literature. The goal of this safety summary and analysis is to inform DCN as they conduct a review of the New Drug Application (NDA) 22231 for terlipressin to treat adults with hepatorenal syndrome Type 1 (HRS-1).

1.1 BACKGROUND

Terlipressin

Terlipressin is a synthetic vasopressin analog with high selectivity for vasopressin V1 receptors. Terlipressin acts as both a prodrug for vasopressin, as well as having pharmacologic activity of its own. In HRS-1 patients, the V1 receptor-mediated vasoconstrictor activity of terlipressin, particularly in the splanchnic area, results in an increase in effective arterial volume, an increase in mean arterial pressure (MAP), normalization of endogenous vasoconstrictor systems (renin-angiotensin-aldosterone and sympathetic nervous system) resulting in increased renal blood flow leading to restoration of renal function in the hypo-perfused kidneys. Terlipressin is approved in over 40 countries outside the U.S., where it is the current standard of care in patients with decompensated cirrhosis complicated with HRS-1.[1]

Hepatorenal Syndrome

Hepatorenal syndrome is characterized as renal dysfunction secondary to reduction in renal blood flow (RBF) occurring in the setting of underlying cirrhosis and portal hypertension.[2] Other than cirrhosis, HRS can also develop in patients with portal hypertension due to severe alcoholic hepatitis, or (less often) metastatic tumors, but can also occur with fulminant hepatic failure from any cause. HRS represents the end-stage of a sequence of reductions in renal perfusion induced by increasingly severe hepatic injury. The onset of kidney failure is typically insidious but can be precipitated by an acute insult, such as bacterial infection (often spontaneous bacterial peritonitis) or gastrointestinal (GI) bleeding.[3] The estimated U.S. annual incidence of HRS-1 is 35,000 patients.[4]

Hepatorenal syndrome is a diagnosis of exclusion and is associated with a poor prognosis. HRS Type 1 is characterized as a *rapidly developing* acute kidney injury (AKI), whereas, HRS type 2 is a *slowly progressive* chronic kidney disease (CKD).[5] Both types of HRS are associated with a decrease in RBF and glomerular filtration rate (GFR). HRS-1 is a frequently fatal complication of cirrhosis with a median survival of approximately 1 month.[6] The outcome of patients with HRS, as well as recovery of kidney function, is strongly dependent upon reversal of the hepatic failure.[7]

[a] VigiBase is a global database of individual case safety reports (ICSRs) received by the Uppsala Monitoring Centre (UMC) in its role as the World Heath Organization (WHO) Collaborating Centre for International Drug Monitoring.

Therapy in patients with HRS is mainly directed at the underlying liver disease, such as antiviral therapy for hepatitis B, or liver transplantation. Nonetheless, medical therapy can be instituted in an attempt to reverse the AKI associated with HRS until improvement of the liver dysfunction can be achieved. Initial medical therapies for patients with HRS in an intensive care unit (ICU) is norepinephrine in combination with albumin, with the goal of raising the MAP by 10 mmHg. Intravenous vasopressin may also be effective. For patients who were not admitted to the ICU, patients in the U.S. are initially treated with midodrine, octreotide, and albumin; however, treatment with terlipressin is recommended when available in other countries. For patients who do not respond to medical therapies, transjugular intrahepatic portosystemic shunt (TIPS) or renal replacement therapy can be considered as a bridge to liver transplantation or liver recovery.

Identified Safety Issues for Terlipressin (NDA 22231)

The clinical development program for terlipressin (NDA 22231) consists of three randomized, double-blind, multicenter, placebo-controlled studies in subjects with HRS-1: CONFIRM, OT-0401, and REVERSE. Cumulatively, these studies included 354 subjects treated with terlipressin. Based on these 354 subjects, Mallinckrodt Hospital Products IP Limited (hereafter referred to as the Applicant) identified the following safety issues for terlipressin:[8]

- ***Respiratory Disorders*** – Terlipressin, by increasing cardiac afterload and effective circulating volume, particularly in the setting of albumin loading, may unmask or aggravate diastolic dysfunction or other cardiopulmonary effects of terlipressin. The incidence of respiratory adverse events (AEs) and serious adverse events (SAEs) in the terlipressin group was generally similar across the 3 studies; however, the incidence of *respiratory failure* or *acute respiratory failure* was higher in the pooled terlipressin group than in the pooled placebo group. Detailed review of individual subjects suggested that subjects with more advanced disease, a significant history of prior cardiorespiratory events, or recent upper GI hemorrhage are more likely to develop respiratory failure/acute respiratory failure with terlipressin treatment.
- ***Ischemic Complications*** – The vasoconstrictor effects of terlipressin are well-described AEs and may include skin pallor/blanching, *local* skin necrosis, ischemic bowel, peripheral ischemia, and myocardial ischemia. In the 3 studies, the most common ischemia associated AEs were skin discoloration (6 subjects), cyanosis (5 subjects), and intestinal ischemia (4 subjects). No cases of skin necrosis were observed in any of the 3 studies. There were no deaths due to ischemia associated AEs.
- ***Infections*** – In the pooled studies, the incidence of *sepsis* and *septic shock* were higher in the terlipressin group versus placebo (*sepsis*: terlipressin 5.2% vs. placebo 1.6%; *septic shock*: terlipressin 2.6% vs. placebo 0.8%). The majority of sepsis/septic shock events in the terlipressin group occurred after treatment, usually after more than 72 hours, and frequently after more than 10 days. The post-treatment period in these subjects was complicated by concomitant additional serious or severe AEs.
- ***Gastrointestinal Disorders (e.g., diarrhea, abdominal pain, vomiting)*** – In the pooled studies, more terlipressin-treated subjects had GI AEs (52.1%) than did placebo-treated subjects (42.6%) and included abdominal pain, nausea, diarrhea, vomiting, and abdominal distension. Rarely, 2.7% of subjects in the terlipressin group with abdominal pain also experienced mesenteric ischemia.
- ***Hypotension*** – Overall in the pooled studies, AEs of hypotension were reported by 41 subjects (11.7%) in the terlipressin group and 19 subjects (7.6%) in the placebo group.

An in-depth analysis of the pooled data for a single MAP value of < 70 mmHg or by a series of successive measurements trending downward from 70 mmHg, however, did not find a similar pattern seen with the reported AEs of hypotension.

- ***Bradycardia*** – Bradycardia was the only Cardiac Disorder AE reported more frequently (≥ 2% difference between treatment groups) for terlipressin-treated subjects compared with placebo-treated subjects; however, none of the bradycardia events were considered serious. Bradycardia is an expected event with terlipressin based on terlipressin vasopressor activity increasing MAP, leading to an arterial baroreflex decrease in heart rate.

In parallel to the Applicant's identification of safety issues for terlipressin, DCN identified the following safety issues based on the results of the CONFIRM study: ischemia-associated AEs, respiratory AEs, gastrointestinal AEs, edema and fluid overload, serious infections, and bradycardia. Details of the safety findings from DCN are available in the FDA Briefing Document for the July 15, 2020 Advisory Committee Meeting for NDA 22231 Telipressin.[9]

2 PROPOSED LABEL

Safety information relative to the identified safety issues from the Applicant and DCN is listed below from the proposed U.S. Prescribing Information (USPI) for terlipressin (TERLIVAZ). The complete proposed label is available at the following Electronic Document Room link.

(b) (4)

6.2 Postmarketing Experience

Adverse reactions reported from the worldwide postmarketing experience with terlipressin include headache and hyponatremia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to terlipressin exposure.

3 METHODS

DPV-I searched for information from FAERS, VigiBase, and medical literature reported for terlipressin; and conducted a disproportionality reporting analysis of FAERS data using Empirica Signal for terlipressin. In addition, DPV-I also screened the periodic safety report for terlipressin submitted within NDA 22213.

3.1 FAERS

DPV-I searched the FAERS database with the strategy described in Table 2.

Table 2. FAERS Search Strategy*	
Date of search	April 13, 2020
Time period of search	Through April 12, 2020
Search type	FBIS Quick Query

Table 2. FAERS Search Strategy*	
Product terms	Product Active Ingredient: TERLIPRESSIN, TERLIPRESSIN DIACETATE ANHYDROUS
MedDRA version	22.1
* See Appendix B for a description of the FAERS database.	

3.2 DATA MINING

DPV-I conducted a disproportionality analysis of FAERS data using Empirica Signal with the strategy described in Table 3.

Table 3. Data Mining Search Strategy*	
Data refresh date	April 2, 2020
Product terms	Terlipressin
Empirica Signal run name	PAM (S)
MedDRA search strategy	All adverse events, retrieved at the MedDRA PT level
* See Appendix B for a description of data mining of FAERS using Empirica Signal and Appendix A for a list of terms in the FDA medical query	

3.3 VIGIBASE

DPV-I searched the VigiBase database with the strategy described in Table 4.

Table 4. VigiBase Search Strategy*	
Date of search	April 12, 2020
Time period of search	Through April 12, 2020
Search tool	VigiLyze
Drug	Active Ingredient: Terlipressin
MedDRA version	22.1
* See Appendix B for a description of the VigiBase database.	

3.4 MEDICAL LITERATURE

DPV-I searched the medical literature with a step-wise strategy to identify relevant safety information from case reports and case series of adverse events experienced with use of terlipressin. Supplemental searches were conducted to identify additional information for notable adverse events identified through analysis of FAERS and VigiBase data and review of the results of the initial medical literature search. Table 5 describes the medical literature search strategies used for this review.

Table 5. Literature Search Strategy	
Initial Search	
Date of search	April 13, 2020
Database	PubMed@FDA
Search terms	"terlipressin"[MeSH Terms] OR "terlipressin"[All Fields]
Filters	Article types: Editorial, Case Reports, Clinical Conference, Letter, Observational Study Species: Humans Language: English

Table 5. Literature Search Strategy	
Years included in search	All
Supplemental Searches	
Date of search	May 4, 2020
Database	PubMed@FDA
Search terms	• Hyponatremia: ("terlipressin"[MeSH Terms] OR "terlipressin"[All Fields]) AND ("hyponatraemia"[All Fields] OR "hyponatremia"[MeSH Terms] OR "hyponatremia"[All Fields]) • Hypokalemia: ("terlipressin"[MeSH Terms] OR "terlipressin"[All Fields]) AND ((("hypokalaemia"[All Fields] OR "hypokalemia"[MeSH Terms]) OR "hypokalemia"[All Fields]) OR "hypokalemias"[All Fields]) • Seizures: ("terlipressin"[MeSH Terms] OR "terlipressin"[All Fields]) AND ("seizures"[MeSH Terms] OR "seizures"[All Fields]) • Cardiac arrhythmias: ("terlipressin"[MeSH Terms] OR "terlipressin"[All Fields]) AND ("arrhythmias, cardiac"[MeSH Terms] OR ("arrhythmias"[All Fields] AND "cardiac"[All Fields]) OR "cardiac arrhythmias"[All Fields] OR "arrhythmia"[All Fields]) • Torsade de pointes: ("terlipressin"[MeSH Terms] OR "terlipressin"[All Fields]) AND torsades[All Fields] • Cardiomyopathy: ("terlipressin"[MeSH Terms] OR "terlipressin"[All Fields]) AND ("cardiomyopathies"[MeSH Terms] OR "cardiomyopathies"[All Fields] OR "cardiomyopathy"[All Fields]) • Skin necrosis: ("terlipressin"[MeSH Terms] OR "terlipressin"[All Fields]) AND ("skin"[MeSH Terms] OR "skin"[All Fields]) AND ("necrosis"[MeSH Terms] OR "necrosis"[All Fields]) • Metabolic acidosis: ("terlipressin"[MeSH Terms] OR "terlipressin"[All Fields]) AND ("acidosis"[MeSH Terms] OR "acidosis"[All Fields] OR ("metabolic"[All Fields] AND "acidosis"[All Fields]) OR "metabolic acidosis"[All Fields])
Years included in search	All

3.5 PERIODIC SAFETY REPORTS

DPV-I screened the following periodic safety report:

- Periodic Benefit Risk Evaluation Report (PBRER) for terlipressin 0.85 mg powder for injection (Lucassin®) for the period of January 9, 2018 through January 8, 2019.

(b) (4)

4 RESULTS

4.1 FAERS

The FAERS search on April 13, 2020 yielded 53 reports. Appendix C contains a list of the reported PTs for these 53 FAERS reports.

Of the 53 FAERS reports, 24 were duplicate reports, 6 reported terlipressin was administered for treatment of the reported adverse event associated with another drug, 3 reported the adverse event was not temporally associated with the use of terlipressin (i.e., the adverse event occurred after the terlipressin was discontinued), and one did not mention terlipressin within the case narrative. Table 6 provides the descriptive characteristics of the remaining 19 FAERS reports for terlipressin.

Table 6. Descriptive Characteristics of FAERS Reports with Terlipressin, Received by FDA Through April 12, 2020 n=19

Characteristic		Result
Sex	Male	9
	Female	8
	Unknown	2
Age	3 to < 17 years	0
	≥ 17 to < 65 years	11
	≥ 65 years	4
	Null	4
Country	Foreign*	19
Report type	Expedited	19
Serious outcomes‡	Death	10
	Life-threatening	5
	Hospitalization	7
	Other serious	12
(b) (6)		

† For the purposes of this document, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), or other serious important medical events. A report can have one or more outcome.

Table 7 lists the most frequently reported MedDRA preferred terms (PTs) in the 19 FAERS reports and the labeling status of each PT, per the proposed label for terlipressin (NDA 22231).

Table 7. Reported MedDRA Preferred Terms (PTs) With Terlipressin Received by FDA Through April 12, 2020, Sorted by Decreasing Number of FAERS Reports per PT (n=19)

MedDRA PT	Number of FAERS Reports*	Labeled (Yes/No), Location† or Other Category
Cardiac arrest	3	No, U
Cardiac failure congestive	3	No
Peripheral ischaemia	2	Yes, W&P (ischemic events)
Skin necrosis	2	Yes, W&P (ischemic events)
Thrombocytopenia	2	No

Table 7. Reported MedDRA Preferred Terms (PTs) With Terlipressin Received by FDA Through April 12, 2020, Sorted by Decreasing Number of FAERS Reports per PT (n=19)		
MedDRA PT	**Number of FAERS Reports***	**Labeled (Yes/No), Location† or Other Category**
Upper gastrointestinal haemorrhage	2	No
Ventricular fibrillation	2	No
Acute generalised exanthematous pustulosis	1	No
Acute respiratory failure	1	Yes, W&P
Bradycardia	1	Yes, AR
Compartment syndrome	1	No
Diarrhoea	1	Yes, AR
Ear disorder	1	No, U
Electrocardiogram QT prolonged	1	No
Extremity necrosis	1	Yes, W&P (ischemic events)
Feeling cold	1	Yes, W&P (ischemic events)
Hyperaemia	1	No
Hypokalaemia	1	No
Hyponatraemia	1	Yes, AR
Long QT syndrome	1	No
Metabolic acidosis	1	No
Necrosis	1	Yes, W&P (ischemic events)
Penile ulceration	1	Yes, W&P (ischemic events)
Penis disorder	1	No, U
Pulmonary oedema	1	Yes, AR
Purpura	1	No
Scrotal disorder	1	No, U
Scrotal ulcer	1	Yes, W&P (ischemic events)
Skin discolouration	1	Yes, W&P (ischemic events)
Stevens Johnson syndrome	1	No
Swollen tongue	1	No, U
Thrombocytopenic purpura	1	No
Thrombophlebitis superficial	1	No
* A report can contain more than one MedDRA PT. † If the event is included in multiple sections of labeling, only the section of highest importance is listed. Abbreviations: W/P = Warnings/Precautions, AR = Adverse Reactions, DR = Disease-related, IR = Indication-related, U = Uninformative		

4.1.1 Fatal FAERS Reports

Of the 19 FAERS reports for terlipressin, 10 reported a fatal outcome. Table 8 lists the PTs coded for the 10 fatal FAERS reports and the labeling status of each PT according to the proposed terlipressin label.

Table 8. Preferred Terms (PT) listed for FAERS Reports with Death as an Outcome for Terlipressin received by the FDA through April 12, 2020, Sorted by Decreasing Number of FAERS Reports per PT		
MedDRA PT	**Number of FAERS Reports***	**Labeled (Yes/No), Location† or Other Category**
Cardiac arrest	2	No, U
Cardiac failure congestive	2	No
Peripheral ischaemia	2	Yes, W&P (ischemic events)
Skin Necrosis	2	No
Acute generalised exanthematous pustulosis	1	No
Bradycardia	1	Yes, AR
Ear disorder	1	No, U
Extremity necrosis	1	Yes, W&P (ischemic events)
Feeling cold	1	Yes, W&P (ischemic events)
Hyperaemia	1	No
Necrosis	1	Yes, W&P (ischemic events)
Penile ulceration	1	Yes, W&P (ischemic events)
Penis disorder	1	No, U
Purpura	1	No
Scrotal disorder	1	No, U
Scrotal ulcer	1	Yes, W&P (ischemic events)
Swollen tongue	1	No, U
Thrombocytopenic purpura	1	No
Upper gastrointestinal haemorrhage	1	No
Ventricular fibrillation	1	No

* A report may contain more than one MedDRA PT.
† If the event is included in multiple sections of labeling, only the section of highest importance is listed.
Abbreviations: W/P = Warnings/Precautions, AR = Adverse Reactions, DR = Disease-related, IR = Indication-related, U = Uninformative

We reviewed the report narratives of the 10 fatal reports to determine the cause of death. The causes of death were either reported by the reporter or assessed by DPV-I when no cause was provided. The causes of death were septicemia (n=1); bradycardia (n=1); cardiorespiratory arrest (n=1); pneumonia, sepsis, and multiorgan failure (n=1); metabolic acidosis, cardiomyopathy, and acute liver failure (n=1), bilateral necrosis of the legs (n=1), congestive heart failure (n=1); hemoperitoneum after paracentesis, probable sepsis (n=1), and hepatorenal syndrome (n=1). We assess one case as unrelated to terlipressin as the reporter reported the cause of death due to necrosis following the administration of an irrigation solution administered intravenously. Additional details for many of these fatal reports are provided in the following section.

4.1.2 Analysis of FAERS data

Overall, ischemic adverse events were the most commonly reported PTs (n=12) in FAERS reports for terlipressin and included *Peripheral ischaemia* (n=2), *Skin necrosis* (n=2), *Extremity necrosis* (n=1), *Feeling cold* (n=1), *Necrosis* (n=1), *Penile ulceration* (n=1), *Penis disorder* (n=1), *Scrotal disorder* (n=1), *Scrotal ulcer* (n=1), and *Skin discolouration* (n=1). Cardiac adverse events were the second most commonly reported PTs (n=11) and included *Cardiac arrest* (n=3), *Cardiac failure congestive* (n=3), *Ventricular fibrillation* (n=2), *Bradycardia* (n=1),

Electrocardiogram QT prolonged (n=1), *Long QT syndrome* (n=1). A report may be coded with more than one PT.

For the ischemic adverse events, five distinct FAERS reports together captured the 12 PTs noted above. Patients in all five reports died; however, one death (FAERS (b) (6)) occurred in a patient who experienced a 15 x 15 cm necrotic area on (b) (6) leg following inadvertent use of sodium chloride marketed for irrigation via venous cannula for rewarming. The remaining four reports are briefly summarized below:

- The first report (FAERS (b) (6)) was of a (b) (6)-year-old (b) (6) patient hospitalized for pleural effusion and hepatic encephalopathy who experienced necrotic thrombocytopenic purpura with areas of necrosis or purpura located on his scrotum, penis, and lower limbs 5 days after starting terlipressin for an unspecified indication and died 3 weeks later from a cardio-respiratory arrest. Details of the patient's hospitalization and outcome of the thrombocytopenic purpura and necrosis were not reported.
- The second report (FAERS (b) (6)) involved a (b) (6)-year-old (b) (6) patient who developed distal ischemia of hands and legs, and extended purpura two days after initiating treatment with terlipressin for septic shock related to necrotizing fasciitis secondary to a *Streptococcus pyogenes* infection. Terlipressin therapy was discontinued on the same day of the ischemic adverse events; however, the patient's conditioned worsened the following day when (b) (6) developed compartment syndrome and necrosis of both legs, requiring amputation of one leg 3 days later. The patient ultimately died 7 days after development of the ischemic events (9 days after initial terlipressin therapy).
- The third report (FAERS (b) (6)) involved a (b) (6)-year-old (b) (6) patient who was hospitalized for hypovolemic shock and treated with terlipressin 2 mg x 6 doses for one day due to suspected bleeding esophageal varices. The patient subsequently developed multiorgan failure and experienced ischemic, discolored areas on the upper and lower extremities, as well as ears and genitals. The patient became hypotensive and died on hospital Day 4.
- The last report (FAERS (b) (6)) was from a published article[10] and involved a 54-year-old male patient who was admitted with acute esophageal variceal bleeding. Vancomycin was initiated for an unknown indication. Terlipressin was subsequently initiated for the treatment of HRS-1 and vancomycin was discontinued due to the risk of nephrotoxicity. Two weeks later, linear IgA bullous dermatosis was diagnosed via skin biopsy. An additional week later, the patient developed a large, progressive necrotic area on his lower extremities. A second skin biopsy was performed, and the patient was diagnosed with skin necrosis induced by terlipressin and terlipressin was discontinued. Although the skin lesions improved after discontinuation, hepatorenal syndrome worsened and the patient died five days later.

For the cardiac adverse events, there were three FAERS reports with the PT *Cardiac failure congestive* and one report for each of the PTs *Electrocardiogram QT prolonged*, *Ventricular fibrillation*, and *Long QT syndrome*, in total five reports. Of the three congestive heart failure (CHF) reports, two (FAERS (b) (6)) were from the same published article of a (b) (6) clinical study.[11] In addition to the CHF, both patients also experienced upper GI bleeding one day following terlipressin initiation for treatment of HRS-1. The patient in FAERS (b) (6) had a "slight pulmonary edema before the study" and ultimately, succumbed to the

CHF. Disposition for the patient in FAERS [redacted] was not reported. The third report (FAERS [redacted]) was of a patient who experienced CHF induced by terlipressin, per the reporting physician, that had improved following its discontinuation; however, the patient later died from presumed sepsis following hemoperitoneum from a paracentesis.

The remaining two reports were confounded by concomitant medications associated with cardiac arrhythmias. One report (FAERS [redacted]) involved a [redacted]-year-old [redacted] patient who experienced QT prolongation, ventricular fibrillation, and cardiac arrest two days after initiation of terlipressin. According to the reporting pharmacist, terlipressin was used for the treatment of GI hemorrhage and was the most recent addition to [redacted] medication regimen. Concomitant medications included ondansetron, initiated on an unknown date, and citalopram, initiated two weeks prior to terlipressin. Terlipressin was discontinued following the QT prolongation. Reported potassium and magnesium laboratory results were within the normal range. Citalopram was discontinued a day after terlipressin and ondansetron was discontinued on an unknown date. The patient recovered. One report (FAERS [redacted]) was of a [redacted]-year-old [redacted] patient who experienced ventricular fibrillation one day after haloperidol dose increase and two days after initiation of terlipressin for alcohol withdrawal-induced delirium and variceal bleeding, respectively; ventricular fibrillation is listed as an AE in the haloperidol label. The other report (FAERS [redacted]) was of a [redacted]-year-old [redacted] patient who experienced QT prolongation, but lacked clinical details and was confounded by a concomitant use of sulfamethoxazole/trimethoprim, which is labeled for QT prolongation.[12]

Although infrequently reported, several other PTs from the FAERS reports are clinically significant and are discussed below.

- ***Hyponatremia* (n=1):** The report of hyponatremia (FAERS [redacted]) was of a [redacted]-year-old [redacted] patient who received terlipressin and high dose intravenous esomeprazole (160 mg daily for three days followed by 120 mg daily for three days) for esophageal variceal bleeding and experienced hyponatremia 4 days later, which rapidly deteriorated from serum sodium of 131 mEq/L on Day 4 to a nadir of 110 mEq/L on Day 7. Concomitant drugs included prednisone for auto-immune hepatitis and ofloxacin for infection prophylaxis. On an unknown date, ofloxacin and terlipressin were discontinued, but prednisolone and oral esomeprazole 20 mg daily as maintenance were continued. No corrective treatment was otherwise reported for the hyponatremia. The hyponatremia improved on Day 8 with a serum sodium of 131 mEq/L.
- ***Metabolic acidosis* (n=1):** One distinct report (FAERS [redacted]) of metabolic acidosis was identified in FAERS but was confounded by concurrent presence of pneumonia and sepsis.
- ***Hypokalemia* (n=1):** One distinct report (FAERS [redacted]) described a patient who experienced hypokalemia, though no relevant laboratory results were reported prior to or during treatment with terlipressin. Furthermore, the report stated the patient also concurrently suffered from diarrhea.
- ***Thrombocytopenia* (n=2):** Two distinct reports (FAERS [redacted]) of thrombocytopenia were reported in FAERS. Both reports lacked clinical details and neither reported platelet counts either before or during terlipressin treatment.
- ***Acute generalised exanthematous pustulosis* (n=1), *Stevens Johnson syndrome* (n=1):** One FAERS report each of acute generalized exanthematous pustulosis (FAERS

(b) (6) and Stevens Johnson syndrome (FAERS (b) (6)) were reported. Both reports were confounded by the concomitant administration of multiple antibiotics proximal to terlipressin therapy. One patient had not recovered at the time of reporting and the other patient died.

Of note, the PTs *Ventricular fibrillation*, *Electrocardiogram QT prolonged, Acute generalized exanthematous pustulosis,* and *Stevens Johnson syndrome* are Designated Medical Events (DMEs), which are adverse events that are considered serious and, from a pharmacovigilance perspective, may often be caused by exposure to drugs from many pharmacological or therapeutic classes. Review of the reports with the PTs *Acute generalized exanthematous pustulosis* and *Stevens Johnson syndrome* did not suggest an association with terlipressin (see Section 4.1.2). For the reports containing the PTs for *Ventricular fibrillation* and *Electrocardiogram QT prolonged*, see discussion in Section 4.1.2 for additional details regarding a potential association with terlipressin. Appendix D contains a list of the Office of Surveillance and Epidemiology's (OSE) DMEs.

4.2 VIGIBASE

The VigiLyze search on April 13, 2020 yielded 1,474 reports for terlipressin from VigiBase. A case-level analysis was not performed because case narratives are not available for our review. Report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), miscoded reports, or unrelated reports. Reported outcomes for this section are the coded outcomes; causality and the role of the product in the coded outcome have not been determined for all reports (see Appendix B for VigiBase limitations). Table 9 provides the descriptive characteristics of the VigiBase reports retrieved by the search strategy described in Table 5.

Table 9. Descriptive Characteristics of VigiBase Reports with Terlipressin, Received by the World Health Organization Through April 13, 2020 n=1,474*

Characteristic		Result
Sex	Male	1026
	Female	410
	Unknown	38
Age	< 3 years	10
	3 to < 7 years	11
	7 to < 17 years	19
	17 to < 65 years	983
	≥ 65 years	384
	Null	67
Top Countries (n=1377)	Korea (the Republic of)	668
	India	197
	China	135
	Italy	112
	France	95
	Spain	64
	United Kingdom	49
	Germany	23

Table 9. Descriptive Characteristics of VigiBase Reports with Terlipressin, Received by the World Health Organization Through April 13, 2020 n=1,474*		
Characteristic		**Result**
	Denmark	20
	Portugal	14
Report type	Non-Serious	875
	Serious	411
	Unknown	188
VigiBase seriousness criteria*	Death	97
	Life threatening	48
	Caused/prolonged hospitalization	122
	Disabling/incapacitating	10
	Other medically important condition	131
Fatal cases	Yes	150
* May include duplicates.		

Table 10 lists the most frequent MedDRA PTs of *serious* reports for terlipressin in VigiBase and the labeling status for each PT. Although only PTs with a frequency ≥ 5 for *serious* reports are listed in the table, we reviewed all PTs for new potential safety signals. Appendix E contains a list of PTs from all (serious and non-serious) VigiBase reports for terlipressin.

Table 10. Most Frequently Reported MedDRA Preferred Terms (PTs) with n ≥ 5 in VigiBase Reports Coded as *Serious* with Terlipressin Through April 12, 2020, Sorted by Decreasing Number of VigiBase Reports per PT		
MedDRA PT	**Number of VigiBase Reports***	**Labeled (Yes/No), Location† or Other Category**
Hyponatraemia	57	Yes, AR
Diarrhea	37	Yes, AR
Peripheral ischemia	27	Yes, W&P (Ischemic events)
Cyanosis	23	Yes, W&P
Skin necrosis	21	Yes, W&P (Ischemic events)
Abdominal pain	20	Yes, AR
Bradycardia	16	Yes, AR
Dyspnoea	11	Yes, W&P
Off label use	11	No, U
Rhabdomyolysis	11	No
Arrythmia	10	No, U
Blister	9	No, U
Cardiac arrest	9	No
Blood pressure increased	7	No, U
Death	7	No, U
Electrocardiogram QT prolonged	7	No
Hepatic failure	7	No, DR
Hypokalemia	7	No
Intestinal ischemia	7	Yes W&P (Ischemic events)
Necrosis	7	Yes, W&P
Ventricular fibrillation	7	No
Chest pain	6	No, U

Table 10. Most Frequently Reported MedDRA Preferred Terms (PTs) with n ≥ 5 in VigiBase Reports Coded as *Serious* with Terlipressin Through April 12, 2020, Sorted by Decreasing Number of VigiBase Reports per PT

MedDRA PT	Number of VigiBase Reports*	Labeled (Yes/No), Location† or Other Category
Gangrene	6	Yes, W&P (Ischemic events)
Hypertension	6	No
Product use in unapproved indication	6	No
Seizure	6	No
Torsade de Pointe	6	No
Atrial fibrillation	5	No
Colitis ischaemic	5	Yes, W&P (Ischemic events)
Ischaemia	5	Yes, W&P (Ischemic events)
Nausea	5	Yes, AR
Pallor	5	No, U
Sepsis	5	Yes, AR
Vomiting	5	Yes, AR

* A report can contain more than one MedDRA PT and may include duplicate reports.
† If the event is included in multiple sections of labeling, only the section of highest importance is listed.
Abbreviations: W&P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, DR = Disease-related, IR = Indication-related, U = Uninformative

4.2.1 Fatal VigiBase Reports

Table 11 lists the most frequent MedDRA PTs in fatal reports of terlipressin in VigiBase and the labeling status for each PT.

Table 11. Most Frequently Reported MedDRA Preferred Terms (PTs) with n ≥ 3 in Fatal VigiBase Reports with Terlipressin Through April 12, 2020, Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	Number of VigiBase Reports*	Labeled (Yes/No), Location† or Other Category
Peripheral ischaemia	16	Yes, W&P (Ischemic events)
Skin necrosis	11	Yes, W&P (Ischemic events)
Death	9	No, U
Hepatic failure	8	No, DR
Rhabdomyolysis	7	No
Abdominal pain	5	Yes, AR
Cyanosis	5	Yes, W&P
Diarrhoea	5	Yes, AR
Gastrointestinal haemorrhage	5	No
Intestinal ischaemia	5	Yes, W&P (Ischemic Events)
Myocardial infarction	5	Yes, W&P (Ischemic Events)
Off label use	5	No
Sepsis	5	Yes, AR
Condition aggravated	4	No
Haematemesis	4	No
Hepatic encephalopathy	4	No, DR
Necrosis	4	Yes, W&P (Ischemic events)
Product use in unapproved indication	4	No

Table 11. Most Frequently Reported MedDRA Preferred Terms (PTs) with n ≥ 3 in Fatal VigiBase Reports with Terlipressin Through April 12, 2020, Sorted by Decreasing Number of FAERS Reports per PT

MedDRA PT	Number of VigiBase Reports*	Labeled (Yes/No), Location† or Other Category
Pulmonary oedema	4	Yes, AR
Varices oesophageal	4	No, DR
Acute hepatic failure	3	No, DR
Aortic thrombosis	3	No
Blister	3	No, U
Gastrointestinal necrosis	3	Yes, W&P (Ischemic Events)
Hepatorenal syndrome	3	No, DR
Incorrect route of product administration	3	No, U
Product use issue	3	No, U
Rash erythematous	3	No
Renal failure	3	No, DR

* A report can contain more than one MedDRA PT and may include duplicate reports.
† If the event is included in multiple sections of labeling, only the section of highest importance is listed.
Abbreviations: W&P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, DR = Disease-related, IR = Indication-related, U = Uninformative

4.2.2 Analysis of VigiBase data

There are significantly more terlipressin reports in VigiBase compared to FAERS; however, reporter narratives are not available for our review limiting this analysis. Nonetheless, review of high-level data from VigiBase identified the following notable trends:

- Reports for males are nearly twice as frequent than for female patients.
- Most VigiBase reports were considered non-serious
- *Hyponatraemia* is the most frequently reported PT for all serious VigiBase reports but not listed as a frequent PT in the fatal reports
- Other notable PTs in addition to *Hyponatraemia* are: *Rhabdomyolysis* (n=11), *Arrythmia* (n=10), *Electrocardiogram QT prolonged* (n=7), *Hypokalemia* (n=7), *Ventricular fibrillation* (n=7), *Seizure* (n=6), and *Torsade de Pointe* (n=6).

4.3 DATA MINING OF FAERS DATABASE

DPV-I uses Empirica Signal software to perform disproportionality analyses on FAERS data and to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. If a drug-event combination has a score (EB05) of ≥ 2, this score indicates 95% confidence that a drug-event combination appears at least twice the expected rate when considering all other drugs and events in the database. Data mining scores do not, by themselves, demonstrate causal associations; rather, they can serve as a signal for further investigation. Table 12 provides the disproportionality scores, sorted by descending EB05 scores.

Table 12. FAERS Data Mining Results Using Empirica Signal for Events with EB05 ≥ 2 Reported with Terlipressin Use, Sorted by Descending EB05 Scores				
Row	**MedDRA PT**	**N**	**EBGM**	**EB05**
1	Hepatorenal syndrome	4	148.446	56.522
2	Multiple organ dysfunction syndrome	7	49.003	23.946
3	Linear IgA disease	3	72.078	2.881
4	Thrombocytopenia	6	6.374	2.645
5	Metabolic acidosis	4	16.787	2.376
A score (EB05) of ≥ 2 indicates 95% statistical confidence that a drug-event combination has been reported at least twice the expected ratio relative to all other drugs and events in the database, considering the database as a background "expected."				

No additional PTs of interest were identified following the disproportionality analysis. The PTs in Table 12 were duplicate driven (e.g., there was one distinct report of Linear IgA with two duplicates) or were assessed as indication-related or as unlikely related to terlipressin; see Section 4.1.2 for discussion of report of metabolic acidosis and thrombocytopenia.

4.4 MEDICAL LITERATURE

Using the strategy for the initial search including applying the filters listed in Table 6, DPV-I identified 190 citations from the published medical literature for terlipressin. Review of the titles and abstracts of these 190 articles identified potential safety issues and additional supplemental searches of PubMed were performed to identify articles specific to these safety issues. These supplemental searches yielded 114 articles. Analysis of the combined articles from the initial search strategy (190 articles) and supplementary searches (114 articles) and de-duplication of the combined articles (304 articles) identified 119 articles for further review.

Of these 119 articles regarding terlipressin, 69 articles were excluded for further review for the following reasons:

- 2 articles had already been accounted/included in the FAERS case series
- 26 were unrelated to our topic (terlipressin-related adverse events) or dealt with research animal studies or contained flagrant confounding factors (e.g., sepsis) which would severely nullify support for the possible terlipressin-related adverse event.
- 41 were of composed of review articles (19), letters to the editor (5), studies [retrospective (10), prospective (7)], and one symposium.

From the medical literature, DPV-I identified 50 articles that contained a total of 57 case reports of adverse events associated with the use of terlipressin. Adverse events from these 57 case reports and their citations (if noted) in the current proposed label are listed in Table 13. Appendix E contains a list of the 50 citations with reported adverse events and outcomes.

Table 13. Reported Adverse Events with Terlipressin from Medical Literature and Listing/Location in the Current Proposed U.S. Label for Terlipressin		
Adverse Event	**Number of Case Reports***	**Labeled (Yes/No), Location† or Other Category**
Cutaneous necrosis	23	No
Hyponatremia	13	Yes, AR (PE)
Cutaneous ischemia	10	Yes, W&P, PCI
Cardiac arrest	5	No

Table 13. Reported Adverse Events with Terlipressin from Medical Literature and Listing/Location in the Current Proposed U.S. Label for Terlipressin		
Adverse Event	**Number of Case Reports***	**Labeled (Yes/No), Location† or Other Category**
Gangrene of extremity	4	Yes, W&P (Ischemic events)
Gastrointestinal ischemia	4	Yes, W&P
Myocardial infarction	4	Yes, W&P (Ischemic Events)
Seizure	4	No
Torsade de Pointe	4	No
Gastrointestinal necrosis	3	Yes, W&P (Ischemic events)
Hypokalemia	3	No
Cardiomyopathy	2	No
Extremity necrosis	2	Yes, W&P (Ischemic events)
Metabolic acidosis	2	No
Non-cardiac muscular infarction	2	No
Pulmonary edema	2	Yes, AR
QT-prolongation	2	No
Asystole	1	No
Osteonecrosis	1	No
Rhabdomyolysis	1	No
Ventricular fibrillation	1	No
* A case report can contain more than one adverse event. † If the event is included in multiple sections of labeling, only the section of highest importance is listed. Abbreviations: PCI = Patient Counseling Information, PE = Post-marketing Experience, W&P = Warnings/Precautions, AR = Adverse Reactions, DI = Drug Interactions, DR = Disease-related, IR = Indication-related		

Of the reported adverse events for terlipressin, ischemic events and cardiac events were the most frequently reported in the medical literature. Ischemic events affect many different organ systems including the skin (cutaneous necrosis and ischemia), the myocardium, and the GI tract. Furthermore, the ischemic events manifested internally as well as peripherally, and occasionally with extensive involvement of the skin or extremities leading to gangrene[13,14,15,16] and amputations[15] in some case reports. Cardiac adverse events were also frequently reported. These events included cardiomyopathy,[16,17] left ventricular failure,[17] asystole,[18] myocardial infarction,[19,20,21,22] cardiac arrest,[18,21,22,23,24] and cardiac arrhythmias that included ventricular fibrillation[24] and four case reports of Torsade de Pointe/QT-prolongation.[18,23,24,25]

There were also three case reports with positive re-challenges, which are reviewed below. Additionally, one representative case report of a seizure in the presence of hyponatremia following terlipressin treatment is reviewed below. It is of note that all four cases of seizure occurred in association with hyponatremia.

The first positive re-challenge case report involved a (b) (6)-year-old (b) (6) patient (b) (6) who developed severe and extensive cutaneous necrosis during treatment with terlipressin for HRS-1.[26] His past medical history included cirrhosis and advanced liver failure secondary to alcoholic liver disease, ischemic stroke with non-significant internal carotid stenosis, and subarachnoid hemorrhage due to a ruptured brain aneurysm. The patient presented to the hospital with worsening liver failure and worsening ascites. His admitting laboratory results were significant for elevated blood urea nitrogen (BUN) of 229 mg/dL and serum creatinine of 5.13 mg/dL, thrombocytopenia with platelet count of 22,000 /µL, and anemia with hemoglobin

8 g/dL. The patient was diagnosed with HRS-1 and terlipressin treatment was started at 1 mg/4 hrs. Upon improvement of his serum creatine level to 3.77 mg/dL seven days later, terlipressin treatment was stopped. During the seven days of treatment with terlipressin, the patient had developed progressively worsening cutaneous lesions (purpuric lesions with hemorrhagic blisters in lower extremities, buttocks, back, and abdomen) without signs of an infection. When the patient's HRS-1 worsened and the development of hepatic encephalopathy, the patient was transferred to a university hospital, where treatment with terlipressin was restarted, initially at 1 mg/4 hrs to 2 mg/4 hrs. The patient's renal function responded well and started to improve, but the cutaneous lesions worsened developing into star-shaped ulcers with extensive areas of scarification after a few days. Two skin biopsies revealed superficial cutaneous necrosis with extravasation of red blood cells in the superficial dermis and dermal vascular neogenesis; however, vasculitis, thrombosis, and vascular calcification were not identified. Terlipressin treatment was suspended given the findings from the biopsy and improvement in the patient's renal function (creatinine level of 1.47 mg/dl). The cutaneous lesions subsequently started to improve, but the patient's overall hemodynamic status as well as renal function gradually deteriorated with oliguria. Furthermore, the patient experienced another episode of upper GI bleeding secondary to portal hypertensive gastropathy and esophageal varices leading to a third course of terlipressin treatment, this time at the minimum effective dose of 1 mg/4 hrs. Following these events, the cutaneous lesions again worsened, but were controlled with local treatments and surgical debridement. Unfortunately, the patient liver failure acutely deteriorated with little therapeutic response leading to his death shortly thereafter.

Reviewer's comments: Several characteristics of the above case report support the relationship between terlipressin and the appearance of cutaneous necrosis. The time course from the start of the first terlipressin treatment to the appearance of the initial cutaneous lesions support this relationship. Furthermore, a positive de-challenge was noted upon discontinuation of the first course of terlipressin treatment. A positive re-challenge was noted when the patient was started on a second course of terlipressin treatment. Both of these types of challenges support the relationship between terlipressin use and the appearance/worsening of the cutaneous lesions. It can be argued that the patient's decreased renal function may have been the etiology for the appearance and worsening of the cutaneous lesions. However, it is interesting to note that upon suspension of the terlipressin treatment, the cutaneous lesions started to improve, but there was gradual deterioration in the renal function associated with oligo-anuria, thereby, strengthening the possible relationship between terlipressin and cutaneous necrosis. Finally, it is of note that although the patient had a complicated past medical history, cutaneous necrotic lesions were not listed in the patient's history.

The second positive re-challenge case report involved a (b) (6)-year-old (b) (6) patient (b) (6) with a history of alcoholic cirrhosis who experienced QT_c prolongation and Torsade de Pointe following administration of terlipressin for treatment of HRS.[24] The patient presented to the hospital for dyspnea, weakness and ascites. His admission laboratory results were significant for an increased serum creatinine level at 300 µmol/L (normal 72 to 127 µmol/L), decreased GFR at 18 mL/min/1.73 m^2 (normal 130 mL/min/1.73 m^2), a normochromic/normocytic anemia (hemoglobin level not reported), hypoalbuminemia, but normal transaminase, urea, and bilirubin levels. The patient was diagnosed with decompensated alcoholic cirrhosis and chronic kidney disease. An intravenous treatment of crystalloids, albumin, and terlipressin (at 1 mg/8 hrs) was

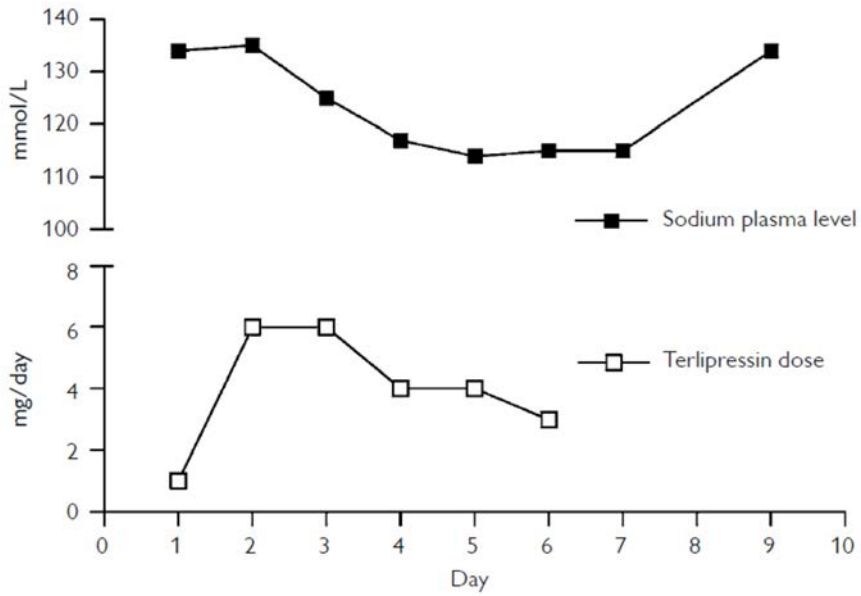
initiated for his decreased renal function. "A few hours" after the first dose of terlipressin, the patient was noted to be in cardiac arrest. After a single defibrillation, ventricular fibrillation was noted followed by conversion to sinus rhythm. The patient was then transferred to the ICU where an electrocardiogram (EKG) revealed a QT_c prolongation. Because the oliguric renal failure was persisting and concerns with the cardiac arrhythmia following the administration of terlipressin, terlipressin was re-administered under intensive medical supervision. "A few hours later" after the second course of terlipressin, another episode of ventricular fibrillation with Torsade de Pointe tachycardia occurred. A single defibrillation restored the rhythm to a sinus rhythm. Measurement of electrolytes including, sodium, potassium, and magnesium, revealed no imbalances. A coronary angiography revealed diffuse coronary stenosis and left ventricular hypertrophy. Fluid balancing and intermittent dialysis were initiated. Additionally, a pacemaker was placed. Some improvement in renal function was noted along with some re-compensation of liver cirrhosis. No further episode of ventricular fibrillation or Torsade de Pointe was recorded during the patient's hospital stay and the patient was stable at the two-month follow-up visit.

Reviewer's comments: The possible relationship between terlipressin and cardiac arrhythmias (i.e., ventricular fibrillation, QT_c prolongation, and Torsade de Pointe)/cardiac disorder (i.e., cardiomyopathy) in the above case report is supported by several points. The strongest point to consider is the positive re-challenge that occurred with terlipressin treatment. The patient exhibited cardiac arrhythmias on two occasions shortly after the initiation of terlipressin. The patient's past medical history was devoid of any cardiac arrhythmias or any cardiac disorder, and the fact that the cardiac events occurred after terlipressin treatment strongly supports the relationship. Additionally, the time course from the initiation of the terlipressin to the development of the cardiac abnormalities further supports the possible relationship between terlipressin and cardiac disorders/arrhythmias.

The third positive re-challenge case report was of a (b) (6)-year-old (b) (6) patient (b) (6) with alcoholic cirrhosis, portal hypertension, and esophageal varices who experienced hyponatremia during treatment with terlipressin.[27] The patient presented to a hospital with hematemesis. Upon admission, (b) (6) was hypotensive with a blood pressure (BP) of 90/55 mm of Hg and (b) (6) notable laboratory results included: low normal serum sodium level at 134 mmol/L, elevated prothrombin time and international normalized ratio (INR) level at 17.5 seconds and 1.43, respectively, and elevated alkaline phosphatase 162.94 IU/L, and elevated ɣ-glutamyl transferase 377.65 IU/L. An upper endoscopy confirmed bleeding varices in the esophagus and cardia of the stomach that was ligated. The patient was admitted to the ICU where terlipressin treatment was started for management of the variceal bleeding, initially at 1 mg/4 hours for two days, followed by 1 mg/6 hours for another two days, and then at 1 mg/8 hours for one day. Severe hyponatremia with a serum sodium nadir of 115 mmol/L with rapid onset began to develop on the second day of terlipressin treatment (refer to Figure 1 below). The terlipressin treatment was stopped and serum sodium levels returned to the physiologic range within three days. Variceal bleeding had stopped and after stabilization, the patient was transferred to a standard care unit, where (b) (6) remained stable and was discharged after three days. The patient was hospitalized again for hematemesis 15 months later. (b) (6) admitting serum sodium level was normal at 137 mmol/L. (b) (6) again was treated with terlipressin under the same schedule as in the earlier admission. Severe hyponatremia "rapidly" developed again (time period not reported)

with a serum sodium level of 126 mmol/L. The patient's hyponatremia was not accompanied by clinical symptoms in either hospitalization and management included clinical monitoring and hypertonic saline administration.

Figure 1. Terlipressin dosing and serum sodium levels*



* Šíma M, Pokorný M, Paďour F, Slanař O. Terlipressin induced severe hyponatremia. Prague Medical Report. 2016;117(1):68-72.

Reviewer's comments: The above case report presents several points that support the possible relationship between terlipressin and hyponatremia. The time course from the start of the terlipressin treatment to the appearance of hyponatremia during both hospitalizations supports the relationship. A strong support for the relationship comes from re-challenging the patient with terlipressin during (b) (6) *hospital admission about 15 months later. A patient who had no history of hyponatremia and who was stable from the sodium level standpoint prior to* (b) (6) *two hospitalizations, exhibited hyponatremia shortly after terlipressin treatments. Finally, the graph above depicting terlipressin dosing and serum sodium levels during the first hospitalization course shows a strong relationship between the start and progression of terlipressin and the fall in the serum sodium levels as time progresses.*

The fourth case is a representative report of terlipressin-associated hyponatremia accompanied with a seizure episode in a (b) (6)-year-old (b) (6) patient (b) (6) who presented with acute esophageal variceal bleeding.[28] The patient's past medical history was significant for primary biliary cirrhosis. (b) (6) underwent banding of the acute variceal esophageal bleeding and received five doses of terlipressin (at 2 mg over a 26-hour period). The patient suffered a tonic-clonic seizure and (b) (6) serum sodium level was noted to have decreased from 132 mmol/L to 115 mmol/L. Terlipressin treatment was stopped and 0.9% saline fluid therapy was started leading to normalization of the serum sodium level over 12 hours. The authors did not detect any clinical, radiologic, pharmacologic, or biochemical evidence of an alternative cause of hyponatremia.

Reviewer's comments: The above patient developed a tonic-clonic seizure secondary to hyponatremia most likely as a result of the terlipressin treatment. No other radiologic, pharmacologic, or biochemical etiologies were detected by the authors to account for the development of hyponatremia. It is also of note that the patient had no past medical history of a seizure disorder that would increase the chances of a second seizure episode during the patient's admission for esophageal bleeding. Finally, the time course of the initiation of the terlipressin treatment to the appearance of the hyponatremia, and subsequent seizure episode, further support the relationship.

4.5 PERIODIC SAFETY REPORTS

The PBRER reviewed is an annual submission for Terlipressin 0.85 mg Powder for Injection (Lucassin) that was approved by the Therapeutic Goods Administration (TGA) in Australia on January 9, 2012 for the treatment of patients with hepatorenal syndrome Type 1 who are actively being considered for a liver transplant. Lucassin was also approved by TGA on June 7, 2018 for the treatment of bleeding esophageal varices.

Important identified risks, important potential risks, and missing information are summarized in Table 14. For the reporting period of the PBRER (January 9, 2018 through January 8, 2019), no new signals were detected, and no signals were ongoing from the prior PBRER reporting period.

Table 14. Important Identified and Potential Risks of Terlipressin Identified by the Applicant

Important Identified Risks	***Cardiovascular***: Myocardial infarction and bradycardia ***Respiratory***: Wheezing/bronchospasm, dyspnea, and pulmonary edema ***Gastrointestinal***: Vomiting, diarrhoea, abdominal pain and intestinal ischaemia ***Skin disorders***: Peripheral cyanosis, livedo reticularis and skin necrosis ***Electrolyte disturbances***: Hypomagnesemia and hyponatremia ***Vascular effects***: Hypertension and peripheral ischaemia
Important Potential Risks	***Cardiovascular***: Torsade de Pointe, QT Prolongation, Ventricular Fibrillation

Of the Important Identified Risks, hypomagnesemia, wheezing/bronchospasm, and hypertension are not included in the proposed label for terlipressin. Notable adverse events such as ischaemic events (including myocardial infarction) and pulmonary edema are listed in the Warnings and Precautions section. Although considered an Important Identified Risks, hyponatremia is only listed in the Postmarketing Experience section in the proposed label.

Torsade de Pointe, QT Prolongation, and ventricular fibrillation have been identified as Important Potential Risks and are not mentioned in the proposed terlipressin USPI; however, are listed in the Australian Product Information for Lucassin (terlipressin).[29] The Applicant indicated that the potential for QT interval prolongation was assessed in Study OT-0401. Of the 111 patients in the safety population, baseline electrocardiograms (ECGs) were available for 52

of 56 patients in the terlipressin group and 54 of 55 patients in the placebo group. The magnitude of the QTc interval increase with terlipressin compared with placebo is very small and statistically nonsignificant. Additionally, a review of cases of patients who experienced QT/QTc interval increases and/or cardiac AEs did not indicate there is an increased risk of ventricular arrhythmias, including Torsade de pointes with terlipressin. The Applicant acknowledges that drug-induced long QT and Torsade de pointes may be potentiated by the development of hypokalemia and bradycardia as well as patients with HRS-1 have underlying end-stage liver disease, which has been reported to be associated with a high prevalence of QT interval prolongation: 46.8% in cirrhotic vs. 5.4% non-cirrhotic controls ($p<0.001$).[30] The Applicant cannot exclude terlipressin having a small effect on QT interval duration.

5 REVIEWER COMMENTS

5.1 IDENTIFIED POSTMARKET ADVERSE EVENTS OF CONCERN

Following review of FAERS and VigiBase reports, disproportionality analysis of FAERS data using Empirica Signal, published medical literature, and the Applicant's periodic safety report, DPV-I identified the following three groups of postmarket adverse events of concern reported with the use of terlipressin: ischemia/necrosis, cardiac adverse events (including arrythmias), and hyponatremia. All three types of adverse events were associated with serious, and sometimes, fatal outcomes. Positive re-challenge information was also reported in the medical literature for all three groups of adverse events (refer to section 4.4 above). These three adverse event groups are either (1) unlabeled adverse events in the proposed terlipressin USPI with the potential for serious outcomes, or (2) labeled adverse events with unexpected characteristics, such as an increase in severity. It is also important to note that even if an adverse event is not fatal, the weakening effect of the specific adverse event on the host, coupled with the baseline fragility of a patient with HRS Type 1, opens the door for other adverse events (e.g., opportunistic infections, worsening liver failure) that may further contribute to morbidity and mortality.

Ischemia/Necrosis

The ischemia related events identified in post-marketing cases were generally consistent with the information in the WARNINGS AND PRECAUTIONS section of the proposed terlipressin USPI that describe these events observed in clinical studies. However, the ischemic cutaneous manifestations noted in the post-marketing reports for this review were more severe and included cutaneous manifestations of skin necrosis. Ischemic adverse events, including those associated with necrosis were the most commonly reported AEs in FAERS, VigiBase, and the medical literature. Ischemia and necrosis manifested in several forms and occurred throughout the skin and the GI tract, as well as in muscles (cardiac and non-cardiac), and the extremities. Rhabdomyolysis was also noted in one report;[31] however, the etiology of rhabdomyolysis appears to be unclear because both ischemia and electrolyte imbalances (noted in HRS Type 1 patients and in patients receiving terlipressin treatment) can contribute to rhabdomyolysis.[32] With regards to necrosis in the extremities, both upper and lower extremities and upper and lower digits were present in the case series. One FAERS report (FAERS [redacted]) noted that skin necrosis was verified via skin biopsy, and improved following discontinuation of terlipressin therapy.[10] Gangrene [occurring secondary to the necrosis of the extremities (particularly the digits)[13,14,15,16]] and amputation of digits or limb(s)[15] were other reported

complications. Another serious adverse event secondary to ischemia/necrosis following use of terlipressin in the case series was osteomyelitis/osteonecrosis.[15] Lower extremity pain and discoloration were noted 11 days after initiation of terlipressin treatment in the case report. The conditions worsened in spite of the medical team's aggressive treatments, leading to severe osteomyelitis/osteonecrosis of three toes of the left lower extremity necessitating amputation of the toes, and ultimately, amputation of the left lower extremity below the knee. A very serious complication to ischemia/necrosis is extensive epidermal necrosis leading to diffuse desquamation and it was noted in two case reports in the medical literature.[33,34] Skin discoloration did initially appear on various surface areas of the patients, followed by extensive epidermolysis leading to progressive skin detachment. It is important to note that epidermolysis and skin detachment predispose to opportunistic infections and multi-organ failure in these frail cirrhotic patients.

Ischemic complications were identified by the Applicant as a key adverse event during the clinical studies for terlipressin. The most common presentation of ischemia-associated adverse events during the clinical studies were skin discoloration, cyanosis, and intestinal ischemia. No cases of skin necrosis were observed in the clinical studies and no deaths were due to ischemia associated AEs in the clinical studies.

The Applicant's proposed labeling for terlipressin includes a section for Ischemic Events in the WARNINGS AND PRECAUTIONS. Skin discoloration, cyanosis, and intestinal ischemia are specifically noted in the Applicant's proposed label. Necrosis is not specifically mentioned. We noted necrosis which was associated with serious outcomes, including death, amputations, and osteomyelitis/osteonecrosis in postmarket case reports. A positive dechallenge was also noted. It is important to note that "skin discoloration" by itself does not convey the full significance of the possible ramifications of worsening ischemic situations (as noted earlier) that may ensue in these fragile patients where terlipressin treatment is initiated for stabilization and prolongation of the lives of patients who are awaiting future liver transplantations.

Cardiac Adverse Events

The cardiac ischemic adverse events identified in post-marketing reports were generally consistent with the proposed WARNINGS AND PRECAUTIONS that describe events observed in clinical studies for terlipressin. However, additional adverse cardiac events (i.e., torsade de pointe, sudden death, syncope, and QT interval prolongation) were noted in post-marketing case reports that had not been observed in the pre-marketing clinical studies. Cardiac adverse events were the second most commonly reported adverse events in FAERS and were also among the most frequently reported adverse events in VigiBase. Furthermore, review of the medical literature identified cardiomyopathy, [16,17] left ventricular failure,[17] asystole,[18] myocardial infarction,[19,20,21 ,22] cardiac arrest,[18,21,22,23,24] and cardiac arrhythmias that included ventricular fibrillation[24] and four case reports of Torsade de Pointe/QT-prolongation associated with terlipressin use[18,23,24,25] (including one positive re-challenge case report[24] – refer to section 4.4).

Awareness of the wide range of noted cardiac adverse events reported with terlipressin use is important, given the rapidity with which these cardiac adverse events may occur in the hospital setting. Furthermore, these cardiac adverse events can lead to further morbidity, and even mortality. Although these patients are usually admitted to monitored units of hospitals, it is

essential for the ICU teams to be aware of the possibility of these adverse events during, and shortly after terlipressin treatment.

The proposed USPI (b) (4)

(b) (4)

Hyponatremia

Although hyponatremia is common in cirrhotic patients[35] and hyponatremia was not identified as an adverse drug reaction in the pre-marketing clinical studies, *Hyponatremia* was the most commonly reported PT in VigiBase and the second most frequent individually reported adverse event in the medical literature for terlipressin; however, only one FAERS report of hyponatremia was identified. Hyponatremia was also associated with serious complications such as seizures in some literature reports.[28,36,37,38] Seizure, as an adverse event secondary to terlipressin use, was not noted in pre-marketing clinical studies. Additionally, the rapid replenishment of hyponatremia following terlipressin use was accompanied by cortical laminar necrosis in one case report.[39] The medical literature also contained a case report of hyponatremia regarding a positive re-challenge of terlipressin (discussed earlier in section 4.4).[27]

Furthermore, seven observational studies that sought to characterize the hyponatremia risk with terlipressin use were identified from the medical literature.[40,41,42,43,44,45,46] The Division of Epidemiology's informal review of these seven studies found that six lacked a comparator group of patients who were not treated with terlipressin.[b] Thus, in six of the studies, it could not be determined if terlipressin use was associated with an excess risk above any baseline risk in the patient populations studied. In the seventh (and most recently published study),[46] higher rates of: (a) reduction in serum sodium concentration (SSC) $\geq$ 5 mmol/L, and (b) hyponatremia (lowest SSC reduced to < 130 mmol/L) were observed for cirrhotic patients with acute gastrointestinal bleeding treated with terlipressin compared to those treated without terlipressin. Only one

[b] Information provided directly from Margie Goulding and Efe Eworuke on June 16, 2020 via email.

study[44] reported results for a small subgroup of terlipressin-treated patients who had HRS (n=28), with no untreated comparator group. Due to these important limitations, these seven studies cannot persuasively inform a discussion of hyponatremia risk from terlipressin in the HRS patient population for which terlipressin (NDA 22231) approval is being sought.

It is interesting to note the differences in the current U.S. proposed terlipressin label from some foreign approved terlipressin product labels, including those products from this Applicant for NDA 22231.[29] Hyponatremia is listed in the proposed U.S. label in the ADVERSE EVENTS Postmarketing Experience section. (b) (4)

(b) (4)

5.2 Advisory Committee Meeting

On July 15, 2020, an advisory committee met to review and discuss the efficacy and safety findings in CONFIRM and to obtain input on whether the benefits of terlipressin for the treatment of HRS-1 outweigh its risks. The advisory committee voted eight to seven in favor of approving NDA 22231 for terlipressin. Some advisory committee members had concerns with the selected efficacy endpoints and safety issues, mainly respiratory failure, were raised regarding inadequate number of follow-up evaluations during the study. Additionally, concerns were raised regarding the lack of long-term safety data and the presence of substantial safety risks involved with terlipressin therapy. Furthermore, the committee members voiced concerns regarding the lack of any true risk mitigation strategy for the risk of respiratory failure by the Applicant. Some members also noted that the risks involved with terlipressin treatment outweighed its benefits and raised concerns that the presented data had not shown improvements in the survival of patients receiving terlipressin treatment as compared to patients in the placebo group. There were no substantive discussions regarding the post-market experience from use of terlipressin outside of the U.S.

6 CONCLUSION

The events described in the available post-marketing data were generally consistent with those observed in clinical trials. In addition, several post-marketing cases describing more specific and/or severe manifestations of some events [i.e., skin necrosis, hyponatremia, and select cardiac events (e.g., arrhythmias)] were identified that may inform labeling for the USPI for terlipressin (NDA 22231) if the application is approved for marketing in the U.S.

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(b) (6)

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8 APPENDICES

8.1 APPENDIX A. FDA MEDICAL QUERY

FDA Medical Queries (FMQs) are standard groupings of similar adverse event terms to assist with the identification of potential safety issues during review of adverse event data. They are similar to Standardised MedDRA Query (SMQ) groupings produced by MedDRA, but designed with terms and clinical concepts FDA reviewers encounter on a frequent basis. Likewise, FMQs promote and ensure consistent and meaningful use across Office of New Drug (OND) Divisions.

Additional information for FMQs is available at the following link.

http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofDrugEvaluationScienceODES/DivisionofBiomedicalInformaticsResearchandBiomarkerDevelopmentBIRBD/BiomedicalInformaticsandRegulatoryReviewScienceBIRRS/ucm647756.htm

FDA Medical Query	MedDRA Preferred Terms
Hypotension	Arterial pressure NOS decreased; Blood pressure decreased; Blood pressure diastolic decreased; Blood pressure systolic decreased; Diastolic hypotension; Hypotension; Hypotension aggravated; Hypotension NOS; Hypotension on induction; Hypotension postural aggravated; Hypotensive anaesthesia procedure; Hypotensive transfusion reaction; Intraoperative hypotension; Neonatal hypotension; Orthostatic hypotension; Postoperative hypotension; Postural hypotension; Procedural hypotension
Hemorrhage	Abdominal aortic aneurysm haemorrhage; Abdominal haematoma; Abdominal wall haematoma; Abdominal wall haemorrhage; Acute haemorrhagic leukoencephalitis; Acute haemorrhagic ulcerative colitis; Administration site bruise; Administration site haematoma; Administration site haemorrhage; Adrenal haematoma; Adrenal haemorrhage; Anal fissure haemorrhage; Anal haemorrhage; Anal ulcer haemorrhage; Anastomotic haemorrhage; Anastomotic ulcer haemorrhage; Anastomotic ulcer haemorrhage, obstructive; Aneurysm ruptured; Anorectal varices haemorrhage; Antepartum haemorrhage; Aortic aneurysm rupture; Aortic annulus rupture; Aortic dissection rupture; Aortic intramural haematoma; Aortic perforation; Aortic rupture; Aortoenteric fistula; Aponeurosis contusion; Application site bleeding; Application site bruise; Application site bruising; Application site haematoma; Application site haemorrhage; Application site purpura; Arterial haemorrhage; Arterial haemorrhage NOS; Arterial intramural haematoma; Arterial perforation; Arterial rupture; Arterial rupture NOS; Arteriovenous fistula site haematoma; Arteriovenous fistula site haemorrhage; Arteriovenous graft site haematoma; Arteriovenous graft site haemorrhage; Atrial rupture; Auricular haematoma; Basal ganglia haematoma; Basal ganglia haemorrhage; Basilar artery perforation; Battle's sign; Benign familial haematuria; Biliary-vascular fistula; Bladder tamponade; Bladder thrombotic tamponade; Bleeding peripartum; Bleeding tendency; Bleeding varicose vein; Blood blister; Blood in stool; Blood loss anaemia; Blood urine; Blood urine present; Bloody airway discharge; Bloody discharge; Bloody drainage; Bloody peritoneal effluent; Bone contusion; Bone marrow haemorrhage; Brain contusion; Brain stem haematoma; Brain stem haemorrhage; Brain stem microhaemorrhage; Breast haematoma; Breast haemorrhage; Broad ligament haematoma; Bronchial haemorrhage; Bronchial varices haemorrhage; Bursal haematoma; Cardiac contusion; Carotid aneurysm rupture; Carotid artery perforation; Catheter site bruise; Catheter site ecchymosis; Catheter site haematoma; Catheter site haemorrhage; Central nervous system haemorrhage; Cephalhaematoma; Cerebellar haematoma; Cerebellar haematoma NOS; Cerebellar haemorrhage; Cerebellar microhaemorrhage; Cerebral aneurysm perforation; Cerebral aneurysm ruptured syphilitic; Cerebral arteriovenous malformation haemorrhagic; Cerebral

	artery perforation; Cerebral cyst haemorrhage; Cerebral haematoma; Cerebral haemorrhage; Cerebral haemorrhage foetal; Cerebral haemorrhage neonatal; Cerebral microhaemorrhage; Cervix haematoma uterine; Cervix haemorrhage uterine; Chest wall haematoma; Choroidal haematoma; Choroidal haemorrhage; Chronic gastrointestinal bleeding; Chronic pigmented purpura; Ciliary body haemorrhage; Clotted haemothorax; Coital bleeding; Colitis haemorrhagic; Colonic haematoma; Colonic haemorrhage; Conjunctival haemorrhage; Contusion; Contusion pulmonary; Corneal bleeding; Coronary artery atheroma haemorrhage; Cullen's sign; Cystitis haemorrhagic; Deep dissecting haematoma; Diarrhoea haemorrhagic; Diverticulitis intestinal haemorrhagic; Diverticulum intestinal haemorrhagic; Duodenal haemorrhage; Duodenal ulcer haemorrhage; Duodenal ulcer haemorrhage, obstructive; Duodenitis haemorrhagic; Dysfunctional uterine bleeding; Ear haemorrhage; Ecchymosis; Encephalitis haemorrhagic; Enteritis haemorrhagic; Enterocolitis haemorrhagic; Epidural haemorrhage; Epistaxis; Exsanguination; Extra-axial haemorrhage; Extradural haematoma; Extraischaemic cerebral haematoma; Extravasation blood; Eye contusion; Eye haematoma; Eye haemorrhage; Eye haemorrhage NOS; Eyelid bleeding; Eyelid contusion; Eyelid haematoma; Eyelid haemorrhage; Femoral artery perforation; Femoral vein perforation; Gardner-Diamond syndrome; Gastric haemorrhage; Gastric mucosal hypertrophy, haemorrhagic; Gastric ulcer haemorrhage; Gastric ulcer haemorrhage, obstructive; Gastric varices haemorrhage; Gastritis alcoholic haemorrhagic; Gastritis atrophic haemorrhagic; Gastritis haemorrhagic; Gastritis haemorrhagic aggravated; Gastroduodenal haemorrhage; Gastroduodenitis haemorrhagic; Gastrointestinal angiodysplasia haemorrhagic; Gastrointestinal haemorrhage; Gastrointestinal haemorrhage NOS; Gastrointestinal organ contusion; Gastrointestinal polyp haemorrhage; Gastrointestinal ulcer haemorrhage; Gastrointestinal vascular malformation haemorrhagic; Genital contusion; Genital haemorrhage; Genital haemorrhage NOS; Gingival bleeding; Graft haemorrhage; Grey Turner's sign; Haemarthrosis; Haematemesis; Haematidrosis; Haematochezia; Haematocoele; Haematoma; Haematoma infection; Haematoma NOS; Haematomyelia; Haematosalpinx; Haematospermia; Haematotympanum; Haematuria; Haematuria aggravated; Haematuria traumatic; Haemobilia; Haemopericardium; Haemoperitoneum; Haemophilic pseudotumour; Haemoptysis; Haemorrhage; Haemorrhage coronary artery; Haemorrhage foetal; Haemorrhage in pregnancy; Haemorrhage into ovarian cyst; Haemorrhage intracranial; Haemorrhage neonatal; Haemorrhage NOS; Haemorrhage NOS aggravated; Haemorrhage NOS foetal; Haemorrhage NOS neonatal; Haemorrhage subcutaneous; Haemorrhage subepidermal; Haemorrhage urinary tract; Haemorrhagic adrenal infarction; Haemorrhagic anaemia; Haemorrhagic arteriovenous malformation; Haemorrhagic ascites; Haemorrhagic breast cyst; Haemorrhagic cerebral infarction; Haemorrhagic cholecystitis; Haemorrhagic cyst; Haemorrhagic diathesis; Haemorrhagic disease of newborn; Haemorrhagic disorder; Haemorrhagic erosive gastritis; Haemorrhagic hepatic cyst; Haemorrhagic infarction; Haemorrhagic necrotic pancreatitis; Haemorrhagic ovarian cyst; Haemorrhagic pneumonia; Haemorrhagic stroke; Haemorrhagic thyroid cyst; Haemorrhagic transformation stroke; Haemorrhagic tumour necrosis; Haemorrhagic urticaria; Haemorrhagic varicella syndrome; Haemorrhagic vasculitis; Haemorrhoidal haemorrhage; Haemothorax; Hemorrhagic tumour necrosis; Hemorrhoidal bleeding; Henoch-Schonlein purpura; Henoch-Schonlein purpura nephritis; Hepatic haemangioma rupture; Hepatic haematoma; Hepatic haemorrhage; Hereditary haemorrhagic telangiectasia; Hereditary renal microhaematuria; Hyperfibrinolysis; Hyphaema; Idiopathic purpura; Ileal haemorrhage; Iliac artery perforation; Iliac artery rupture; Iliac vein perforation; Implant site bruising; Implant site haematoma; Implant site haemorrhage; Incision site haematoma; Incision site haemorrhage; Induced abortion haemorrhage; Inferior vena cava perforation; Infusion site bruising; Infusion site haematoma; Infusion site haemorrhage; Injection site bruising; Injection site haematoma; Injection site haemorrhage; Instillation site bruise; Instillation site haematoma; Instillation site haemorrhage; Intermenstrual bleeding; Internal haemorrhage; Intestinal haematoma; Intestinal haemorrhage; Intestinal polyp haemorrhage; Intestinal stoma site bleeding; Intestinal varices haemorrhage; Intra-abdominal haematoma; Intra-abdominal haemorrhage; Intra-abdominal haemorrhage NOS; Intracerebral haematoma evacuation; Intracerebral haematoma evacuation NOS; Intracranial epidural haematoma; Intracranial haematoma; Intracranial haemorrhage NOS; Intracranial tumour haemorrhage; Intraocular haematoma; Intraoperative haemorrhage; Intrapartum haemorrhage; Intraventricular

	haemorrhage; Intraventricular haemorrhage neonatal; Intraventricular haemorrhage NOS; Iris haemorrhage; Jejunal haemorrhage; Joint microhaemorrhage; Kidney contusion; Lacrimal haemorrhage; Large intestinal haemorrhage; Large intestinal ulcer haemorrhage; Large intestinal ulcer NOS haemorrhage; Laryngeal haematoma; Laryngeal haemorrhage; Lip haematoma; Lip haemorrhage; Liver contusion; Loin pain haematuria syndrome; Lower gastrointestinal haemorrhage; Lower limb artery perforation; Lymph node haemorrhage; Majocchi's purpura; Mallory-Weiss syndrome; Maxillary sinus haematoma; Mediastinal haematoma; Mediastinal haemorrhage; Medical device site bruise; Medical device site haematoma; Medical device site haemorrhage; Melaena; Melaena neonatal; Meningorrhagia; Menometrorrhagia; Menorrhagia; Mesenteric haematoma; Mesenteric haemorrhage; Metrorrhagia; Mouth haemorrhage; Mucocutaneous haemorrhage; Mucosal haemorrhage; Mucosal haemorrhage NOS; Muscle contusion; Muscle haemorrhage; Myocardial haemorrhage; Myocardial rupture; Naevus haemorrhage; Nail bed bleeding; Nasal septum haematoma; Neonatal gastrointestinal haemorrhage; Nephritis haemorrhagic; Nipple exudate bloody; Ocular retrobulbar haemorrhage; Oesophageal haemorrhage; Oesophageal intramural haematoma; Oesophageal ulcer haemorrhage; Oesophageal varices haemorrhage; Oesophagitis haemorrhagic; Operative haemorrhage; Optic disc haemorrhage; Optic nerve sheath haemorrhage; Oral contusion; Oral mucosa haematoma; Oral mucosal petechiae; Osteorrhagia; Ovarian haematoma; Ovarian haemorrhage; Palpable purpura; Pancreatic contusion; Pancreatic haemorrhage; Pancreatitis haemorrhagic; Papillary muscle haemorrhage; Paranasal sinus haematoma; Paranasal sinus haemorrhage; Parathyroid haemorrhage; Parotid gland haemorrhage; Pelvic haematoma; Pelvic haematoma obstetric; Pelvic haemorrhage; Penile contusion; Penile haematoma; Penile haemorrhage; Peptic ulcer haemorrhage; Peptic ulcer haemorrhage, obstructive; Perforation of great vessels; Pericardial haemorrhage; Perineal haematoma; Periorbital contusion; Periorbital haematoma; Periorbital haemorrhage; Periosteal haematoma; Peripartum haemorrhage; Peripheral artery aneurysm rupture; Peripheral artery haematoma; Perirenal haematoma; Peritoneal effusion bloody; Peritoneal haematoma; Peritoneal haemorrhage; Periventricular haemorrhage neonatal; Petechiae; Pharyngeal haematoma; Pharyngeal haemorrhage; Pituitary haemorrhage; Placenta praevia haemorrhage; Pleural haemorrhage; Polymenorrhagia; Post abortion haemorrhage; Post coital bleeding; Post procedural contusion; Post procedural haematoma; Post procedural haematuria; Post procedural haemorrhage; Post transfusion purpura; Post-menopausal bleeding; Postmenopausal haemorrhage; Postoperative bruise; Postoperative haematoma; Post-operative haemorrhage; Postpartum haemorrhage; Post-partum haemorrhage; Post-traumatic punctate intraepidermal haemorrhage; Premature separation of placenta; Procedural haemorrhage; Proctitis haemorrhagic; Prostatic haemorrhage; Pulmonary alveolar haemorrhage; Pulmonary contusion; Pulmonary haematoma; Pulmonary haemorrhage; Pulmonary haemorrhage neonatal; Puncture site bruise; Puncture site haematoma; Puncture site haemorrhage; Purpura; Purpura cerebri; Purpura fulminans; Purpura neonatal; Purpura nonthrombocytopenic; Purpura non-thrombocytopenic; Purpura NOS; Purpura senile; Putamen haemorrhage; Radiation associated haemorrhage; Rectal bleeding; Rectal haemorrhage; Rectal ulcer haemorrhage; Renal artery perforation; Renal cyst haemorrhage; Renal haematoma; Renal haemorrhage; Respiratory tract haemorrhage; Respiratory tract haemorrhage neonatal; Respiratory tract haemorrhage NOS; Retinal aneurysm rupture; Retinal bleeding; Retinal haemorrhage; Retinopathy haemorrhagic; Retroperitoneal haematoma; Retroperitoneal haemorrhage; Retroplacental haematoma; Ruptured cerebral aneurysm; Schamberg's disease; Scleral haemorrhage; Scrotal haematocoele; Scrotal haematoma; Shock haemorrhagic; Skin bleeding; Skin haemorrhage; Skin neoplasm bleeding; Skin ulcer haemorrhage; Small intestinal haemorrhage; Small intestinal ulcer haemorrhage; Small intestinal ulcer NOS haemorrhage; Soft tissue haemorrhage; Spermatic cord haemorrhage; Spinal cord haematoma; Spinal cord haemorrhage; Spinal epidural haematoma; Spinal epidural haemorrhage; Spinal haematoma; Spinal subarachnoid haemorrhage; Spinal subdural haematoma; Spinal subdural haemorrhage; Spleen contusion; Splenic artery perforation; Splenic haematoma; Splenic haemorrhage; Splenic varices haemorrhage; Splinter haemorrhages; Spontaneous haematoma; Spontaneous haemorrhage; Spontaneous hyphaema; Stoma site haemorrhage; Stomatitis haemorrhagic; Subarachnoid haematoma; Subarachnoid haemorrhage; Subarachnoid haemorrhage NOS; Subchorionic haematoma; Subchorionic haemorrhage; Subcutaneous haematoma; Subdural

	haematoma; Subendocardial haemorrhage; Subgaleal haematoma; Subgaleal haemorrhage; Subretinal haematoma; Thrombocytopenic purpura; Thrombotic thrombocytopenic purpura; Tongue haematoma; Tooth pulp haemorrhage; Traumatic haematoma; Traumatic intracranial haematoma; Umbilical haematoma; Urinary occult blood positive; Urticaria haemorrhagica; Uterine haematoma; Vaccination site bruising; Vaccination site haematoma; Vaccination site haemorrhage; Vaginal haematoma; Vaginal haemorrhage; Vascular access site bruising; Vascular access site contusion; Vascular access site haematoma; Vascular access site haemorrhage; Vascular graft haemorrhage; Vascular purpura; Vessel puncture site bruise; Vessel puncture site haematoma; Vitreous haematoma; Vulval haematoma; Withdrawal bleeding irregular; Wound haematoma
Pneumonia	Actinomycotic pulmonary infection; Acute pulmonary histoplasmosis; Amoebic lung abscess; Atypical mycobacterial pneumonia; Atypical pneumonia; Bronchopneumonia; Burkholderia cepacia complex infection; Candida pneumonia; Chronic pulmonary histoplasmosis; Congenital pneumonia; Embolic pneumonia; Empyema; Enterobacter pneumonia; Hantavirus pulmonary infection; Herpes simplex pneumonia; Infectious pleural effusion; Infective exacerbation of bronchiectasis; Infective exacerbation of chronic obstructive airways disease; Infective pulmonary exacerbation of cystic fibrosis; Lobar pneumonia; Loeffler's syndrome; Lung abscess; Lung consolidation; Lung infection; Lung infection pseudomonal; Miliary pneumonia; Neonatal pneumonia; Paragonimiasis; Parasitic lung infection; Parasitic pneumonia; Pleural infection; Pleural infection bacterial; Pleurisy viral; Pneumocystis jirovecii pneumonia; Pneumonia; Pneumonia acinetobacter; Pneumonia adenoviral; Pneumonia anthrax; Pneumonia aspiration; Pneumonia bacterial; Pneumonia blastomyces; Pneumonia bordetella; Pneumonia chlamydial; Pneumonia cryptococcal; Pneumonia cytomegaloviral; Pneumonia escherichia; Pneumonia fungal; Pneumonia haemophilus; Pneumonia helminthic; Pneumonia herpes viral; Pneumonia influenzal; Pneumonia klebsiella; Pneumonia legionella; Pneumonia measles; Pneumonia moraxella; Pneumonia mycoplasmal; Pneumonia necrotising; Pneumonia parainfluenzae viral; Pneumonia pneumococcal; Pneumonia primary atypical; Pneumonia proteus; Pneumonia pseudomonal; Pneumonia respiratory syncytial viral; Pneumonia salmonella; Pneumonia serratia; Pneumonia staphylococcal; Pneumonia streptococcal; Pneumonia toxoplasmal; Pneumonia tularaemia; Pneumonia viral; Pneumonic plague; Pulmonary echinococciasis; Pulmonary mycosis; Pulmonary sepsis; Pulmonary syphilis; Pulmonary trichosporonosis; Pulmonary tuberculoma; Pulmonary tuberculosis; Severe acute respiratory syndrome; Tuberculosis; Tuberculous pleurisy; Varicella zoster pneumonia

8.2 APPENDIX B. DATABASE DESCRIPTIONS

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid trade names or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a

product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

VigiBase

VigiBase is a global database of individual case safety reports (ICSRs) received by the Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring. VigiLyze is a tool used to search and analyze VigiBase. VigiBase includes ICSRs submitted by over 130 countries, including the U.S., for allopathic medicines, traditional medicines (herbals), and biological medicines, including vaccines. The FDA does not have access to case narratives in VigiBase but may request them from the regulatory authorities that submitted the ICSRs. Some cases in VigiBase may also be in the FDA Adverse Event Reporting System (FAERS). The limitations and qualifications that apply to VigiBase information and its use include:

Tentative and variable nature of the data
Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication

Variability of source: Reports submitted to national centers come from both regulated and voluntary sources. Practice varies: some national centers accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centers make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national center until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centers.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

8.3 APPENDIX C. PREFERRED TERMS FROM FAERS REPORTS OF TERLIPRESSIN THROUGH APRIL 2, 2020, SORTED BY DECREASING NUMBER OF FAERS REPORTS PER PT (N=53)

MedDRA Preferred Term (PT)	Number of FAERS Reports for each PT*
Electrocardiogram QT prolonged	11
Cardiac arrest	9
Ventricular fibrillation; Multiple organ dysfunction syndrome	7
Thrombocytopenia; Hepatorenal syndrome	6
Hepatic encephalopathy; Ventricular tachycardia; Thrombophlebitis superficial; Sepsis; Necrosis; Blister	5
Skin necrosis; Incorrect route of product administration; Metabolic acidosis; Rash erythematous; Drug interaction	4
Pulmonary oedema; Weight increased; Pneumonia; Linear IGA disease; Hypokalaemia; Diarrhoea; Cardiac failure congestive; Acute generalised exanthematous pustulosis	3
Acute pulmonary oedema; Acute respiratory failure; Anuria; Blood creatinine increased; Cardio-Respiratory arrest; Compartment syndrome; Death; Fall; Hepatic failure; Hypotension; Intentional product misuse; Malaise; Nephropathy toxic; Penile ulceration; Peripheral ischaemia; Platelet count decreased; Pleural effusion; Product use in unapproved indication; Scrotal ulcer; Thrombocytopenic purpura; Toxicity to various agents; Upper gastrointestinal haemorrhage	2
Abdominal pain; Acute kidney injury; Acute respiratory distress syndrome; Anaemia; Arrhythmia; Ascites; Autoimmune haemolytic anaemia; Bacterial sepsis; Blood albumin decreased; Blood creatinine abnormal; Blood urea increased; Bradycardia; Bronchitis; Cerebrovascular accident; Confusional state; Dilatation ventricular; Disease recurrence; Drug ineffective; Drug level increased; Drug titration error; Ear disorder; Eczema infected; Ejection fraction abnormal; Erythema; Extremity necrosis; Feeling cold; Gastric varices haemorrhage; General physical health deterioration; Haemoglobin decreased; Haemoptys; Heart rate increased; Hepatic cirrhosis; Hepatic function abnormal; Hepatorenal failure; Hyperaemia; Hyperglycaemia; Hypertension; Hyperventilation; Hyponatraemia; Hypoventilation; Hypoxia; Hypoxic-ischaemic encephalopathy; Jaundice; Long QT syndrome; Mallory-Weiss syndrome; Medication error; Off label use; Oliguria; Overdose; Penis disorder; Peritoneal haemorrhage; Portal vein thrombosis; Productive cough; Purpura; Pyrexia; Rales; Rash; Renal failure; Renal impairment; Respiratory distress; Scrotal disorder; Skin discolouration; Skin warm; Stevens-Johnson Syndrome; Suicide attempt; Swollen tongue; Therapy non-responder; Thrombosis; Transfusion-related acute lung injury; Transient ischaemic attack; Tumour lysis syndrome	1
* A report can contain more than one MedDRA PT.	

8.4 APPENDIX D. LIST OF OSE DESIGNATED MEDICAL EVENTS

System Organ Class	Preferred Terms (MedDRA version 21.0)
Blood and lymphatic system disorders	Agranulocytosis
	Aplastic anaemia
	Bone marrow failure
	Coombs negative haemolytic anaemia
	Coombs positive haemolytic anaemia
	Haemolytic anaemia
	Pancytopenia
	Thrombotic thrombocytopenic purpura
Cardiac disorders	Torsade de pointes
	Ventricular fibrillation
Ear and labyrinth disorders	Deafness
	Deafness bilateral
	Deafness neurosensory
	Deafness permanent
	Deafness transitory
	Deafness unilateral
	Ototoxicity
	Sudden hearing loss
Eye disorders	Blindness
	Blindness transient
	Blindness unilateral
	Optic ischaemic neuropathy
	Sudden visual loss
	Toxic optic neuropathy
Gastrointestinal disorders	Haemorrhagic necrotic pancreatitis
	Pancreatic necrosis
	Pancreatitis haemorrhagic
	Pancreatitis necrotising
General disorders and administration site conditions	Sudden cardiac death
	Sudden death
Hepatobiliary disorders	Acute hepatic failure
	Drug-induced liver injury
	Hepatic failure
	Hepatic necrosis
	Hepatitis fulminant
Immune system disorders	Anaphylactic reaction
	Anaphylactic shock
	Anaphylactoid reaction
	Anaphylactoid shock
Infections and infestations	Progressive multifocal leukoencephalopathy
	Suspected transmission of an infectious agent via product
	Transmission of an infectious agent via product
Investigations	Electrocardiogram QT prolonged
Musculoskeletal and connective tissue disorders	Myopathy toxic
	Rhabdomyolysis
Nervous system disorders	Generalised tonic-clonic seizure
	Seizure
	Serotonin syndrome
	Status epilepticus
Product issues	Product compounding quality issue

System Organ Class	Preferred Terms (MedDRA version 21.0)
	Product contamination
	Product contamination chemical
	Product contamination microbial
	Product contamination physical
Psychiatric disorders	Completed suicide
Renal and urinary disorders	Acute kidney injury
Skin and subcutaneous tissue disorders	Acute generalised exanthematous pustulosis
	Drug reaction with eosinophilia and systemic symptoms
	Stevens-Johnson syndrome
	Toxic epidermal necrolysis
Surgical and medical procedures	Liver transplant

8.5 APPENDIX E. PREFERRED TERMS FOR VIGIBASE TERLIPRESSIN REPORTS THROUGH APRIL 12, 2020

MedDRA PT	Number of VigiBase Reports for each PT *
Diarrhoea	425
Abdominal pain	272
Hyponatraemia	85
Headache	80
Nausea	77
Bradycardia	66
Cyanosis	53
Vomiting	51
Chest pain	50
Peripheral ischaemia	36
Skin necrosis	34
Dizziness	32
Hypertension	32
Arrhythmia	30
Blood pressure increased	24
Pyrexia	23
Hyperhidrosis	20
Dyspnoea	19
Pallor	19
Rash	16
Vasospasm	15
Cardiac arrest	13
Feeling hot	13
Rhabdomyolysis	12
Hypokalaemia; Pain; Off label use	11
Angina pectoris; Blister; Intestinal ischaemia; Palpitations; Pruritus	10
Death; Gastrointestinal haemorrhage; Paraesthesia; Ventricular fibrillation	9
Electrocardiogram QT prolonged; Gangrene; Hepatic failure; Malaise; Skin discolouration; Hot flush	8
Abdominal discomfort; Burning sensation; Chest discomfort; Necrosis; Pain in extremity; Seizure; Torsade de pointes; Urticaria	7
Anxiety; Atrial fibrillation; Flushing; Myocardial infarction; Pulmonary oedema; Respiratory failure; Sinus bradycardia; Tachycardia; Skin burning sensation; Product use in unapproved indication	6

MedDRA PT	Number of VigiBase Reports for each PT *
Asthenia; Colitis ischaemic; Haematemesis; Heart rate decreased; Hypotension; Livedo reticularis; Peripheral coldness; Rash erythematous; Sepsis; Ischaemia	5
Abdominal pain upper; Acute hepatic failure; Acute myocardial infarction; Blood sodium decreased; Condition aggravated; Confusional state; Erythema; Generalised tonic-clonic seizure; Hepatic encephalopathy; Hypoaesthesia; Metabolic acidosis; Myocardial ischaemia; Oliguria; Respiratory distress; Skin ulcer; Sweat gland disorder; Vasoconstriction; Dry gangrene; Varices oesophageal; Stress cardiomyopathy	4
Abdominal pain lower; Acute pulmonary oedema; Alanine aminotransferase increased; Anaphylactoid reaction; Aortic thrombosis; Aspartate aminotransferase increased; Breast pain; Drug ineffective; Dyspepsia; Frequent bowel movements; Gastrointestinal necrosis; Haematoma; Hemiparesis; Hepatorenal syndrome; Injection site necrosis; Lactic acidosis; Necrosis ischaemic; Nervousness; Paralysis; Pulse absent; Renal failure; Thrombocytopenia; Ventricular tachycardia; Necrotising oesophagitis; Epidermal necrosis; Drug intolerance; Acute kidney injury; Product use issue; Incorrect route of product administration	3
Abdominal distension; Acidosis; Altered state of consciousness; Anaemia; Anaphylactic reaction; Ascites; Atrioventricular block; Bleeding varicose vein; Bronchospasm; Burning sensation mucosal; Cardiac failure congestive; Cardio-respiratory arrest; Cerebral infarction; Circulatory collapse; Cold sweat; Coma; Disorientation; Electrocardiogram abnormal; Electrolyte imbalance; Face oedema; Feeling cold; Gastric ulcer haemorrhage; Hepatic cirrhosis; Hepatorenal failure; Hyperglycaemia; Hyperkalaemia; Hypernatraemia; Hypersensitivity; Hypertensive crisis; Injection site pain; Liver disorder; Long QT syndrome; Oxygen saturation decreased; Pain of skin; Penis disorder; Pleural effusion; Poor peripheral circulation; Purpura; Rash pruritic; Rectal haemorrhage; Skin exfoliation; Spleen disorder; Tongue ulceration; Toxic epidermal necrolysis; Tremor; Upper gastrointestinal haemorrhage; Epigastric discomfort; Troponin increased; Embolia cutis medicamentosa; Peripheral embolism; Endotracheal intubation; Product administration error	2
Aggression; Agitation; Anaphylactic shock; Angina unstable; Angioedema; Aortic dissection; Aphasia; Application site oedema; Application site pain; Application site pruritus; Areflexia; Arterial thrombosis; Back pain; Blood creatine phosphokinase increased; Blood creatine phosphokinase MB increased; Blood creatinine abnormal; Blood lactate dehydrogenase increased; Blood lactic acid increased; Blood potassium decreased; Blood pressure abnormal; Blood pressure fluctuation; Budd-Chiari syndrome; Cardiac failure; Cardiogenic shock; Cerebral haemorrhage; Cerebral ischaemia; Cerebrovascular disorder; Chills ; Coagulopathy; Constipation; Delirium; Demyelination; Depressed level of consciousness; Dermatitis bullous; Disturbance in attention; Dry mouth; Dysaesthesia; Dysarthria; Dysphagia; Dysuria; Ecchymosis; Electrocardiogram T wave inversion; Encopresis; Eosinophilia; Epilepsy; Erythromelalgia; Extravasation; Facial pain; Faeces discoloured; Fatigue; Fluid retention; Fournier's gangrene; Gait disturbance; Gastrointestinal pain; Graft versus host disease; Haematochezia; Haemoglobin decreased; Haemorrhagic infarction; Head discomfort; Hepatic pain; Hepatosplenomegaly; Hiccups; Hyperbilirubinaemia; Hypertensive encephalopathy; Hypocalcaemia; Hypochloraemia; Hypothermia; Hypovolaemic shock; Impaired gastric emptying; Infection; Injection site atrophy; Injection site erythema; Injection site irritation; Injection site rash; Injection site reaction; Insomnia; Intestinal infarction; Intestinal perforation; Intestinal pseudo-obstruction; Intraocular pressure increased; Leg amputation; Leukopenia; Lip swelling; Lipase increased; Melaena; Memory impairment; Migraine; Monoparesis; Muscular weakness; Myalgia; Nervous system disorder; Nikolsky's sign; Oedema; Oedema peripheral; Oesophageal ulcer; Osteomyelitis; Pancytopenia; Peritoneal haemorrhage; Peritonitis; Peroneal nerve palsy; Petechiae; Polyuria; Portal vein thrombosis; Pulmonary embolism; Pulse abnormal; Rash pustular; Raynaud's	1

MedDRA PT	Number of VigiBase Reports for each PT *
phenomenon; Respiratory acidosis; Respiratory arrest; Right ventricular failure; Sedation; Septic shock; Shock; Skin warm; Sleep disorder; Spermatorrhoea; Stevens-Johnson syndrome; Stomatitis necrotizing; Sudden death; Testicular pain; Thrombocytopenic purpura; Thrombophlebitis superficial; Tic; Tongue movement disturbance; Vascular purpura; Vasculitis; Ventricular extrasystoles; Ventricular flutter; Visual impairment; Yellow skin; Hypoacusis; Musculoskeletal chest pain; Prescribed overdose; Acute coronary syndrome; Infusion related reaction; Electrocardiogram repolarisation abnormality; Drug tolerance decreased; Cardiac flutter; Musculoskeletal stiffness; Inappropriate antidiuretic hormone secretion; Secretion discharge; Wound necrosis; Splenic necrosis; Hepatic ischaemia; Gastric disorder; Gastric varices haemorrhage; Administration site pain; Troponin I increased; Hypoperfusion; Extremity necrosis; Gastrointestinal motility disorder; Mental disorder; Decreased appetite; Feeling of body temperature change; Disease recurrence; Obstructive airways disorder; Psychotic disorder; Scrotal disorder; Unevaluable event; Limb immobilization; Acute left ventricular failure; Catheter site bruise; Renal ischaemia; Breath sounds abnormal; Soft tissue necrosis; Skin plaque; Brain injury; Oropharyngeal pain; Osmotic demyelination syndrome; Product used for unknown indication; Haemorrhagic vasculitis; Hyponatraemic seizure; Autoimmune haemolytic anaemia; Catheter site vesicles; Disease susceptibility; Fine motor skill dysfunction; Multiple organ dysfunction syndrome; Anal incontinence; Product storage error; Acute cardiac event; Wrong patient received product; Product dose omission	

8.6 APPENDIX F. PUBLISHED CASE REPORTS FOR TERLIPRESSIN ADVERSE EVENTS

No.	Article	Reported Adverse Event (s)	Disposition/Outcome	No. of Case Reports
1	Ahmed R, Haseeb A. Ischemic Skin Necrosis in Hepatorenal Syndrome Patient Secondary to Terlipressin. Journal of the College of Physicians and Surgeons--Pakistan: JCPSP. 2019 Jun;29(6):S26-8.	Ischemic skin necrosis of the right hand, right elbow, toes (bilaterally), distal phalanges of left hand	Severe hypotension and dyspnea during hemodialysis leading to cardiac arrest, death	1
2	Barnes A, Cock C. Rapid reversal of hyponatraemia in a patient with non-cirrhotic portal hypertension treated with terlipressin. Internal medicine journal. 2020 Feb;50(2):254.	Hyponatremia, lower extremity and abdominal wall edema	Recovery	1
3	Borrego R, López-Herce J, Mencía S, Carrillo A, Sancho L, Bustinza A. Severe ischemia of the lower limb and of the intestine associated with systemic vasoconstrictor therapy and femoral arterial catheterization. Pediatric Critical Care Medicine. 2006 May 1;7(3):267-269.	Ischemic lesions in right lower extremity and lower abdomen; ischemia of GI tract (proximal ileum to rectum) and abdominal wall	Death	1
4	Carmo LS, Baima DC, Blefari V, Zonta V, Troncon LE, Rossi MA. Involvement of the microvasculature in the pathogenesis of terlipressin-related myocardial infarction. European Heart Journal: Acute Cardiovascular Care. 2016 Dec;5(8):505-511.	Pulmonary edema, sustained ventricular tachycardia, cardiac arrest, myocardial infarction	Death	1
5	Carvalho e Branco J, Anapaz V, Santos L, Reis J. A rare and threatening complication in a cirrhotic patient. Internal and emergency medicine. 2018;13:957-958.	Necrosis of left great toe tip and right foot with cyanosis of all toes with initial signs of necrosis of 3rd, 4th, and 5th toes	Improvement	1
6	Chang YH, Yen FC, Hsieh MC, Lin KD, Shin SJ, Hsin SC. Diabetic muscle infarction in association with terlipressin therapy: a case report. The Kaohsiung journal of medical sciences. 2009 Jan;25(1):25-28.	Right posterior thigh muscle infarction	Able to walk and discharged home	1
7	Chiang CW, Lin YJ, Huang YB. Terlipressin-Induced peripheral cyanosis in a patient with liver cirrhosis and hepatorenal syndrome. The American journal of case reports. 2019;20:5.	Cyanosis of fingers, toes, area around umbilical hernia, and scrotum	Recovery	1
8	Coskun BD, Karaman A, Gorkem H, Buğday I, Poyrazoğlu OK, Senel F. Terlipressin-induced ischemic skin necrosis: a rare association. The American journal of case reports. 2014;15:476.	Cutaneous necrosis of the right forearm (extensor side)	Skin graft of necrotic area	1
9	Di Micoli A, Buccione D, Degli Esposti D, Santi V, Bastagli L, Borghi C, Bernardi M, Trevisani F. Terlipressin infusion induces Tako-Tsubo syndrome in a cirrhotic man with hepato-renal syndrome. Internal and emergency medicine. 2011 Oct 1;6(5):437-440.	Cutaneous ischemia of breasts	Recovery	1

No.	Article	Reported Adverse Event (s)	Disposition/Outcome	No. of Case Reports
10	Donnellan F, Cullen G, Hegarty JE, McCormick PA. Ischaemic complications of Glypressin in liver disease: a case series. British journal of clinical pharmacology. 2007 Oct;64(4):550-552.	1. Cutaneous necrosis of LEs 2. Cutaneous ischemia of LEs and abdominal wall 3. Ischemia of right groin and right flank	1. Death due to liver/renal failure 2. Liver failure, hypotension, death 3. Aspiration pneumonia and multi-organ failure, death	3
11	Dunwoodie E, Jowett S. Terlipressin causing a hyponatraemic seizure. Scandinavian journal of gastroenterology. 2007 Jan 1;42(5):665.	Tonic clonic seizure	Recovery	1
12	Efthymakis K, Massacesi C, Milano A, Laterza F, Tafuri E, Cipollone F, Neri M. Acute esophageal necrosis: possible association with terlipressin. Endoscopy. 2014;46(S 01):E279-280.	Esophageal ischemia	Recovery	1
13	Elzouki AN, El-Menyar A, Ahmed E, Elbadri ME, Imam YZ, Gurbanna BA. Terlipressin-induced severe left and right ventricular dysfunction in patient presented with upper gastrointestinal bleeding: case report and literature review. The American journal of emergency medicine. 2010 May 1;28(4):540-e1.	Supraventricular tachycardia, palpitations, pulmonary edema, shock, ventricular cardiomyopathy; ischemia: upper extremities (UEs) and LEs; gangrene: distal phalanges of fingers (bilat.) and toes (bilat.)	Ventricular function improvement; gangrene outcome not reported	1
14	Fellahi JL, Benard P, Daccache G, Mourgeon E, Gerard JL. Vasodilatory septic shock refractory to catecholamines: is there a role for terlipressin?. Annales francaises d'anesthesie et de reanimation. 2003 Jul (Vol. 22, No. 7, pp. 631-634).	1. Cutaneous necrosis of LEs/toes and left chest area 2. Cutaneous necrosis of LEs and left chest area	1. Acute renal/respiratory failure, death 2. Hypotension, death	2
15	Gatos-Gatopoulos P, Kostantoudakis S, Panayiotides IG, Dimitriadis GD, Triantafyllou K. Embolia cutis medicamentosa: an unusual adverse reaction to terlipressin. Annals of gastroenterology. 2017;30(6):700.	Cutaneous necrosis of left UE, breasts, and lower abdomen	Sepsis, death	1
16	Ghatak T, Poddar B, Mahindra S. Left ventricular failure and left ventricular inferior wall hypokinesia following terlipressin injection. Annals of Cardiac Anesthesia. 2014 Jul-Sep;17(3):257-259.	Left ventricular cardiomyopathy	Ventricular function improvement	1
17	Giudicelli H, Thabut D, Rudler M. An unusual cause of massive hematemesis after treatment with terlipressin. Clinics and research in hepatology and gastroenterology. 2017 Dec;41(6):615.	Gastric ischemic necrosis	Death	1
18	Herrera I, Leiva-Salinas M, Palazón JM, Pascual JC, Niveiro M. Extensive cutaneous necrosis due to terlipressin use. Gastroenterologia y Hepatologia. 2015 Jan;38(1):12-13.	Cutaneous necrosis in LEs, buttock, and abdominal areas	Worsening of cutaneous necrosis, deterioration of liver function, death	1
19	Huang Y, Wang M, Wang J. Hyponatraemia induced by terlipressin: a case report and literature review. Journal of clinical pharmacy and therapeutics. 2015 Dec;40(6):626-628.	Hyponatremia, encephalopathy	Recovery	1

No.	Article	Reported Adverse Event (s)	Disposition/Outcome	No. of Case Reports
20	Hyun JJ, Seo YS, Lee KG, Keum B, Yim HJ, Jeen YT, Chun HJ, Um SH, Kim CD, Ryu HS. Terlipressin-induced hyponatremic seizure. Scandinavian journal of gastroenterology. 2010 Apr 1;45(4):501-504.	Hyponatremia, generalized tonic clonic seizure	Recovery	1
21	Iglesias-Julian E, Badia-Aranda E, Bernad-Cabredo B, Corrales-Cruz D, Romero-Arauzo MJ. Cutaneous necrosis secondary to terlipressin therapy. A rare but serious side effect. Case report and literature review. Revista Espanola de Enfermadades Digestivas (REED). 2017 May 1;109(5):380-383.	Cutaneous necrosis of peri-areolar areas of breasts, and lower abdominal area	Recovery	1
22	Jao YT. Refractory torsade de pointes induced by terlipressin (Glypressin). International journal of cardiology. 2016 Nov 1;222:135-140.	Torsade de Pointe, QT-prolongation, ventricular arrhythmia, asystole, cardiac arrest, metabolic acidosis	Pacemaker placement, coma, death	1
23	Khandelwal A, Gupta D, Haldar R, Rai A. Isolated lower limb gangrene: a caveat of terlipressin therapy. Anaesthesiol Intensive Ther. 2016 Jan 1;48:370-372.	Gangrene: left foot/toes, right great toe and right 2nd toe	Sepsis, acute respiratory distress syndrome, death	1
24	Kim HR, Lee YS, Yim HJ, Lee HJ, Ryu JY, Lee HJ, Yoon EL, Lee SJ, Hyun JJ, Jung SW, Koo JS. Severe ischemic bowel necrosis caused by terlipressin during treatment of hepatorenal syndrome. Clinical and molecular hepatology. 2013 Dec;19(4):417.	Mesenteric ischemia/necrosis leading to "bowel necrosis"	"Bowel resection," hypotension, metabolic acidosis, death	1
25	Lee HJ, Oh MJ. A case of peripheral gangrene and osteomyelitis secondary to terlipressin therapy in advanced liver disease. Clinical and molecular hepatology. 2013 Jun;19(2):179-184.	Cutaneous ischemia: right foot (1st/2nd toes), left foot (1st/2nd/3rd toes); osteonecrosis: left foot; osteomyelitis: right and left feet	Amputation of 1st/2nd/3rd toes (left foot); amputation of left foot	1
26	Lee MY, Chu CS, Lee KT, Lee HC, Su HM, Cheng KH, Sheu SH, Lai WT. Terlipressin-Related Acute Myocardial Infarction: A Case Report and Literature Review. The Kaohsiung journal of medical sciences. 2004 Dec;20(12):604-608.	Myocardial infarction	Cardiogenic shock, multi-organ failure, death	1
27	Lehmann M, Bruns T, Herrmann A, Fritzenwanger M, Stallmach A. 54-year-old male with hepatic cirrhosis and therapy-associated torsade de pointes tachycardia. Der Internist. 2011 Apr;52(4):445-448.	Cardiac arrest, ventricular fibrillation x 2, Torsade de Pointe x 2	Pacemaker placement, recovery	1
28	Liu X, Zhao X, Yang J, Han X, Ruan X, Du Y. Cortical laminar necrosis following the rapid correction of drug-induced hyponatremia. Neurological Sciences. 2015 Sep 1;36(9):1725-1727.	Hyponatremia, cortical laminar necrosis, coma	Improving eating/speech/gait deficits and neurologic deficits (e.g., memory and daily living activities)	1
29	Lu YY, Wei KC, Wu CS. Terlipressin-induced extensive skin necrosis: A case report and published work review. The Journal of dermatology. 2012 Oct;39(10):866-868.	Cutaneous ischemia/necrosis of abdomen, buttocks, thighs	Recovering	1

No.	Article	Reported Adverse Event (s)	Disposition/Outcome	No. of Case Reports
30	Macedo SS, Cabral C, Novais A, Teixeira M, Knock A. Terlipressin-related Ischaemic Necrosis of the Skin: A Rare Complication. European Journal of Case Reports in Internal Medicine. 2019;6(11).	Cutaneous necrosis of UEs, LEs, scrotum, abdomen	Improving lesions, but death secondary to decompensated cirrhosis	1
31	Mégarbané H, Barete S, Khosrotehrani K, Izzedine H, Moguelet P, Chosidow O, Frances C, Aractingi S. Two Observations Raising Questions about Risk Factors of Cutaneous Necrosis Induced by Terlipressin (Glypressin®). Dermatology. 2009;218(4):334-337.	1. Cutaneous ischemia/necrosis in LEs, trunk, tongue, and scrotum 2. Cutaneous necrosis of scalp	1. Staphylococcal septicemia, death 2. Death due to metastatic adenocarcinoma of unknown primary	2
32	Meng Q, Dang X, Li L, Liu Z, Wang H. Severe hyponatraemia with neurological manifestations in patients treated with terlipressin: Two case reports. Journal of clinical pharmacy and therapeutics. 2019 Dec;44(6):981-984.	1. Hyponatremia, mental status changes 2. Hyponatremia, tonic clonic seizure	1. Recovery 2. Recovery	2
33	Niemann MJ, Qayyum AA. Terlipressin Induced Cardiac Arrest: A Case Report. Cardiology Cases and Systematic Reviews. 2019 May 24;1(1).	Cardiac arrest, myocardial infarction	Death from hepatic encephalopathy	1
34	Oh JE, Ha JS, Cho DH, Yu GJ, Shim SG. A case of ischemic skin necrosis after glypressin therapy in liver cirrhosis. The Korean Journal of Gastroenterology= Taehan Sohwagi Hakhoe chi. 2008 Jun;51(6):381-384.	Cutaneous necrosis of thighs (proximally), scrotum, and abdominal areas	Hepatic failure and GI hemorrhage, death	1
35	Posada C, Feal C, García-Cruz A, Álvarez V, Álvarez M, Cruces MJ. Cutaneous necrosis secondary to terlipressin therapy. Acta Dermato-venereologica. 2009 Jun 15;89(4):434-435.	Cutaneous necrosis of LEs	Renal/hepatic failure, recurrent GI bleeding, death	1
36	Poulsen A, Krag A. Severe hyponatraemia to terlipressin treatment. Ugeskrift for laeger. 2013 Sep;175(39):2250-1.	Hyponatremia	Recovery	1
37	Rosario R, Lalanne B, Lebre P, Lepesan D, Martelet JP, Dupont M, Camatte R, Lambot G, Bourlière M. Myocardial infarction after injection of terlipressin for digestive hemorrhage. Gastroenterologie clinique et biologique. 1996;20(8-9):712-713.	Myocardial infarction	Hepatic/Renal failure, death	1
38	Sahu S, Panda K, Patnaik SB, Rath J. Telipressin induced peripheral ischaemic gangrene and skin necrosis. Tropical Gastroenterology. 2010 Dec 1;31(3):229-230.	Cutaneous ischemia/necrosis of LEs and digital gangrene of toes/fingers (right index and right middle)	Not reported	1
39	Schmitt W, Wagner-Thiessen E, Lux G. Ischaemic colitis in a patient treated with glypressin for bleeding oesophageal varices. Hepato-gastroenterology. 1987 Jun;34(3):134-6.	Ischemic colitis	GI hemorrhaging, shock, death	1
40	Sidhu SK, Das D. Terlipressin-induced QT prolongation. Internal medicine journal. 2013 Sep;43(9):1050-1051.	Cardiac arrest, Torsade de Pointe	Recovery	1
41	Šíma M, Pokorný M, Paďour F, Slanař O. Terlipressin induced severe hyponatremia. Prague Medical Report. 2016;117(1):68-72.	Hyponatremia x 2	Recovery	1

No.	Article	Reported Adverse Event (s)	Disposition/Outcome	No. of Case Reports
42	Stéphan F, Paillard F. Terlipressin-exacerbated hypokalaemia. Lancet (British edition). 1998;351(9111):1249-1250.	1. Hypokalemia 2. Hypokalemia	1. Recovery 2. Recovery	2
43	Sundriyal D, Kumar N, Patnaik I, Kamble U. Terlipressin induced ischaemia of skin. Case Reports. 2013 Aug 1;2013:bcr2013010050.	Cutaneous ischemia/necrosis in LEs	Recovery	1
44	Tasliyurt T, Erdemir F, Yelken B. Ischemic skin necrosis following terlipressin therapy: Report of two cases and review of the literature. GASTROENTEROLOGY. 2012 Dec.	1. Cutaneous necrosis of scrotum 2. Cutaneous necrosis of scrotum	1. GI tract hemorrhaging, renal failure, death 2. Progressive renal/hepatic failure, death	2
45	Ürge J, Šincl F, Procházka V, Urbanek K. Terlipressin-induced ventricular arrhythmia. Scandinavian journal of gastroenterology. 2008 Jan 1;43(9):1145-1148.	Torsade de Pointe, QT-prolongation	Recovery	1
46	Vaccaro F, Giorgi A, Riggio O, De Santis A, Laviano A, Rossi-Fanelli F. Is spontaneous bacterial peritonitis an inducer of vasopressin analogue side-effects? A case report. Digestive and liver disease. 2003 Jul 1;35(7):503-6.	Cutaneous ischemia of abdomen, LEs, scrotum, and penis; ischemic colitis	Death	1
47	Wang YK, Hwang DY, Wang SS, Hwang SJ, Chen LT, Kuo MC. Terlipressin-induced hyponatremic encephalopathy in a noncirrhotic patient. The Kaohsiung journal of medical sciences. 2013 Dec 1;29(12):69169-4.	Hyponatremia, mental status changes	Recovery	1
48	Yefet E, Gershovich M, Farber E, Soboh S. Extensive epidermal necrosis due to terlipressin. The Israel Medical Association journal: IMAJ. 2011 Mar;13(3):180-181.	Epidermolysis of abdominal areas and UEs/LEs (not including hands or feet)	Deteriorating hepatic and renal functions, coma, acidosis, hypotension, death	1
49	Zaki SA. Terlipressin-induced hyponatremic seizure in a child. Indian journal of pharmacology. 2013 Jul;45(4):403.	Hyponatremia, generalized tonic clonic seizure	Recovery	1
50	Zimmer V, Lammert F. Terlipressin-induced skin necrosis and rhabdomyolysis. The American journal of the medical sciences. 2010 Dec 1;340(6):506.	Cutaneous necrosis of flanks, extremities, scrotum, rhabdomyolysis	Septicemia, death	1

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/s/

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LABEL AND LABELING REVIEW

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

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Date of This Review:	August 7, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 022231
Product Name, Dosage Form, and Strength:	Terlivaz (terlipressin) for Injection, 0.85 mg per vial (0.85 mg of terlipressin free base equivalent to 1 mg of terlipressin acetate)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Mallinckrodt Hospital Products IP Limited
FDA Received Date:	February 21, 2020
OSE RCM #:	2020-528
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Mallinckrodt Hospital Products IP Limited submitted a Class 2 resubmission for Terlivaz for Injection (NDA 022231) on February 21, 2020, a 505(b)(1).

This review evaluates the proposed container label, carton labeling, and Prescribing Information (PI) for Terlivaz for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

The original application was a rolling NDA with the complete submission on May 1, 2009. The application received a Complete Response (CR) Letter on November 4, 2009 for product quality issues, facility inspection issues, and the requirement of an additional clinical trial for safety and efficacy.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review

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

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, and PI, for Terlivaz (terlipressin) to identify deficiencies that may lead to medication errors and other areas of improvement. We identified areas of the proposed container label, carton labeling, and PI that could be revised to improve clarity and readability of important information. For the Division, we note that the product description is listed as: “a white to off-white lyophilized powder” in Section 3: Dosage Forms and Strengths of the PI, however, this information is not included in Section 16: How Supplied/ Storage and Handling. For the applicant we recommend changes to the container label and carton labeling to improve readability and prominence of important information. Specifically, we recommend revisions to the route, package type term, Rx only statement, and format of the expiration date, and storage information.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed carton labels, container labeling and prescribing information can be improved to promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for Mallinckrodt Hospital Products IP Limited to address our concerns.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. General Comments

   a. The route of administration should be presented as a non-abbreviation. We recommend removing the error prone abbreviation "IV" throughout the prescribing information.

   b. The instructions included in the (b) (4) section of the "Highlights of Prescribing Information" is redundant. We recommend replacing the instructions with the statement: "See Full prescribing information for instructions on preparation and administration (2.2).".

2. How Supplied/Storage and Handling Section

   a. Include the product description "white to off-white", before the descriptor "lyophilized powder" in the statement: "TERLIVAZ (terlipressin) is supplied as a sterile, preservative-free, lyophilized powder in single-dose vials".

4.2 RECOMMENDATIONS FOR MALLINCKRODT HOSPITAL PRODUCTS IP LIMITED

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

A. General Comments (Container labels & Carton Labeling)

1. We recommend changing the strength presentation throughout the container labels, carton labeling and prescribing information from (b) (4) to "0.85 mg/vial terlipressin" in accordance with the USP salt rule.

2. We recommend changing the statement (b) (4) to "For Intravenous Use Only" (b) (4)

B. Carton Labeling

1. We recommend revising the statement "Single-Dose Only" to "Single-Dose Vial" as this is the appropriate package-type term. In addition, we recommend adding "Discard Unused Portion" right after the single-dose vial statement to prevent confusion.

2. To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information."

3. Change the statement: [redacted] (b) (4) to "Store at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze." for clarity. We recommend bolding this statement to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

4. We recommend including the statement: "Protect from light" for consistency with the Prescribing Information.

5. Replace the term [redacted] (b) (4) on the side panel with appropriate terminology as "0.9% Sodium Chloride Injection, USP".

6. As currently presented, the format for the expiration date is defined as MMYYY. To minimize confusion and reduce the risk for deteriorated drug medication errors FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

7. Add the statement "Reconstituted vials can be kept for up to 48 hours in the refrigerator at 2°C to 8°C (36°F to 46°F)." to alert providers of post-reconstitution storage requirements.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Terlivaz received on February 21, 2020 from Mallinckrodt Hospital Products IP Limited.

Table 2. Relevant Product Information for Terlivaz	
Initial Approval Date	N/A
Active Ingredient	terlipressin
Indication	Treatment of adults with hepatorenal syndrome (HRS) Type 1.
Route of Administration	Intravenous
Dosage Form	for Injection
Strength	0.85 mg per vial (0.85 mg of terlipressin free base equivalent to 1 mg of terlipressin acetate)

Dose and Frequency	• Days 1-3: 1 mg every 6 hours
	• Day 4: Assess serum creatinine versus baseline
	  ○ If serum creatinine (SCr) has decreased by at least 30% from baseline, continue 1 mg TERLIVAZ every 6 hours.
	  ○ If SCr has decreased by less than 30% from baseline, dose may be increased to (b) (6) mg TERLIVAZ every 6 hours.
	  ○ If SCr is at or above baseline value, discontinue Terlivaz.
	• Continue TERLIVAZ until 24 hours after two consecutive SCr ≤1.5 mg/dL values at least 2 hours apart or a maximum of 14 days.

How Supplied	TERLIVAZ (terlipressin) is supplied as a sterile, preservative-free, lyophilized powder in single-dose vials containing 1 mg terlipressin acetate equivalent to 0.85 mg of terlipressin free base. Each vial is supplied in a carton (NDC 43825-200-01).
Storage	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.
Container Closure	Terlipressin for Injection is packed in a USP (b) (4) glass vial of 6 mL nominal capacity, closed with a 20 mm (b) (4) (b) (4) rubber stopper, and sealed with a 20 mm aluminum crimp with a plastic flip-off cap.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 9, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, “Terlivaz”, “terlipressin” and NDA 022231. Our search did not identify any pertinent reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] we reviewed the following Terlivaz labels and labeling submitted by Mallinckrodt Hospital Products IP Limited.

- Container label received on February 21, 2020
- Carton labeling received on February 21, 2020
- Prescribing Information (Image not shown) received on February 21, 2020, available from \\cdsesub1\evsprod\nda022231\0022\m1\us\terlivaz-pi-clean.pdf

G.2 Label and Labeling Images

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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MAXIMILIAN STRAKA
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08/11/2020 11:43:34 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: August 9, 2016

To: Anna Park, R.Ph., RAC
Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCaRP)

From: Puja Shah, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 22231
Terlivaz (terlipressin) 1mg injection

OPDP acknowledges the receipt of DCaRP's April 29, 2015, labeling consult request for the package insert (PI) and carton/container labeling for Terlivaz (terlipressin) 1mg injection. OPDP notes that DCaRP issued an Acknowledge Incomplete Response letter on May 22, 2015, notifying the applicant that "We [DCaRP] do not consider this submission to be a complete response to our 4 November 2009 action letter to you. . . . deficiencies identified in our action letter need to be addressed before we will begin our review." Therefore, OPDP will close out this labeling consult request and requests that DCaRP submit a new labeling consult request during the subsequent review cycle.

If you have any questions, please contact Puja Shah at 240-402-5040.

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/s/

PUJA J SHAH
08/09/2016

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: October 19, 2009

TO: Anna Park, Regulatory Project Manager
Nancy Xu, Medical Officer
Shari Targum, Team Leader
Division of CardioRenal Drug Products

FROM: Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-231

APPLICANT: Orphan Therapeutics, LLC
Candice Teuber, Pharm.D.
3 Werner Drive, Suite 210
Lebanon, New Jersey 08833

DRUG: Terlipressin (LUCASSIN™)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of Hepatorenal Syndrome Type 1

CONSULTATION REQUEST DATE: June 12, 2009

DIVISION ACTION GOAL DATE: November 4, 2009

PDUFA DATE: November 4, 2009

I. BACKGROUND:

- Data for this Application comes from one pivotal study: # OT-401: "A Double-Blind, Placebo-Controlled, and Randomized Phase 3 Study of Intravenous Terlipressin in Patients with Hepatorenal Syndrome (HRS) Type l." Terlipressin has been approved for use outside the U.S. for over 2 decades. FDA has designated fast-track approval for use of this drug in the U.S.

- Terlipressin is a systemic vasoconstrictor that acts through the vasopressin 1 receptors. Terlipressin itself is inactive, but is transformed into its biologically active form by endo- and exopeptidases to vasopressin.

- The primary efficacy endpoint was: Treatment success at Day 14 defined as the percentage of patients alive who demonstrated a reversal of HRS (SCr ≤1.5 mg/dL on ≥2 measurements obtained 48 ± 2 hours apart) without dialysis or recurrence of HRS.

- The proposed indication is for treatment of type I hepatorenal syndrome (HRS); the route of administration is intravenous injection; the proposed dosing regimen is as follows:

· 1 mg (as a IV bolus over 2 minutes) every 6 hrs for up to 14 days,
· If after 3 days serum creatinine (SCr) is not reduced by 30% then increase to (b) (4) mg every 6 hrs
· Discontinue 2 days after SCr 1.5mg/dL or after 14 days of therapy.
· Discontinue if SCr is not decreased below baseline (b) (4) (b) (4)
· If HRS recurs, terlipressin may be readministered.

- Key safety endpoints include ECG monitoring, as terlipressin may cause myocardial ischemia and prolonged QT, resulting in ventricular fibrillation and torsades de pointes, as per post-marketing reports outside the U.S. A 12-lead ECG was to be obtained from each patient at various time points.

- Hepatic Renal Syndrome (HRS) describes a condition that typically occurs in end-stage liver disease (i.e., advanced cirrhosis) where the renal impairment seems to be driven by the circulatory changes often underlying liver failure. In HRS, kidney tubular function is intact and renal impairment can be returned to normal by liver transplantation. In this syndrome there are abnormalities in renal blood flow, including active renal vasoconstriction, thus decreasing effective renal circulation, especially to the renal cortex. The cause of this is unknown, but is best thought of as an imbalance between systemic vasodilators and renal vasoconstricting mechanisms.

Sites were selected for inspection due to high enrollment, being foreign sites, and based on some discrepancies noted in the preliminary review.

II. RESULTS (by Site):

Name of CI/ CRO and Location	Protocol #: and # of Subjects:	Inspection Dates	Final Classification
Site 171 Dr. Tilman Sauerbruch Site University of Bonn, Sigmund-Freud-Strasse 25, 53105 Bonn, FRG Germany	Study OT ~0401 7 subjects	August 24-28, 2009	Pending (field classification VAI)
Site 181 Valentine Moiseyev M.D., Ph.D./ Moscow City Hospital N 64, Vavilova Street, 61, Moscow, 117298, Russian Federation Moscow, Russia	Study OT ~0401 8 subjects	August 31-September 3, 2009	NAI
Site 104 Andres Blei, .D(deceased) Site Coordinator: Jeane Gottstein Northwestern Memorial 303 E. Chicago Avenue, Searle 10-573 Chicago, IL 60611	Study OT ~0401 5 subjects	August 3-August 17, 2009	Pending (field classification VAI)
Site 157 Samuel H. Sigal, M.D. Columbia University Medical Center 1305 York Avenue York New York, New York 10032	Study OT ~0401 5 subjects	September 15-19, 2009	Pending (field classification VAI)
(b) (4)	Study OT ~0401 CRO	(b) (4)	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Dr. Tilman Sauerbruch
University of Bonn,
Sigmund-Freud-Strasse 25,
53105 Bonn, FRG Germany

What was inspected: Case report forms, medical records, ECGs, laboratory reports, study drug administration records, Informed Consent Documents, correspondence with the CRO, monitor and ethics committee, eligibility criteria, and all adverse events for all 7 subjects at this site. The inspection confirmed data points through review of lab report printouts, ECG recordings and medication records. The inspection checked concomitant medications and confirmed administration of albumin with study drug.

***As per special instructions in the assignment memo, the inspection reviewed the medical records for Subjects (b) (6) relating to treatment emergent adverse events, and documented findings in the EIR. The inspection collected source records relating to last dose date and time in CRF versus dose dataset for Subject (b) (6) (b) (6). The inspection reviewed the medical records for all concomitant therapies and albumin that were administered; and reviewed and confirmed medical records of the initial historical serum creatinine to help define HRS type I.

General observations/commentary: Fourteen subjects were screened for the study. The 7 subjects who were enrolled appeared to meet eligibility criteria. No significant discrepancies were noted in the comparison of reported study data with raw data contained in medical records, test results and procedure reports.

According to the protocol, terlipressin (or placebo) was to be initially administered at the rate of 1 mg every 6 hours, to be increased to 2 mg every 6 hours if indicated. The inspection observed that the time between study drug doses ranged from 2 hours to 13 hours. The inspection reported that of 184 doses of study drug administered after the initial dose, approximately 60% were administered at least 2 hours outside the recommended time frame. Dr. Appendrodt stated in a Note to File that deviations in dosing intervals were due to necessary medical intervention, unavailability of patients and administrative problems. The significance of these deviations in dosing intervals is not clear.

The protocol required that paired 12-lead ECGs be performed 30 minutes apart as follows: as a baseline, prior to study drug administration; on Day 3, 7 and at end of treatment or Day 14, whichever comes first. Of 24 paired ECGs performed during the study, the inspection found that 21 were conducted at intervals of 5 minutes or less. The significance of this finding is not clear. In a Note to File dated April 2, 2006, Dr. Apprendrodt stated that performing the ECGs at 30 minute intervals was not practical due to time constraints and other treatment priorities.

The protocol required that a comprehensive metabolic panel be collected at baseline, Day 14, Day 30 and Day 60. Elements of comprehensive and basic metabolic panels for Subjects (b) (6) were not always completed or recorded on the CRF. Comprehensive panels included electrolytes, glucose, BUN, creatinine, calcium protein, albumin, alkaline phosphatase, ALT and AST. A basic panel consisted of electrolytes, glucose, BUN, creatinine and calcium. Dr. Appendrodt stated that occasionally not enough blood was drawn, or the laboratory was not able do perform

the analyses.

The protocol required that after 3 days, the starting dose of study drug (1 mg every 6 hours) should be increased to 2 mg every 6 hours, if patient did not show a 30% reduction in SCr. The inspection found that 3 subjects (b) (6) appeared to qualify for the increased dose, but that Dr. Appendrodt elected not to increase the dosage to 2 mg every 6 hours. A Note to File dated (b) (6) stated that it was a physician decision not to increase the dosage for these subjects. However, there was no correspondence indicating that the sponsor or IRB was informed of this decision.

On October 16, 2009, DSI Reviewer Sharon Gershon spoke with Team Leader Shari Targum, concerning the significance of the observational findings, in terms of data validity. Dr. Targum stated that the FDA does not intend to approve this application, as the study failed on its pre-specified primary endpoint – decrease in SCr. With respect to the paired ECGs not performed within the specified timeframes, Dr. Targum did not consider this as problematic as the fact that lab tests were not always completed, as SCr (lab test) was a primary endpoint. She was also troubled by the subjects who were not up-titrated with study drug, as the question remains whether the drug could have been effective if it had been up-titrated. As this site appeared not to adhere to the recommended dosage regimen, she considered this problematic.

The inspection reviewed adverse events and serious adverse events with documentation in medical records. No SAEs were determined to be related to use of study drug. AEs and SAEs were adequately reported, according to the inspection report. The inspection noted one discrepancy on the SAE narrative report for Subject (b) (6). It was reported that the subject received dialysis from (b) (6) to (b) (6). The SAE report states the patient declined dialysis based on religious reasons.

Both Medical Officer Nancy Xu and Team Leader Shari Targum considered this discrepancy in reporting dialysis treatment for Subject (b) (6) problematic; dialysis would affect the SCr endpoint, which should have been an important benefit of the drug (terlipressin should decrease the need for dialysis). The fact that there was a discrepancy in reported dialysis treatment might indicate a more pervasive problem with accurate data being reported.

In general, the inspection reported that there was no evidence that Dr. Sauerbruch participated in the conduct of Study OT-0401, although he was listed as Principal Investigator on the Form FDA 1572. The inspection did not observe his signature or initials on any relevant records related to the subjects or their medical treatment.

Additional Information Noted during Inspection: Subject (b) (6) received open-label terlipressin at a dose of 1 mg 4 times a day between (b) (6) and (b) (6). This subject had been discontinued from the protocol dosage on (b) (6). The subject experienced right heart failure on (b) (6) Dr. Appendrodt indicated that terlipressin may have been responsible for the right heart failure in an SAE report. The Safety Narrative reporting right heart failure and the SAE report were in agreement.

With respect to Subject (b) (6), the inspection reported that the safety narrative reported intra-abdominal bleeding, acute cardiac insufficiency, and intra-cardiac thrombosis leading to death of subject. The SAE report by Dr. Appendrodt is in agreement.

With respect to Subject (b) (6) the inspection did not collect source documents relating to this subject's last dose date and time in the CRF. However, the inspection reported that there were no significant discrepancies in a comparison of reported study data with raw data contained in medical records, test results and procedure reports.

Assessment of data integrity: The inspection found the following: ECGs routinely were not performed at the time intervals required by the protocol; dosing of the study drug was often not performed within the time frame required by the protocol; some subjects did not follow the recommended dosage recommendations; all laboratory testing was not performed as required; and Dr. Beate Appendrodt, designated as a sub-investigator appeared to make all decisions and final reviews related to the clinical study, including the decision not to increase the dosage of study drug when it was clearly indicated. The most problematic findings in terms of data integrity were that all laboratory testing was not performed; that some subjects were not appropriately up-titrated, thus did not follow the dosage regimen prescribed by the protocol. In addition, the inspection noted discrepancies in the reported dialysis treatment for Subject (b) (6) (b) (6)– the SAE reported contraindications to dialysis based on religious reasons, whereas the medical records documented that dialysis was administered from (b) (6) to (b) (6) (b) (6). This reported discrepancy and the other deficiencies causes DSI to consider the data as unreliable at this site.

2. **Valentine Moiseyev**
M.D., Ph.D./ Moscow City
Hospital N 64, Vavilova
Street, 61, Moscow, 117298,
Russian Federation
Moscow, Russia

What was inspected: the inspection reviewed signed Informed Consent documents; case report forms; original medical records, ECG reports and laboratory results; adverse events for all 8 study subjects; correspondence with the sponsor, ethics committees, and the CRO. The inspection compared data and clinical notes recorded in medical charts with data documented on the CRF, and confirmed data points through review of lab reports, ECG recordings, and medication records. The inspection checked concomitant medications and confirmed administration of albumin with study drug.

***As per special instructions with the assignment, the inspection additionally addressed the following specific issues for the Review Division: 1) For Subject (b) (6) the inspection collected source records with respect to the listed death date; 2) For Subject (b) (6) the inspection collected source records relating to the last dose date and time in the CRF versus the dose dataset; and 3) for Subject (b) (6) the inspection

reviewed source medical records for the 1.5 Liter Normal Saline, and withdrawal of diuretics, and reported findings in the EIR. Finally, the inspection reviewed the medical records for all concomitant therapies and albumin that were administered; and reviewed and confirmed medical records of the initial historical serum creatinine to help define HRS type I.

Dr. Olga Moryleva, M.D., Ph.D., translated documents and was the interpreter during the inspection. Dr. Moryleva was Managing Director of Focus Clinical Drug Development.

General observations/commentary: The inspection reported 17 subjects were screened and 8 subjects enrolled between (b) (6) and (b) (6). Subject (b) (6) was withdrawn from the study due to concomitant use of prohibited medications. The inspection reported that the primary reason for non-inclusion of subjects in the study was screen failure based on absence of increasing serum creatinine value to at least 2.5 mg/dL.

According to the Terlipressin Trial Protocol dosing regimen, dosing should be terminated in the case of treatment success, where the serum creatinine has decreased to less than 1.5 mg/dL for at least 48 hours. The inspection reported that Subjects (b) (6) (b) (6) all experienced decreases in serum creatinine levels to less than 1.5 mg/dL in the following treatment periods, respectively: 5, 3, 4, 3. The principal investigator continued dosing these subjects with terlipressin through Treatment Period 14, as per communication with the sponsor Orphan Therapeutics.

The inspection reported that the Monitoring Log documented that 9 monitoring visits, including the initiation visit, were made between (b) (6) and (b) (6). All visits were initialed by one of the clinical investigators. The inspection reviewed freezer temperature logs for the period (b) (6) to (b) (6) and found no significant temperature excursions.

The inspection provided the following table that summarized cause of death for 8 subjects, as per autopsy reports:

Subject	**Date of IFC/ Randomization**	**Periods Completed:**	**Serum Creatinine Trend:**	**Outcome:**
(b) (6)		3	increase	Treatment failure, **Death** (b) (6) due to post-hemorrhagic anemia
		2	<30% decrease	Ventricular Fibrillation, use of atropine. Withdraw date (b) (6), **Death** (b) (6) (b) (6) due to hepatic insufficiency
		14	decrease	Treatment success, **Death** on (b) (6) due to liver cirrhosis
		14	decrease	Treatment success, **Death** on (b) (6) due to hepatocellular insufficiency

(b) (6)	14	decrease	Dose increase to 2 mg/dL every 6 hours. Creatinine decreased, partial response, transplant free survival >180 days
	14	decrease	Treatment success, patient **died** at home 1DEC05. No autopsy was done.
	14	decrease	Treatment success, **Death** (b) (6) due to hepatic insufficiency
	0	N/A	Patient received 2 doses at Period 1. **Death** on (b) (6) due to hepatorenal insufficiency

The inspection provided a response to specific instructions from the Review Division, as per the assignment:

1) For Subject (b) (6), the listed death date is not documented on the CRF.

Response: The inspection confirmed that the death of Subject (b) (6) on (b) (6) was due to hepatocellular insufficiency.

2) For Subject (b) (6), there was a discrepancy between the last dose date and time in the CRF versus the DOSE dataset.

Response: The inspection reviewed the source records and reported that the second (last) dose of the study drug was started at (b) (6) of (b) (6)

3) For Subject (b) (6), review source documents for administration of 1.5 Liters of Normal Saline and withdrawal of diuretics.

Response: The inspection reported that according to source documents, the patient received 4-400 cc bottles of normal saline after withdrawal of diuretic on (b) (6)

Assessment of data integrity: The inspection corroborated source records with case report forms for all 8 subjects, confirming that the primary efficacy and safety endpoints were verifiable, with no significant discrepancies. Five subjects completed 14 weeks of treatment; all 8 subjects eventually died. DSI recommends the data as acceptable at this site in support of the NDA.

3. **Andres Blei, .D (deceased)**
Site Coordinator, Jeanne Gottstein
Northwestern Memorial
303 E. Chicago Avenue,
Searle 10-573
Chicago, IL 60611

What was inspected: The inspection: audited the source medical records, and corroborated them with the CRFs and data listings for all 5 subjects; reviewed adverse events, ECG monitoring, and drug accountability records; ensured protocol was followed with respect to inclusion and exclusion criteria; and ensured accuracy of the primary efficacy endpoints.

***As per the special instructions from the Review Division and associated with this assignment, the inspection collected electronic medical records to document Subject (b) (6) withdrawal from treatment; checked medical records for concomitant therapies and albumin administration; and reviewed medical records to confirm the initial historical serum creatinine used to define hepatorenal syndrome.

Jeanne Gottstein, Study Coordinator to the OT-0401 study, and on behalf of Dr. Blei, responded in writing to the FDA-483 in a letter dated August 18, 2009.

General observations/commentary: The primary efficacy endpoint data was verifiable; however, many of the key safety endpoints including ECG monitoring were not performed by the site. The inspection reported that all clinical assessments and laboratories required by the protocol were not completed; however, these involved secondary or safety endpoints. Examples include: PK sampling, vital signs, the completion of all ECGs and post treatment antigenicity samples. These examples could be found for all subjects. For example:
• On (b) (6) Subject (b) (6) did not receive the second ECG during Treatment period 2
• On (b) (6) PK laboratory samples were not drawn during Treatment period 3 for Subject (b) (6)

In addition, the inspection reported 2 dosing regimen deviations:
• Subject (b) (6) was administered 2 doses of study drug for Dose 1 treatment period. According to the Study Coordinator, this mistake occurred because a new nurse inadvertently administered this dose by IV push at (b) (6) on (b) (6), because she read the medical chart and did not realize that only appointed medical staff was allowed to administer drugs by IV push. The (b) (6) dose was in the refrigerator, and she inadvertently administered this dose at (b) (6) as she came onto her shift. This incident was reported immediately to the sponsor and the IRB.
• Subject (b) (6) did not received Dose 2 during treatment period 6. According to Study Coordinator Jeanne Gottstein, this mistake occurred because the resident failed to pick up the (b) (6) dose to administer to the subject, and later realized this mistake when the person went to pick up the (b) (6) dose.

The inspection cited the site for inadequate drug disposition records. The firm had just transferred to an electronic charting system at the time of this study. The electronic medical records that were used to chart the administration of the study drug were often incomplete and varied widely in the amount of detail indicated in each note. For example, the inspection reported:
• the source documentation for Subjects (b) (6) did not indicate the quantity of the study drug administered during treatment periods. According to the response letter submitted by Jeanne Gottstein, the medical resident or nurse practitioner who administered study drug entered the administration time in the electronic charting system, but did not always include if it was 1 or 2 mg. In her response letter dated (b) (6) Ms. Gottstein stated that the Medication Administrative Record of the electronic chart actually does list if 1 or 2 mg was given, and that only the notes section did not document if 1 or 2 mg was given.

• the drug accountability log was not reconciled for Subject (b) (6) Four vials of study drug were unaccounted for.
In her response letter, Jeanne Gottstein stated that the drug accountability logs for all subjects except Subject (b) (6) do tally the correct number of vials used for the doses of drug administered.
Subject (b) (6) agreed to withdraw from the study and be placed in palliative care due to disease progression that would not likely be slowed by dialysis.

*****As per special instructions associated with this assignment, electronic medical records were collected to document Subject (b) (6) withdrawal from the study.**

The consult specifically asked if the "baseline" serum creatinine was done after meeting the diagnostic criteria for HRS Type I and before receiving study drug. The EIR has not come in for this inspection, and DSI Reviewer Sharon Gershon is trying to find out from the field inspector if this issue was addressed during the inspection. If issues are noted relative to this item after review of the EIR, Dr. Gershon will notify the Medical Officer of relevant findings.

Assessment of data integrity: The inspection noted several deficiencies at this site, including the fact that 2 ECGs were often not administered; medical residents and nurse practitioners who administered study drug did not always enter the strength (1 or 2 mg) of the drug in the notes section of the electronic chart; however, the MAR apparently did document the correct dose of drug. Subject (b) (6) was administered 2 doses at Dose treatment period 1 and Subject (b) (6) did not receive Dose 2 during Treatment period 6. The primary efficacy data is considered acceptable at this site in support of this NDA. However, the review division may choose to consider the lack of a complete safety dataset in their assessment of safety.

Observations noted above for Dr. Blei are based on the Form FDA 483 and communications with the field investigator, an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

4. Samuel H. Sigal, M.D.
Columbia University Medical Center
1305 York Avenue
York New York, New York 10032

What was Inspected: The inspection reviewed case report forms and source data with the line data from the sponsor for all 5 subjects enrolled. The inspection ensured that all subjects met the inclusion and exclusion criteria, as outlined in the protocol. The inspection ensured that all subjects signed the correct version of the informed consent document, and signed the ICD prior to enrollment. The inspection reviewed all adverse events to ensure that they were accurately documented and reported in a timely manner. The inspection reviewed the accuracy of test article accountability records. The inspection also reviewed all concomitant medications and intercurrent illnesses, liver function values, INR labs, electrolyte and calcium values, efficacy variables, renal function and glucose values, and deaths.

*** As per special instruction from the Review Division, and included with the assignment, the inspection reviewed the reported dates of death for Subject (b) (6) and Subject (b) (6); checked medical records for concomitant therapies and albumin administration; and confirmed medical records of the initial historical serum creatinine used to define hepatorenal syndrome.

General Observations/Commentary: Review of CRFs with source data and the line data found that all data was consistent and accurate between data forms. The inspection found that Subject (b) (6) was dropped from the study due to disease progression (b) (6) but continued to be administered study drug for an additional 6 days (b) (6) The inspection found that Dr. Sigal wrote a note in the patient's chart discontinuing the test article on (b) (6) but that the study coordinator failed to notify the research pharmacy, so the subject continued to receive study drug for 6 more days. The inspection found that this subject was on placebo. Study staff was brought together for a meeting after the occurrence of this incident, to discuss corrective action. The inspection found that this subject died on (b) (6) (b) (6) the inspection collected documents during the inspection for this subject's death.

The inspection reviewed case report forms and source data for Subject (b) (6) with respect to baseline serum creatinine and dosage adjustments. The inspection reported that Subject (b) (6) began treatment on (b) (6), with a baseline SCr of 3.4 mg/dL. After Treatment Period #3 ending on (b) (6) SCr was reported as 2.8 mg/dL, which was a decrease of ~ 18% from baseline (not 30%). Subject (b) (6) was maintained at a dose of 1 mg four times a day, but should have been increased to 2 mg four times a day, as per protocol. Further review of case report forms for Subject (b) (6) found that the subject received a dose increase to 2 mg per dose four times a day at Treatment Period #11, beginning (b) (6) (b) (6) through Treatment Period 13. The subject's SCr was 1.8 mg/dL on (b) (6) The inspection collected the MedWatch form and CRF documented that the date of death for Subject (b) (6) was (b) (6)

Assessment of Data: DSI recommends data from Subject (b) (6) be excluded from the dataset, as the dosage of study drug should have been increased to 2 mg four times a day, at the end of Treatment Period #3, when the SCr was reported as 2.8 mg/dL. Otherwise, the data appear acceptable in support of the NDA at this site.

(b) (4)

What Was Inspected? (b) (4)

(b) (4)

General Observations: (b) (4)

(b) (4)

Assessment of Data:

(b) (4)

(b) (4)

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Four clinical investigators and CRO (b) (4) were inspected in support of this application. The study appears to have been conducted adequately at Dr. Moiseyev and Dr. Sigal's site. Additionally, CRO (b) (4) appears to have executed its responsibilities appropriately. At Dr. Blei's site, the primary efficacy data are considered reliable; however, as many of the key safety assessments were not conducted, the safety data is

not considered reliable. Significant issues were noted at Dr. Sauerbruch' site, and the data is not considered reliable.

The final classification of the **CRO** (b) (4) is No Action Indicated (NAI) and the final classification of the Clinical Investigator inspection of Dr. **Valentine Moiseyev** is also NAI.

The preliminary classification for the Clinical Investigator inspection of **Dr. Andres Blei**, is Voluntary Action Indicated (VAI). While regulatory violations occurred at Dr. Andres Blei, site (many of the key safety endpoints including ECG monitoring were not performed by the site; and the inspection reported that all clinical assessments and laboratories required by the protocol were not completed), efficacy data generated by this site may be used in support of the respective indication; however, the safety data are not considered reliable

The preliminary classification of **Samuel H. Sigal** is VAI. While regulatory violations occurred at Dr. Sigal's site, with the exception of efficacy data from Subject (b) (6) (dosage of study drug should have been increased to 2 mg four times a day, at the end of Treatment Period #3), data generated by this site may be used in support of the respective indication.

The field classification of Dr. **Tilman Sauerbruch** is VAI; however, DSI considers the regulatory violations at this site significant: dosing regimens were not followed; ECGs were routinely not performed at the time intervals required; dosing of the study drug was often not performed within the required time frame; laboratory testing was not performed as required; and Dr. Beate Appendrodt appeared to make all decisions and final reviews related to the clinical study. DSI considers the data at this site as unacceptable, and recommends excluding the data from this site from the final analysis.

Note: Upon review of the EIRs for Drs. Sigal, Sauerbruch, and Blei, an addendum to this clinical inspection summary will be forwarded to the review division should there be changes in the final classifications of these inspections or if additional observations of clinical and regulatory significance are discovered after reviewing the EIRs.

{See appended electronic signature page}

Sharon K. Gershon, GCP Reviewer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

TEJASHRI S PUROHIT-SHETH

10/20/2009

Entered on behalf of Sharon Gershon. Signature denotes concurrence with primary reviewer's assessments.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: September 4, 2008

From: CDER DCRP QT Interdisciplinary Review Team

To: Anna-Park-Hong
Regulatory Project Manager
Division of Cardiovascular and Renal Products

Subject: QT-IRT Consult to NDA 22231

This memo responds to your consult to us dated 17 June 2008 regarding the evaluation of the ECG-QT Intervals from the Clinical Study Report OT-0401, titled: "A Double-Blind, Placebo-Controlled, Randomized Phase 3 Study of Intravenous Terlipressin in Patients with Hepatorenal Syndrome Type 1" sponsored by Orphan Therapeutics. The QT-IRT received and reviewed the following materials:

- Your consult
- ECG Evaluation Summary for study OT-0401
- Investigators brochure (April 2004), Clinical Overview (26 May 2008) and Summary of Clinical Safety (24 May 2008)
- ECGs from study OT-0401 submitted as *pdf* files

Background

Terlipressin is a vasopressin analog derived from the natural hormone, lysine vasopressin. This application (NDA 22-231) is for the use of terlipressin (LUCASSIN®) in the treatment of hepatorenal syndrome (HRS) type 1. Given the rare nature of this condition and the existing unmet medical need for treatment, the Agency granted Orphan Drug designation and Fast-Track designation on October 29, 2004 and April 15, 2005, respectively to this application.

Previous Clinical experience

Source: Summary of Clinical safety: 24 May 2008

> "Terlipressin has been marketed outside the US for over 20 years; therefore, data from the literature and the WHO Collaborating Centre for International Drug Monitoring were also evaluated for cases of QT interval prolongation. The WHO data contains 1 report each of QT interval prolongation and Torsades de pointes in 2 patients receiving 6-8

mg/day of terlipressin (Section 6.5.2, Global Safety Data from WHO Uppsala Monitoring Centre). The literature contains 1 case of an alcoholic patient who experienced non-fatal Torsades de pointes and prolonged QT interval following terlipressin administration for duodenal bleeding (Ürge 2008, Section 6.3.3.1).

"Studies OT-0401 and TAHRS were both randomized, controlled trials comparing terlipressin +albumin/placebo treatment with albumin/placebo. OT-0401 was a double-blind, placebo controlled trial that recommended the concomitant administration of albumin to achieve optimal volume expansion in accordance with standard medical practice

"As expected in this population with end-stage liver disease and HRS, overall mortality rates during the study periods (180 days and 90 days) were high in both studies (OT-0401, 57 % in the terlipressin group vs. 64% in the placebo group) and TAHRS (74% in each group). Hepatic events were the most common cause of death in both studies and all treatment groups. However, mortality was lower in both treatment groups in OT-0401 compared to TAHRS, which may be due, at least in part, to the higher transplantation rate in OT-0401 (32%) as compared with TAHRS (2%) [CTD Section 2.7.4/ Section 2.1.2].

"In Study OT-0401, the majority of deaths in both treatment groups were due to hepatic or renal disorders. As expected in a patient population with end-stage liver disease, hepatic deaths were the most common fatal event up to 30 days post-treatment (Table 20) and up to 180 days post-treatment in both treatment groups. The incidence of death due to hepatic failure/cirrhosis up to 180 days post-treatment was identical in both treatment groups (27%; 15 patients;).

"In both studies the incidence of cardiac AEs was higher in terlipressin-treated patients than in control patients (OT-0401: 25% terlipressin; 16% placebo and TAHRS 13% terlipressin; 4% albumin). The incidence of cardiac SAEs was similar in both treatment groups in OT-0401 (terlipressin 11% [6 patients] vs. placebo 13% [7 patients]). Treatment-related cardiac AE were reported in 5 terlipressin-treated patients (myocardial infarction, cyanosis, supraventricular tachycardia, atrial fibrillation, and T wave changes) and 3 placebo-treated patients (atrial fibrillation, arrhythmia, supraventricular extrasystoles, and tachycardia). Study medication was discontinued in 2 terlipressin-treated patients due to a cardiac AE (myocardial infarction and non-serious cyanosis).

"There were no AE reports of Torsades de pointes, sudden death, syncope, or QT interval prolongation in either the OT-0401 or TAHRS studies. In OT-0401, there was 1 case of ventricular tachycardia in the terlipressin group and 1 case of ventricular fibrillation reported in the placebo group. The onset of the cardiac events was after discontinuation of study medication in 6 of the 14 terlipressin-treated patients, including both reports of asystole (Section 2.1.5.4)."

Reviewers Comments: A definitive conclusion regarding QT prolongation related AEs due to terlipressin cannot be made based on information available. There is significant confounding due to the presence of underlying alcoholic /cirrhotic liver disease, multiple organ dysfunction, fluid and electrolyte abnormalities and concomitant medications in the above studies. Terlipressin is associated with myocardial ischemia and other ischemic events

Sponsors Submission for QT assessment

Study OT-0401, entitled *A Double-Blind, Placebo-Controlled, and Randomized Phase 3 Study of Intravenous Terlipressin in Patients with Hepatorenal Syndrome Type 1* was a phase 3 study of the clinical safety and efficacy of terlipressin. QT/QTc interval evaluations were predefined in the protocol as a safety assessment to evaluate the potential effect of terlipressin on the QT interval. In agreement with the Agency at a pre-IND meeting held on January 22, 2004, the potential for QT prolongation was evaluated through the collection of paired ECGs at baseline and on the study days on which peak drug concentrations were expected (Days 3 and 7) and end of study treatment (EOT) or Day 14. In addition, plasma samples collected during the study were used to develop a PK/PD model to investigate the relationship between terlipressin plasma concentrations and QTc intervals.

Patients received up to 14 days of study drug administered intravenously every 6 hours. Terlipressin was administered as intravenous (IV) bolus doses of 1 mg (1 vial) per patient every 6 hours (4 mg/d). If after three days of therapy serum creatinine had not decreased by at least 30% from the baseline value, the dose was to be increased to 2 mg every 6 hours (8 mg/d). If dose limiting side effects occur, dosing could have been stopped until the adverse event was no longer severe and dosing could be re-started, at the discretion of the investigator, at 1 mg each 8-12 hours (2-3 mg/d).

ECG acquisition and interpretation

As per the study OT-0401 protocol, a 12-lead ECG was to be obtained from each patient at the following time points:

- Within 1 week prior to randomization—a single ECG
- Baseline, prior to study drug administration (2 ECGs, 30 minutes apart)
- Day 3, 2 ECGs (30 minutes apart)
- Day 7, 2 ECGs (30 minutes apart)
- Day 14 or end of treatment—2 ECGs (30 minutes apart)

Also, if a patient experienced symptoms suggestive of cardiac ischemia, a minimum of one 12-lead ECG was to be obtained at the time of each episode of >20 minute duration with another obtained 24 hours after the onset of the ischemia episode.

The ECG readings were performed manually using visual determinations ("eyeball"/caliper technique). All ECG readings were performed by a qualified cardiologist (reviewer) from the [redacted] (b) (4) who was blinded to treatment and patient identity. Standard leads I, II, and III were inspected to determine the lead that gave the clearest end point of the T wave. The measurement was made from the trailing margin of the Q or R to the trailing margin of the T wave to reduce the impact of line width.

Two cardiologists independently reviewed the first 50 ECG recordings. Each reviewer's results were entered into the [redacted] (b) (4) database and the results were compared. The 2 physicians reviewed together all ECGs in which the QT measurement differed by more than ±0.03 sec. The new measurements were entered into the database for these cases. Fifty (50) of the next 250 ECGs reviewed by the primary reviewing cardiologist were independently reviewed by the Director of the [redacted] (b) (4). For QA purposes, 10% of all ECGs were selected randomly and re-read by the primary reviewing cardiologist, and the findings were

reviewed by the Director of the [redacted] in accordance with [redacted] Standard Operating Procedures (SOPs).

Table 5-1. Summary of Electrocardiogram Assessments

ECG Assessment	Terlipressin	Placebo	Total
Baseline	52	55[a]	107[a]
Baseline and at least 1 post-baseline	41	48[a]	89[a]
Day 3 / EOT	40	48[a]	88[a]
Day 7 / EOT	29	30	59
Day 14 / EOT	19	14	33

EOT = end of treatment.

a: Includes initial and retreatment assessments for 1 placebo patient (patient 148-03, 148-03R).
Source: Table 1.1.0 (19 Oct 2006).

Reviewer's Comments for ECG acquisition and interpretation:

1) *As expected, several patients had baseline ECG abnormalities increasing variability and limiting quantification of effect*
2) *Almost 50% of patients had no ECGs on Day 7 and 14.*
3) *2 paper ECGs were obtained 30 minute apart vs. digital ECGs in triplicates*
4) *Overall, although the methodology followed by the [redacted] lab is acceptable, ECG acquisition and interpretation was adequate to determine large effects (>30- 60 ms), but not for accurate quantification of the QT effect of terlipressin.*

Sponsor's Results

Central tendency analysis

The mean baseline QTcF interval was 437 ms in the terlipressin group and 440 ms in the placebo group. Two (2) patients in the terlipressin group and 1 patient in the placebo group had a baseline QTcF interval >500 msec.

Mean changes from baseline in QT/QTc interval are presented for each treatment group by study day in Table 5-8.

Table 5-8. Mean Change in QT, QTcB, and QTcF Intervals from Baseline by Treatment Group and Treatment Period

Interval	Terlipressin Group (msec)	Placebo Group (msec)	Mean Difference (msec)	95% CI Upperbound (msec)	P-value[a]	Treatment Effect[b] (msec)	Treatment Effect P-value[c]
Day 3/EOT (N=39 Terlipressin, 48 Placebo)							
QT	8.8	–12.1	20.95	33.99	0.001	19.1	0.016
QTcB	–5.1	–5.0	–0.10	12.16	0.821	–5.7	0.412
QTcF	–0.1	–7.7	7.60	19.10	0.052	3.3	0.615
Day 7/EOT (N=29 Terlipressin, 30 Placebo)							
QT	0.9	–10.5	11.45	29.03	0.289	8.3	0.409
QTcB	–1.9	–13.2	11.31	26.41	0.223	6.4	0.465
QTcF	–0.8	–12.4	11.58	26.18	0.197	6.7	0.422
Day 14/EOT (N=19 Terlipressin, 14 Placebo)							
QT	3.3	–26.3	29.67	55.57	0.069	16.2	0.319
QTcB	–0.7	–16.2	15.53	36.60	0.234	1.0	0.937
QTcF	0.7	–20.2	20.89	41.71	0.109	4.6	0.721

a: Difference of change from baseline between treatment groups analyzed by t-test or non-parametric test without adjustment.
b: The difference between treatment groups adjusted for baseline.
c: F test after baseline adjustment.

Source: Tables 1.3.0, 1.3.1, 1.3.2, and 1.3.3 (19 Oct 2006).

The change from baseline in QT/QTc interval was also evaluated using overall time-averaged data. Since the study involved a small number of patients and was not powered to detect differences in QT/QTc intervals, all data from each patient's post-baseline assessments were averaged in order to maximize the number of observations and provide the greatest statistical power for the analysis.

Table 5-9 presents the overall change from baseline for the QT/QTc interval data combined across study days (mean of Days 3/EOT, 7/EOT, 14/EOT) between the terlipressin and placebo groups.

Table 5-9. Overall Mean Change from Baseline in QT/QTc Intervals

Interval	Terlipressin Group (N=41) (msec)	Placebo Group (N=48) (msec)	Mean Difference (msec)	P-value[a]	Treatment Effect[b] (msec)	Treatment Effect P-value[c]
QT	4.2	–12.1	16.3	0.003	14.1	0.051
QTcB	–5.1	–8.0	2.9	0.497	–2.6	0.679
QTcF	–1.8	–9.6	7.8	0.057	3.3	0.595

a: Difference of change from baseline between treatment groups analyzed by t-test or non-parametric test without adjustment.
b: The difference between treatment groups adjusted for baseline.
c: F test after baseline adjustment.

Source: Tables 1.7.0, 1.7.1, and 1.7.2 (19 Oct 2006).

QT-corrected intervals, whether using Bazett's or Fridericia's correction, show small decreases in QTc interval in both treatment groups. The mean differences in change from baseline between terlipressin- and placebo-treated patients are a 2.9-ms increase in QTc interval using Bazett's correction and a 7.8-ms increase using Fridericia's correction.

Reviewer's Comments

- *An effect on the QT interval is possible and certainly cannot be excluded based on information available.*

- *Quantification of the QT effect by the time-averaged method is not acceptable.*

- *The variability of the data is much higher than a typical TQT study as indicated by the width of the confidence interval.*

- *No conclusions can be made from the sub-group analysis (age/gender) reported by the sponsor due to the small sample size.*

Outlier analysis

Overall, 10 patients in the terlipressin group and 5 patients in the placebo group had QTcF interval increases >30 ms from baseline. Two (2) terlipressin-treated patients and no placebo patient developed a new QTcF interval of >500 ms. None of the differences between the terlipressin and placebo groups was statistically significant, although a numerical trend exists of more outliers in the terlipressin group than the placebo group.

Table 5-10. Incidence of Outlier QT/QTc Interval Values (Worst Scenario)

Outlier Group	Terlipressin (N=41)	Placebo (N=48)	P-value
QT Interval			
Change >30 msec	13 (31.7)	6 (12.5)	0.028
Change of 30–60 msec	8 (19.5)	6 (12.5)	0.365
Change >60 msec	5 (12.2)	0 (0)	0.018
New >500 msec	1 (2.4)	0 (0)	0.461
QTcB Interval			
Change >30 msec	12 (29.3)	8 (16.7)	0.156
Change of 30–60 msec	10 (24.4)	7 (14.6)	0.241
Change >60 msec	2 (4.9)	1 (2.1)	0.593
New >500 msec	6 (15.8)	4 (9.8)	0.509
QTcF Interval			
Change >30 msec	10 (24.4)	5 (10.4)	0.079
Change of 30–60 msec	6 (14.6)	4 (8.3)	0.503
Change >60 msec	4 (9.8)	1 (2.1)	0.176
New >500 msec	2 (4.9)	0 (0)	0.214

Source: Tables 1.8.0 and 1.9.0 (16 Jan 2007).

Reviewer's Comment: As indicated by the sponsor, although not statistically significant, there was a trend for more outliers in the terlipressin group

Exposure-Response Analysis

Sparse samples were collected in OT-0401 for the purpose of a population pharmacokinetic analysis of terlipressin plasma concentrations. Terlipressin plasma concentrations were not measured at the time of ECG measurements, however, in this exposure-response analysis, concentrations were predicted based on the dosing history and terlipressin PK parameters of individual patients obtained from the population PK analysis.

Reviewer's Comment: The sponsor states that there is no significant correlation between terlipressin plasma concentrations and QTc intervals or their changes from the baseline. This was not verified by the QT-IRT since it was felt that no conclusions can be made from this analysis due to limitations of study-OT-0401 (acquisition of ECGs, timing of ECGs and several patients with baseline abnormalities).

Proposed labeling

The sponsor has proposed the following for [redacted] (b) (4)

[redacted] (b) (4)

Reviewers Comment: Proposed labeling is acceptable. Caution could also be advised in patients with hypokalemia/hypomagnesemia and concomitant medications that prolong the QT interval

QT-IRT RECOMMENDATIONS:

1. We cannot come to any conclusions regarding the effect of terlipressin on the QT interval based on ECGs obtained in Study OT-0401. Limitations include design, significant confounding due to the patient population, acquisition of ECGs and time averaged statistical analyses
2. Given the fact that terlipressin will be administered to patients with HRS in an inpatient setting, telemetric monitoring could be recommended if not already in place. Caution could be advised in patients with hypokalemia/hypomagnesemia and concomitant medications that prolong the QT interval
3. A TQT study in healthy volunteers (if feasible) or a repeat QT assessment in patients with more frequent digital ECGs could be considered

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future.

Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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Suchitra Balakrishnan
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