CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022231Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	22231
PDUFA Goal Date	February 18, 2022
OSE RCM #	2020-529
Reviewer Name(s)	Brian Caruth, Pharm.D., BCPS
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	February 10, 2022
Subject	Addendum to the Evaluation of Need for a REMS
Established Name	Terlipressin
Trade Name	Terlivaz
Name of Applicant	Mallinckrodt Pharmaceuticals Ireland Ltd
Therapeutic Class	Vasopressin analogue
Formulation(s)	Lypholized powder of injection
Dosing Regimen	Terlipressin 0.85 mg to 1.7 mg slow intravenous (IV) bolus over 2 minutes every 6 hours according to serum creatinine (SCr) levels to determine dose; not to exceed 14 days

1. Introduction

This addendum serves as an update to the review from September 11, 2020 by the Division of Risk Management (DRM) for the evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Terlivaz (terlipressin) with the proposed indication for the treatment of adults with hepatorenal syndrome type 1 (HRS-1), RCM # 2020-527 and 2020-529.

At the time of the review, DRM was unable to determine if the benefits of terlipressin outweighed the risks. Because of the uncertainties surrounding the proposed risk minimization strategies and benefit-risk profile, a final REMS determination could not be made at that time. The Division of Cardiology and Nephrology (DCN) issued a Complete Response Letter (CRL) citing concerns that the risks of terlipressin may outweigh its benefits. Following several meetings with the Agency regarding a path forward for terlipressin, the Applicant re-submitted the NDA on August 18, 2021 with updated labeling and risk mitigation plan relying on a re-evaluation of the existing data using a mitigated patient population.

2. Regulatory History

The following is a summary of the regulatory history for NDA 22231 relevant to this review:

- 09/11/2020: FDA issued a Complete Response Letter (CRL) stating that the Applicant must conduct an adequate and well-controlled study that demonstrates an acceptable risk-benefit profile, perhaps utilizing the proposed risk mitigation strategy. The study would need to be successful with a two-sided p-value of 0.1 to provide sufficient reassurance that the risk mitigation strategy does not adversely impact the product's efficacy.[1]
- 10/26/2020: Type A meeting held to discuss the CRL and steps that must be taken before the application can be approved.[2]
- 01/29/2021: Type A meeting held to discuss the use of existing study data to address the concerns cited in the CRL.[3]
- 08/18/2021: Mallinckrodt submitted a Class 2 resubmission for NDA 22231 for terlipressin including a non-REMS risk management plan.[4]

3. Risk Management Activities Proposed by the Applicant

The Applicant's resubmission for terlipressin relies on a re-analysis using a mitigated population in the CONFIRM study to support an acceptable risk-benefit profile. The proposed objective criteria for the mitigated population consist of excluding subjects with baseline acute-on-chronic liver failure (ACLF) Grade 3, subjects with baseline SCr ≥ 5 mg/dL, and transplant-listed subjects with a baseline model for end-stage liver disease (MELD) score ≥ 35. The Agency agrees with the Applicant that these objective criteria appear reasonable. The Agency also agreed that monitoring pulse oximetry is important for mitigating the risk of respiratory failure in patients receiving terlipressin. Short term treatment with terlipressin in the mitigated patient population is expected to be reassessed frequently and closely monitored by a multidisciplinary care team in an inpatient setting.

The Applicant did not propose a REMS but did propose a non-REMS risk management plan (RMP) that is similar to the RPM they proposed previously. The RMP consists of updated labeling, an Educational Plan for Healthcare Professionals (HCPs), and routine pharmacovigilance.

The Applicant's proposed labeling updates include a Boxed Warning for the risk of serious or fatal respiratory failure and includes additional recommendations for monitoring using pulse-oximetry, and warnings and precautions for the risk of ischemic events, embryo-fetal toxicity, increased mortality in patients with a serum creatinine of ≥ 5 mg/dL, use in patients listed for liver transplant with a MELD score ≥ 35 and sepsis. The Applicant proposed to include a limitation of use to avoid in patients with ACLF Grade 3 as these patients are at risk of serious or fatal respiratory failure. The Applicant also included guidance in the dosage and administration section to obtain baseline oxygen saturation prior to the first dose and monitor the patient using pulse oximetry during treatment. The review team also added a limitation of use in patients with a serum creatinine of ≥ 5 mg/dL to due to increased mortality.

3.1. Educational Plan for Healthcare Providers (HCPs)

The Applicant included additional information in the voluntary educational plan for HCPs to further align with the updated labeling. The target audience includes HCPs involved in the diagnosis and treatment of patients with hepatorenal syndrome with a rapidly progressive reduction in kidney function. The content of the HCP Educational Program includes a Guide for Healthcare Professionals (GHP) to conform to proposed labeling and the following objectives intended to highlight a narrowly defined patient population supporting an acceptable risk-benefit profile for the use of terlipressin:

- Highlight the higher risk of developing respiratory failure in patients with ACLF-Grade 3 and need to monitor oxygen saturation status using pulse oximetry.
- Importance of patient selection criteria to minimize or mitigate risk, including those with advanced respiratory failure (e.g., ACLF Grade 3), most advanced renal failure (e.g., SCr ≥ 5 mg/dL) and listed for transplant with a MELD score ≥ 35.
- Review TERLIVAZ dose management, especially in the context of an adverse event.
- Discuss the need for fluid management to minimize volume overload and resultant respiratory failure.

Revisions to the HCP Educational Program objectives include the addition of the need to monitor oxygen saturation status using pulse oximetry and the importance of patient selection criteria to mitigate risk for patients with advanced respiratory failure (e.g., ACLF Grade 3) and patients listed for transplant with a MELD score ≥35.

4. Discussion and Conclusion

The review team recommends approval of terlipressin citing safety and efficacy data from the mitigated population in the CONFIRM study, the seriousness of hepatorenal syndrome with a rapidly progressive reduction in kidney function, and an acceptable benefit-risk profile in a narrowly defined patient population.

The primary efficacy endpoint of verified HRS reversal in the mitigated population was statistically significant (p = 0.007) and occurred more frequently in the terlipressin group (36.4% [48/132]) compared to placebo (18.3% [13/71]). The incidence of serious or fatal respiratory failure in the mitigated population occurred more frequently in the terlipressin group (9.8% [13/132]) compared to placebo (7% [5/71]) and was lower compared to the overall CONFIRM safety population (terlipressin group (13.5% [27/200]) compared to placebo (5.1% [5/99])). Overall mortality by Day 30 in the mitigated population occurred less frequently in the terlipressin group (31.8% [42/132]) compared to placebo (36.6% [26/71]) and was lower compared to the overall CONFIRM safety population (terlipressin group (39% [78/200]) compared to placebo (36.4% [36/99])).

Relying on the data available, a REMS is not necessary to ensure the benefits of terlipressin outweigh the risks for fluid overload, serious or fatal respiratory failure, and ischemic events. Short term treatment with terlipressin in the mitigated patient population is expected to be reassessed frequently and closely monitored by a multidisciplinary care team in an inpatient setting. Healthcare providers who treat patients with this serious condition should be familiar with monitoring and treating predicted risks of vasopressin analogue therapy. The risks of fluid overload, serious or fatal respiratory failure, and ischemic events will be communicated using a risk management plan consisting of a Boxed Warning and the Warnings and Precautions section in labeling, and an educational program for healthcare providers. At the time of this review, labeling is still under negotiation and the clinical review is ongoing. Should DCN have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

5. Appendices

5.1. References

[1] Terlipressin Complete Response Letter. DARRTS Reference ID: 4669805. September 11, 2020.

[2] Terlipressin End of Review Type A Meeting Minutes. DARRTS Reference ID: 4707125. November 24, 2020.

[3] Terlipressin Guidance Type A Meeting Minutes. DARRTS Reference ID: 4754230. February 28, 2021.

[4] Mallinckrodt Pharmaceuticals Ireland Ltd. Terlipressin (NDA 22231). Class 2 Resubmission. Submitted August 8, 2021.

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/s/

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

Application Type	NDA
Application Number	22231
PDUFA Goal Date	September 12, 2020
OSE RCM #	2020-527, 2020-529
Team Leader	Laura Zendel, PharmD
Director	Cynthia LaCivita, PharmD
Review Completion Date	September 11, 2020
Subject	Evaluation of Need for a REMS
Established Name	terlipressin
Trade Name	Terlivaz
Name of Applicant	Mallinckrodt Hospital Products IP LTD
Therapeutic Class	Vasopressin receptor agonist
Formulation	Lyophilized powder for injection
Dosing Regimen	0.85 mg terlipressin (equivalent to 1 mg terlipressin acetate) IV bolus over 2 minutes every 6 hours up to 14 days

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Executive Summary

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Terlivaz (terlipressin) for intravenous injection is necessary to ensure the benefits outweigh its risks. Mallinckrodt Hospital Products, IP LTD. submitted New Drug Application (NDA) 22231 for terlipressin with the proposed indication to treat adults with hepatorenal syndrome Type 1 (HRS-1). The risks of concern associated with the use of terlipressin include fluid overload, respiratory failure, and sepsis/septic shock. The applicant did not submit a REMS with this application but proposed a risk management strategy consisting of: labeling including recommendations to avoid use in patients with acute-on-chronic liver failure (ACLF) Grade 3, serum creatinine of ≥ 5 mg/dL, or hepatic encephalopathy > Grade 3, to monitor closely for signs and symptoms of fluid overload and infections, and to decrease the dose or frequency or temporarily or permanently stop terlipressin in patients who have treatment- emergent fluid overload, pulmonary edema, new onset or worsening pneumonia, a post-marketing study, specific adverse event follow-up questionnaire for events of respiratory failure and sepsis, and an educational program for healthcare providers.

At this time, we are unable to determine if benefits of terlipressin outweigh the risks. The most recent clinical trial demonstrated that treatment of HRS-1 with terlipressin, in conjunction with albumin, improved renal function compared with albumin alone. However, there were more deaths and serious adverse events related to fluid overload and respiratory failure as well as sepsis events in patients who received terlipressin. The Applicant's proposed risk minimization strategies were not previously tested, and it remains unknown if the proposed interventions would adequately mitigate the risks. Further, the effect of the proposed interventions on the efficacy of the product also remains unknown. Because of the uncertainties surrounding the proposed risk minimization strategies and benefit-risk profile, a final REMS determination cannot be made at this time. We agree with the Division of Cardiology and Nephrology that because of the uncertainties with the proposed risk mitigation strategies and impact on efficacy, additional data on the impact of the proposed risk minimization strategies on both safety and efficacy of terlipressin is necessary.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Terlivaz (terlipressin) is necessary to ensure the benefits outweigh its risks. Mallinckrodt Hospital Products, IP LTD (Mallinckrodt) submitted New Drug Application (NDA) 22231 for terlipressin with the proposed indication to treat adults with hepatorenal syndrome Type 1 (HRS-1). This application is under review in the Division of Cardiology and Nephrology (DCN). The Applicant did not submit a REMS with this application but proposed a risk management strategy consisting of labeling, a post marketing study, specific adverse event follow-up questionnaire, and educational program for healthcare providers to address the risks of respiratory failure, sepsis, and risks of treatment in patients with elevated serum creatinine.

2 Background

2.1 PRODUCT INFORMATION

Terlipressin, a new molecular entity[a], is a synthetic vasopressin analogue proposed for the treatment of adults with hepatorenal syndrome Type 1 (HRS-1) in an inpatient hospital setting. Terlipressin activates the vasopressin receptor type 1 (V1) leading to vasoconstriction, increased effective intravascular volume and mean arterial pressure (MAP), amelioration of activation of the renin-angiotensin-aldosterone system and sympathetic nervous system hyperactivity, and improvement of renal blood flow leading to improved renal function.[1]

Terlipressin is proposed to be available as a 0.85 mg (equivalent to 1 mg terlipressin acetate) lyophilized powder in a single-dose vial for reconstitution. The product is reconstituted to prepare a 1 mg/5 mL solution to be administered via slow intravenous bolus over 2 minutes every 6 hours for up to 14 days. [b] The Applicant proposes that serum creatinine (SCr) level should be assessed at day 4 and the dose adjusted based on change from baseline[c] using the following algorithm:[2]

- If SCr has decreased by 30% or more from baseline: continue 1 mg every 6 hours until 24 hours after patient achieves a second consecutive SCr value of ≤ 1.5 mg/dL at least 2 hours apart or for a maximum of 14 days.
- If SCr has decreased by less than 30% from baseline: terlipressin may be increased to (b) (4) mg every 6 hours until 24 hours after patient achieves a second consecutive SCr value of ≤ 1.5 mg/dL at least 2 hours apart or for a maximum of 14 days.
- If SCr is at or above baseline value, discontinue terlipressin.

Terlipressin is available in several countries outside the United States such as France, Ireland, brazil, Portugal, Romania, Spain, Italy, New Zealand, and Australia.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 22231 relevant to this review:

- 5/27/2008: Orphan Therapeutics submitted an original NDA 22231 for terlipressin.
- 11/4/2009: FDA issued a Complete Response Letter (CRL) stating that the Applicant must conduct at least one additional adequate and well controlled study to demonstrate efficacy and safety. The study would need to be successful using prespecified endpoints and analytic plan at $p < 0.05$.
- 4/29/2015: Ikaria Therapeutics submitted a Class 2 resubmission for NDA 22231 for terlipressin.
- 5/22/2015: FDA issued an Acknowledge Incomplete Response Letter noting that the Applicant failed to address the deficiency cited in the CRL.
- 9/11/2015: Type A meeting to obtain agreement on the regulatory path forward for terlipressin clinical development including overall trial design, primary endpoint, and statistical analysis.

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] FDAAA factor (D): The expected or actual duration of treatment with the drug.

[c] Baseline SCr is the last available SCr before administration of the first dose.

- 10/1/2015: Follow-up Teleconference to further discuss clinical trial design, primary endpoints and statistical analysis plan.
- 11/30/2015: Mallinckrodt Pharmaceuticals requested a Special Protocol Assessment (SPA).
- 1/14/2016: FDA issued a SPA No-Agreement Letter stating that we expect to see favorable trends in clinical outcomes thought to be predicted by your surrogate. To support approval, the clinical trial ultimately needs to establish a clinical benefit that outweighs the risks.
- 3/7/2016: FDA received the SPA resubmission.
- 4/20/2016: FDA issued a SPA Agreement Letter stating that assuming the trial is well-conducted and successful, using pre-specified endpoint(s) and analytic plan, at $p<0.05$, the proposed trial should provide the data needed to address the deficiencies cited in the CRL.
- 10/21/2019: Pre-NDA Type B meeting where the Applicant presented topline results from CONFIRM. FDA determined CONFIRM could meet the requirement of the 2009 CRL.
- 2/21/2020: FDA received part 1 of the rolling Class 2 re-submission for NDA 22231.
- 3/12/2020: FDA received part 2 of the rolling Class 2 re-submission for NDA 22231. This re-submission did not include a REMS or risk management plan.
- 5/29/2020: DCN issued a General Advice Letter to the Applicant identifying SAEs of respiratory failure and fluid overload as substantive review issues that warranted further discussion.
- 6/4/2020: Teleconference with the Applicant to discuss their initial thinking on a risk mitigation strategy.
- 7/7/2020: Teleconference with the Applicant to have an opportunity to interact prior to the Advisory Committee meeting.
- 7/15/2020: Cardiovascular and Renal Drugs Advisory Committee Meeting was convened to discuss the NDA for terlipressin. The AC voted 8/7 in favor of approval. The Applicant's proposed non-REMS risk mitigation proposals were discussed.
- 7/29/2020: Applicant formally submitted their proposed non-REMS risk management plan.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Hepatorenal syndrome (HRS) is a serious, potentially fatal[d] condition that can develop in patients with acute or chronic liver disease with advanced hepatic failure or decompensated cirrhosis. HRS is thought to be due to the vasodilatation in the splanchnic circulation leading to a reactive vasoconstriction in the renal artery followed by an acute increase in SCr and decrease in urine output. The condition is considered a diagnosis of exclusion and historically has been divided into the more severe phenotype

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

(HRS-1) and less severe phenotype (HRS-2) based upon the rapidity of the rise and absolute level of SCr. HRS-1 may be considered if the serum creatinine increases by at least twofold to a value greater than 2.5 mg/dL during a period of less than two weeks. HRS-1 progresses quickly, within days, leading to kidney failure, reduced urine output, edema, jaundice, and often hepatic encephalopathy. The estimated annual incidence in the United States for HRS-1 ranges from 9,000 to over 35,000 patients[3,e] and the 30-day mortality for HRS-1 is 40 to 70% in the setting of cirrhosis.[4]

3.2 Description of Current Treatment Options

There are currently no available pharmacologic treatments in the United States approved for HRS-1. The only curative therapy for HRS-1 is resolution of the acute hepatic failure or a liver transplant.[5] However, if a patient is not a candidate for a liver transplant or it is not possible to have a transplant performed in the short term, a number of therapies and clinical interventions have been used to try to reverse acute kidney injury associated with hepatorenal syndrome[6,7]. Due to the lack of FDA-approved treatment options for HRS-1, there is a clear unmet medical need.

4 Benefit Assessment

The efficacy and safety of terlipressin to treat adults with HRS-1 was derived primarily from one pivotal Phase 3 study, CONFIRM (NCT02770716), and 2 supportive Phase 3 studies, OT-401 (NCT00089570) and REVERSE (NCT01143246). All 3 studies were randomized, double-blind, placebo-controlled multicenter studies.

CONFIRM was conducted under a special protocol assessment (SPA) Agreement[f,8] and enrolled 300 patients who were randomized 2:1 to terlipressin or placebo, administered as a 1 mg IV bolus injection every 6 hours for up to 14 days. The prespecified primary endpoint was the incidence of verified HRS reversal, defined as 2 consecutive SCr values ≤ 1.5 mg/dL at least 2 hours apart, while on treatment by Day 14 or discharge.[g] In order to be counted in the primary endpoint, patients also needed to be alive without renal replacement therapy for at least 10 days after achieving verified HRS reversal. Key secondary efficacy endpoints included incidence of patients with HRS reversal, durability of HRS reversal, incidence of HRS reversal in the systemic inflammatory response syndrome (SIRS) subgroup, and incidence of verified HRS reversal without HRS recurrence by Day 30.

The trial met its primary endpoint with 58/199 (29%) subjects in the terlipressin arm compared to 16/101 (16%) subjects in the placebo arm achieving verified HRS reversal (p = 0.012). The secondary endpoints also achieved statistical significance by showing more patients in the terlipressin arm

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[f] SPA is a process in which the Applicant may ask to meet with FDA to reach agreement on the design and size of certain clinical trials, clinical studies, or animal studies to determine if they adequately address scientific and regulatory requirements for a study that could support marketing approval. The existence of a SPA agreement does not guarantee FDA will file the application or that the trial results will be adequate to support approval.

[g] On treatment was defined as up to 24 hours after the final dose of the study drug.

experiencing HRS reversal while on treatment by Day 14 or discharge (36% vs 17%, p < 0.001), and HRS reversal without RRT to day 30 (32% vs 16%, p = 0.003). The incidence of HRS reversal while on treatment by Day 14 or discharge in the subgroup of patients meeting criteria for SIRS was also statistically significantly greater in the terlipressin arm compared to placebo (33% vs 6%, P < 0.001). The proportion of patients with verified HRS reversal without HRS recurrence by Day 30 was numerically greater in the terlipressin arm, but the difference was not statistically significant (24% vs 16%, p = 0.09). The clinical reviewer notes that while FDA agreed on the primary endpoint used in CONFIRM, this endpoint captured treatment effects of a laboratory value and therefore FDA considers it to be a surrogate endpoint.

For further analysis and assessment of treatment effects on clinical outcomes including RRT-free survival, post-transplant outcomes, ICU length of stay, and overall mortality, please refer to the clinical review[9], FDA Advisory Committee Briefing Information[10], and the Applicant's Advisory Committee Briefing Information.[11] The clinical reviewer notes that these results are difficult to interpret due to being post-hoc analyses and did not assist in providing a better understanding of the efficacy and benefit to patients.

In the OT-401 study, 112 subjects were randomized 1:1 to terlipressin or placebo. Subjects continued on study therapy until at least 2 SCr values ≤ 1.5 mg/dL were obtained at least 48 hours apart, or up to 14 days. The primary endpoint was incidence of treatment success at Day 14 defined as the percentage of subjects with an initial reduction of SCr to ≤1.5 mg/dL followed by a confirmatory SCr measurement of 1.5 mg/dL 48 hours (± 8 hours) after the initial HRS reversal while still receiving treatment, and an additional SCr value<2.5 mg/dL at Day 14, without intervening liver transplant, dialysis, or recurrence. The incidence of treatment success was higher in the terlipressin group but did not attain statistical significance (25% vs. 12.5% respectively; p=0.093).

In the REVERSE study, 97 subjects received terlipressin and 99 subjects received placebo. The study design and primary endpoint was the same as OT-401. The study did not meet its prespecified endpoint but did show that more patients in the terlipressin group achieved confirmed HRS reversal than in the placebo group, 19/97 (19.6%) versus 13/99 (13.1%), p=0.2214.

5 Risk Assessment & Safe-Use Conditions

The safety evaluation focused on the results from CONFIRM, pooled analysis including results from CONFIRM, OT-401, and Reverse, and terlipressin's postmarketing experience in other countries.

In the clinical development program, the overall incidence of adverse events (AEs) was similar between terlipressin (88% CONFIRM, 91.1% Pooled) and placebo (88.9% CONFIRM, 90.4% Pooled). Common AEs reported with > 5% increased frequency with terlipressin included abdominal pain, diarrhea, dyspnea, and bradycardia. More treatment emergent AEs (TEAEs) were seen in terlipressin compared to placebo in the risks of ischemia (4.5% vs 0%), respiratory events (40% vs 25%), respiratory failure (18% vs. 10%), gastrointestinal (GI) events (48% vs. 35%), fluid overload (28% vs 16%), and bradycardia (5% vs 0%). The TEAEs were generally consistent with the mechanism of action and similar to other products of the same class. The incidence of serious adverse events (SAEs) was higher in the terlipressin arm in both the CONFIRM trial (65% vs 60.6%) and the pooled safety population (64.8% vs. 59.8%). The most commonly

reported SAEs were hepatic disorders with a higher incidence in the placebo arm (25% vs. 33%). There was a higher incidence of SAEs related to respiratory failure, infections including sepsis and septic shock, GI bleeding, and abdominal pain in the terlipressin arm compared to placebo.

5.1 DEATHS

In CONFIRM and in the pooled data, all-cause mortality up to day 90 was higher in terlipressin vs. placebo. Hepatic disorders were the most common cause of death in both arms which is expected given the disease state and was numerically more common in the placebo arm. A higher frequency of death due to respiratory failure and sepsis/septic shock was seen in terlipressin.

5.1.1 Table 1: Deaths up to Day 90

	Terlipressin Pooled N = 349 n (%)	Placebo Pooled N = 249 n (%)	Terlipressin CONFIRM N = 200 n (%)	Placebo CONFIRM N = 99 n (%)
Total Deaths[h]	168 (48.1)	115 (46.2)	102 (51.0)	44 (44.4)
Hepatic Disorders	83 (23.8)	65 (26.1)	49 (24.5)	27 (27.3)
MODS	25 (7.2)	11 (4.4)	11 (5.5)	5 (5.1)
Respiratory Failure	29 (8.3)	9 (3.6)	18 (9.0)	1 (1.0)
Septic Shock	15 (4.3)	3 (1.2)	11 (5.5)	2 (2.0)
Sepsis	14 (4.0)	3 (1.2)	5 (2.5)	0
ARF	9 (2.6)	8 (3.2)	4 (2.0)	0
GI Hemorrhage	6 (1.7)	2 (0.8)	6 (3.0	0
Treatment Emergent Deaths[i]	16 (4.6)	11 (4.4)	9 (4.5)	11 (4.4)
Respiratory Failure	8 (2.3)	2 (0.8)	6 (3.0)	2 (0.8)
Hepatic Disorder	7 (2.0)	7 (2.8)	2 (1.0)	7 (2.8)

5.2 RESPIRATORY FAILURE, FLUID OVERLOAD, AND PULMONARY EDEMA SAES

Review of the terlipressin clinical database shows increased incidence of the SAE of respiratory failure in the terlipressin group compared with the placebo group in the clinical development program. This imbalance was greatest in CONFIRM. The clinical outcomes of the events were concerning. About 40% of the respiratory failure and fluid overload events in the terlipressin arm did not recover or resolve during the follow-up period. More than 80% of pulmonary edema AE's in the terlipressin arm of CONFIRM were moderate to severe, and one was fatal. The clinical reviewer performed subgroup analyses of fluid overload-related AE's using the pooled data and found that the results were consistent across subgroups with an overall risk difference of 8 (95% confidence interval 1.4-14.6), favoring placebo. The clinical reviewer also noted that although baseline diuretic use was similar in the two arms, use of

[h] Total deaths defined as deaths occurring up to 90 days from the start of treatment

[i] Treatment emergent death defined as death occurring on the same day as the last dose of study drug administered

diuretics approximately doubled in the terlipressin arm (25.5%) compared to placebo (13.1%) in the CONFIRM study.

5.2.1 Table 2: Incidence of SAEs related to Edema and Fluid Overload

	Terlipressin Pooled N = 349 n (%)	Placebo Pooled N = 249 n (%)	Terlipressin CONFIRM N = 200 n (%)	Placebo CONFIRM N = 99 n (%)
Hemodynamic edema, effusions and fluid overload SAEs	16 (4.6)	9 (3.6)	10 (5.0)	2 (2.0)
Fluid Overload	2 (0.6)	0	2 (1.0)	0
Pulmonary Edema	7 (2.0)	3 (1.2)	2 (1.0)	1 (1.0)
Ascites	4 (1.1)	3 (1.2)	3 (1.5)	0
Pleural Effusion	0	2 (0.8)	1 (0.5)	0
Peripheral Edema	1 (0.3)	0	1 (0.5)	0
Peripheral swelling	1 (0.3)	1 (0.4)	1 (0.5)	1 (1.0)

The majority of the SAEs for respiratory failure required an intervention such as intubation or the use of bilevel positive airway pressure (BiPAP), see Table 3. There were nine patients who were not intubated, however, 6 (67%) were put on comfort care and died shortly after the event.

5.2.2 Table 3: Interventions for Respiratory Failure SAE in CONFIRM

	Terlipressin N = 200 n (%)	Placebo N = 99 n (%)	Risk Difference (%)
Respiratory Failure SAE	28 (14)	5 (5.1)	8.9
Intubation or BiPAP	23 (11.5)	4 (4.0)	7.5
Intubation	19 (9.5)	4 (4.0)	5.5
Intubation or Comfort Care	25 (12.5)	5 (5.1)	7.4

The Applicant concluded that it is likely that the difference in respiratory failure events in CONFIRM was driven by a shift in clinical practice, in response to changing clinical guidelines, towards greater use of prior albumin over the course of the clinical development program with the highest use during CONFIRM. The clinical review team also noted that the incidence and severity of respiratory AEs increased over time in the terlipressin arm across the three studies and that this trend was not seen in the placebo arm. The clinical review team acknowledges that it is possible that the additional fluid load associated with increased albumin use may have contributed to the observed incidence and severity of respiratory failure and fluid overload events in the terlipressin arm of CONFIRM, but that in all three studies, the frequency of fluid overload related AEs was greater in the terlipressin arm than in the placebo arm.

5.3 POSTMARKETING EXPERIENCE

As terlipressin is approved in other countries, the Division of Pharmacovigilance I (DPV-I) analyzed post-market safety data from case reports or case series from the FDA Adverse Event Reporting System

(FAERS), VigiBase, and medical literature and identified three post-marketing AE's of concern: ischemia/necrosis, cardiac adverse events including arrhythmia, and hyponatremia. The DPV reviewer concluded that the events described in the available post-marketing data were generally consistent with those observed in clinical trials and that the additional more specific information describing some events such as skin necrosis, hyponatremia, and arrhythmias may inform labeling for the prescribing information if the application is approved.[12] The clinical reviewer notes that the ischemia, necrosis and cardiac AEs were consistent with the clinical trial data, however the post-marketing cases were more severe and included more serious outcomes. Hyponatremia is described in some foreign labeling for terlipressin, however, the incidence was similar for terlipressin and placebo in the clinical trials.

6 Expected Postmarket Use

Terlipressin is expected to be used for short term treatment in the inpatient setting where patients can be closely monitored. Likely prescribers may include hepatologists, nephrologists, gastroenterologists, as well as critical care prescribers. These patients are likely to have a multidisciplinary care team including transplant surgeons, pharmacists, advanced practice providers, and nursing staff working together to care for them.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS, but did propose risk management strategies to mitigate the risks of respiratory failure and acute respiratory failure, use in patients with SCr ≥ 5 mg/dL, ischemic events, embryofetal toxicity and the important potential risk of sepsis.

7.1 Risk Minimization Measures

7.1.1 Routine Risk Minimization Measures

The Applicant proposes several updates to the Prescribing Information in sections 2, Dosage and Administration, 5, Warnings and Precautions, 6, Adverse Reactions, and 8, use in specific populations to bring attention to important identified risks and communicate their recommended risk minimization measures, but did not propose a Boxed Warning. Appendix 10.1 provides a summary of the proposed labeling changes including recommendations to avoid use in patients with acute-on-chronic liver failure (ACLF) Grade 3, serum creatinine of ≥ 5 mg/dL, or hepatic encephalopathy > Grade 3, to monitor closely for signs and symptoms of fluid overload and infections, and to decrease the dose or frequency or temporarily or permanently stop terlipressin in patients who have treatment- emergent fluid overload, (b) (4)

7.1.2 Educational Plan for Healthcare Professionals (HCPs)

The Applicant proposes a voluntary educational program to inform HCPs of the risks of respiratory failure/acute respiratory failure associated with the use of terlipressin and how to minimize the risk and to inform HCPs of the risk of treatment with terlipressin in patients with SCr ≥ 5 mg/dL. The Applicant's proposal is based on their interpretation of the clinical trial data where they state that subjects with more advanced decompensated cirrhosis, a history of prior, baseline, or treatment emergent events of respiratory issues or recent upper GI hemorrhage appeared more likely to develop respiratory failure or

acute respiratory failure with terlipressin treatment. Additionally, the Applicant notes that in clinical trials, subjects with SCr ≥ 5 mg/dL had a lower incidence of HRS-1 reversal, were more likely to experience SAEs, and had lower survival compared to placebo-treated patients.

The proposed educational program includes a Guide for Healthcare Professionals with content to highlight the higher risk of developing respiratory failure in patients with ACLF-grade 3, the importance of patient selection to minimize risk (i.e. patients with SCr < 5), review of terlipressin dose management and discussion of the need for fluid management to minimize fluid overload and respiratory failure.

The Applicant proposes the following key risk messages:

Respiratory Failure

- In pooled data from three randomized, controlled trials, 7.7% of TERLIVAZ treated- patients (n=349) experienced serious respiratory failure leading to death compared to 2% of placebo-treated patients (n=249).
- In the primary efficacy trial, 6% of TERLIVAZ-treated patients (n=200) experienced fatal respiratory failure compared to no patients treated with placebo (n=99).
- Patients with ACLF Grade 3 are at significant risk for serious or fatal respiratory failure. In the primary efficacy trial, 22.5% of TERLIVAZ-treated patients with ACLF Grade 3 (n=40) experienced fatal respiratory failure compared to no placebo-treated patients (n=18).
- Recommendations to reduce risk of respiratory failure:
    - Use of TERLIVAZ in patients with ACLF Grade 3 should be considered only when the anticipated benefit to the patients outweighs the potential risk.
    - During treatment with TERLIVAZ, closely monitor patients for signs of fluid overload. Manage fluid overload by reducing or discontinuing the administration of albumin and other fluids and judicious use of diuretics. If symptoms persist, or pneumonia occurs or progresses or pulmonary edema is severe, temporarily interrupt, reduce, or discontinue TERLIVAZ treatment.
    - Do not administer TERLIVAZ in patients with a history of or in the presence of existing or emerging dyspnea, pleural effusion, pneumonia, atelectasis, hematemesis or upper GI hemorrhage until the patient is stabilized
    - Do not administer TERLIVAZ until existing pulmonary edema, pneumonia, tachypnea, or dyspnea has been appropriately treated or has resolved.
    - Due to the risk of aspiration, patients with worsening hepatic encephalopathy (Stage ≥3) should be treated and the airway protected as clinically indicated prior to administration of terlipressin.

Increased Mortality in patients with SCr ≥5 mg/dL

- In an analysis of TERLIVAZ-treated patients (N=349) from three randomized, double-blind, placebo-controlled trials, patients with SCr ≥ 5 mg/dL had higher rates of serious adverse events and mortality compared to patients with SCr <5 mg/dL.
- Overall survival (alive at Day 90) in patients with a baseline SCr ≥5 mg/dL was lower than patients with SCr <5 mg/dL (30% vs. 55%). These patients also experienced a lower rate of HRS reversal compared to patients with SCr <5 mg/dL (37% vs. 9%).
- Use of TERLIVAZ in patients with SCr ≥ 5 mg/dL should be considered only when the anticipated benefit to the patient outweighs the potential risk

The Applicant proposes to target the educational plan towards HCPs involved in the diagnosis and treatment of HRS-1 including hepatologists, transplant surgeons, transplant pharmacists, nephrologists, gastroenterologists, critical care physicians and pharmacists, hepatology advanced practice providers, hospital pharmacy staff, and nursing staff who care for these patients. The proposed dissemination of the educational plan includes direct communication to HCPs and institutions in print, electronic and/or verbal format, content in promotional material, exhibit booths, and interactions with company personnel at Scientific Congress, Speaker programs in person or remote, live or recorded, promotional programs delivered by third party organizations, and a product website.

To evaluate the effectiveness of the interventions, the Applicant proposes to use an outcome indicator in a prospective observational cohort study of patients with HRS-1 treated with TERLIVAZ in the United States. The incidence of respiratory failure in patients treated with TERLIVAZ in standard clinical practice will be compared with the incidence of respiratory failure reported in the terlipressin arm of the CONFIRM trial, see section 7.2 for further details.

Reviewer Comment*: The Applicant's risk mitigation plan as proposed is primarily based on a retrospective analysis of the data and is largely untested in a clinical trial setting. Therefore, the effects of the proposed risk mitigation strategies on the benefit-risk profile are uncertain. As a voluntary educational program, the proposed interventions are not enforceable by the Agency and may not be followed by prescribers in a real-world setting. The use of an observational cohort study to assess the effectiveness of the interventions may be helpful in evaluating the outcomes of treatment with terlipressin as we found it concerning that some of the post-marketing AEs were more severe and included more severe outcomes as noted in the DPV review. However, this type of study but may not fully be able to assess the implementation of such a program or the stakeholders' knowledge of the risk and risk mitigation recommendations*.

7.2 PHARMACOVIGILANCE PLAN

The Applicant's proposed pharmacovigilance plan for terlipressin consists of the following:

- Routine pharmacovigilance for all adverse events reported in patients treated with terlipressin.
- Specific adverse event follow up questionnaires for important identified risks of respiratory failure/acute respiratory failure and sepsis.
- A prospective, observational cohort study of patients with HRS-1 treated with terlipressin in the united states.

The Applicant proposes several routine pharmacovigilance activities beyond adverse reaction reporting and signal detection such as weekly literature review, medication error and product complaint review, monitoring for off label use, compilation of periodic safety update reports, continuous monitoring of adverse reactions and signal detection using external databases such as FAERS, and continuous risk-benefit evaluation and monitoring of outcomes of risk management measures. The Applicant also proposes the use of targeted questionnaires to follow-up on all reports of respiratory failure and sepsis. The questionnaires will be provided to anyone who reports respiratory failure or sepsis either spontaneously or during the proposed prospective observational cohort study.

The purpose of the proposed prospective observational cohort study is to assess the safety of TERLIVAZ in the treatment of patients with HRS-1 under usual care condition and to assess adherence to the risk minimization strategies. The Applicant proposes to conduct the study in adult patients with HRS-1 who are initiating treatment with TERLIVAZ in the United States. The primary objectives include assessment of TERLIVAZ safety under usual care conditions, with focus on events of special interest including respiratory failure, acute respiratory failure, sepsis, and 30-day all-cause mortality as well as to compare the incidence of respiratory failure in patients treated with TERLIVAZ in standard clinical practice with the incidence of respiratory failure reported in the terlipressin arm of the CONFIRM trial.

***Reviewer Comment**: DRM defers review of the pharmacovigilance plan to the Division of Pharmacovigilance (DPV).*

8 Discussion of Need for a REMS

HRS-1 is a rare and serious condition that can develop in patients with acute or chronic liver disease with advance hepatic failure and portal hypertension. This condition is associated with significant morbidity and mortality with poor survival outcomes. The only definitive treatment for HRS is liver transplant or recovery of liver function. There are no approved therapies for the treatment of HRS, accordingly, there is an unmet medical need.

The CONFIRM trial met its primary endpoint with 29% of subjects in the terlipressin arm compared to 16% of subjects in the placebo arm achieving verified HRS reversal. The clinical reviewer notes that the submitted data demonstrate an effect of terlipressin on verified HRS reversal and terlipressin was associated with a favorable trend for reduced need for RRT. Treatment effects on post-transplant RRT-free survival and ICU length of stay are notably difficult to interpret and although numerically in favor of terlipressin, there was no associated survival benefit.

The safety evaluation focused known and potential toxicities of terlipressin based on the mechanism of action. More TEAEs were seen in terlipressin compared to placebo in the expected risks of ischemia (4.5% vs 0%), respiratory events (40% vs 25%), respiratory failure (18% vs. 10%), GI events (48% vs. 35%), fluid overload (28% vs 16%), and bradycardia (5% vs 0%). SAEs also occurred more frequently in patients treated with terlipressin compared to placebo, specifically for respiratory failure (14% vs 5%) and sepsis/septic shock (7% vs 0%), and there was higher mortality at 90 days in the terlipressin group compared to placebo (51% vs 44%).

The most concerning safety events included the greater incidence and severity of respiratory failure and fluid overload in patients treated with terlipressin. The respiratory events tended to occur soon after administration of terlipressin and resulted in poor outcomes. The fatality of the event in the terlipressin group was 61% (17/28) compared to 20% (1/5) in the placebo group and the clinical reviewer noted that most patients in the terlipressin group required intubation or received comfort care and died shortly following the event. The Applicant notes that terlipressin may increase pulmonary vascular congestion through its effects on cardiac afterload and systemic venous return due to its vasoconstriction effects on arterial pressure and the splanchnic bed which may result in pulmonary edema in some patients. The clinical reviewer suggests it is possible that terlipressin could increase the risk of respiratory failure and

fluid overload via its effects on V1a and V2 receptors and that the increased use of albumin for HRS reversal in recent years may exacerbate hypervolemia.

The benefit-risk profile of terlipressin was discussed at the Cardiovascular and Renal Drugs Advisory Committee meeting on July 15, 2020. The committee voted 8 to 7 in favor of approval. Those who voted in favor of approval noted the severity of the condition and unmet need for an approved therapy for HRS. Those that voted against approval were unconvinced by the data on the clinical outcomes in CONFIRM and noted that any potential benefit may be outweighed by the serious risks of respiratory failure and sepsis which were seen more often in the terlipressin treated subjects. Many noted that if terlipressin was to be approved, a strong risk management approach would be needed including strong labeling, post-approval monitoring requirements, a registry, training, and potentially a REMS to limit the use. Others were skeptical of the proposed risk mitigation strategies presented by the Applicant noting that they were unsure it could be effective or implemented in a real-world setting.

The Applicant's proposed risk management activities include labeling changes, pharmacovigilance studies, follow-up for adverse events of respiratory failure and sepsis, and an educational plan for healthcare providers. The clinical review team has concerns of whether the risk management strategies as proposed would effectively mitigate the risks or if the plan could be implemented effectively given the subjective nature of some of the recommendations. Although terlipressin generally causes adverse events consistent with its mechanism of action and class effects that may be manageable, whether or not the serious risk of respiratory failure can be reliably predicted and managed in the post-marketing setting remains unclear. At this time, the review division is unable to determine what interventions may be effective at mitigating the risk of respiratory failure; therefore, we [DRM] are unable to formulate further recommendations for risk management or a REMS for terlipressin at this time.

9 Conclusion & Recommendations

At this time, we are unable to determine if benefits of terlipressin outweigh the risks. The most recent clinical trial demonstrated that treatment of HRS-1 with terlipressin, in conjunction with albumin, improved renal function compared with albumin alone. However, there were more deaths and SAEs related to fluid overload and respiratory failure in patients who received terlipressin. The Applicant's proposed risk mitigation strategies were not previously tested, and it remains unknown if the proposed interventions would adequately mitigate the risks. Further, the effect of the proposed interventions on the efficacy of the product also remains unknown. Because of the uncertainties surrounding the proposed risk mitigation measures and benefit-risk profile, a final REMS determination cannot be made at this time. Additional data on the impact of the proposed risk minimization strategies on both safety and efficacy of terlipressin is necessary.

10 Appendix

10.1 Summary of Applicant's Proposed Labeling Changes

Safety Concern	Product Labeling Summary
Respiratory Failure and Acute Respiratory Failure	**Section 2**: Instructions to avoid increasing terlipressin dose if fluid overload, pneumonia, or pulmonary edema occurs and guidance on management of AE such as dose reduction, interruption, less frequent interval, or permanent discontinuation. **Section 5**: Guidance to prescribers on identification of conditions that may require intervention or monitoring to reduce the incidence of respiratory failure. **Section 6**: Adding language about SAEs that occurred in at least two TERLIVAZ-treated patients in the clinical trials (intestinal ischemia, cyanosis, respiratory distress, vascular skin disorder).
Use in patients with SCr ≥ 5 mg/dL	**Section 5**: Guidance to prescribers to use in patients with SCr ≥ 5 mg/dL only when the anticipated benefit outweighs the potential risk. The Applicant notes that patients with SCr ≥ 5 mg/dL had higher rates of SAE and mortality than those with SCr < 5 mg/dL.
Ischemic Events	**Section 2**: Instructions to avoid increasing terlipressin dose if the patient has pre-existing severe coronary artery disease and guidance on management of AE such as dose reduction, interruption, less frequent interval, or permanent discontinuation. **Section 5**: Includes data on the incidence of serious ischemic events in patients treated with TERLIVAZ and recommends caution in patients with history of ischemic events and cardiac conditions. Recommends temporary interruption or permanent discontinuation if ischemic AE occurs. **Section 6**: Adding language about SAEs that occurred in at least two TERLIVAZ-treated patients in the clinical trials (intestinal ischemia, cyanosis, respiratory distress, vascular skin disorder).
Embryofetal Toxicity	**Section 5**: Includes information about embryofetal toxicity noting that TERLIVAZ may cause fetal harm or death when administered to a pregnant woman based on MOA and published literature. **Section 8**: Includes information about the effects of terlipressin during pregnancy such as induction of uterine contractions and endometrial ischemia leading to fetal abnormalities due to hypoxia.
Sepsis	**Section 5**: Guidance recommending monitoring for signs of infection and prompt treatment if infection is detected.

10.2 REFERENCES

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