Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome

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INDICATION AND LIMITATION OF USE

TERLIVAZ® is indicated to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function.

- Patients with a serum creatinine >5 mg/dL are unlikely to experience benefit.

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WARNING: SERIOUS OR FATAL RESPIRATORY FAILURE

- **TERLIVAZ may cause serious or fatal respiratory failure. Patients with volume overload or with acute-on-chronic liver failure (ACLF) Grade 3 are at increased risk. Assess oxygenation saturation (e.g., SpO_2) before initiating TERLIVAZ.**
- **Do not initiate TERLIVAZ in patients experiencing hypoxia (e.g., SpO_2 <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue TERLIVAZ if SpO_2 decreases below 90%.**

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Type 1 hepatorenal syndrome (HRS-1) is a condition of rapidly progressing kidney failure that occurs in patients with decompensated cirrhosis and ascites.

STUDY OBJECTIVE

The main objective of the CONFIRM study was to assess the efficacy and safety of terlipressin plus albumin, as compared with placebo plus albumin, in adults with cirrhosis and HRS-1.

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Contraindications

TERLIVAZ is contraindicated:

- In patients experiencing hypoxia or worsening respiratory symptoms.
- In patients with ongoing coronary, peripheral, or mesenteric ischemia.

Warnings and Precautions

- **Serious or Fatal Respiratory Failure:** Obtain baseline oxygen saturation and do not initiate TERLIVAZ in hypoxic patients. Monitor patients for changes in respiratory status using continuous pulse oximetry and regular clinical assessments. Discontinue TERLIVAZ in patients experiencing hypoxia or increased respiratory symptoms.

  Manage intravascular volume overload by reducing or discontinuing the administration of albumin and/or other fluids and through judicious use of diuretics. Temporarily interrupt, reduce, or discontinue TERLIVAZ treatment until patient volume status improves. Avoid use in patients with ACLF Grade 3 because they are at significant risk for respiratory failure.

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STUDY DESIGN

CONFIRM was a phase 3, multicenter, 2:1 randomized, placebo-controlled, double-blind trial with patients receiving treatment for up to 14 days

Patients were enrolled based on a diagnosis of HRS-1, cirrhosis, ascites, and progressive kidney failure that included rapid reduction in renal function (with trajectory for serum creatinine [SCr] level to double within 2 weeks) to an SCr ≥2.25 mg/dL without sustained improvement in renal function ≥48 hours after diuretic withdrawal and albumin challenge.

After albumin resuscitation and at randomization, patients had a mean serum albumin of 3.7 g/dL in the terlipressin arm and 4.0 g/dL in the placebo arm.[a]

Clinical and demographic characteristics of the patients at baseline were generally well balanced between the trial groups.

Key demographics

- Mean age was 53.8 years old
- Gender: 59.6% male
- Main cause of cirrhosis:
  - Alcohol use: 67%
  - Nonalcoholic steatohepatitis: 22%
  - Viral hepatitis: 14.3%

Enrolled patients displayed significantly compromised liver and kidney function

Baseline assessment	Terlipressin arm (N=199)	Placebo arm (N=101)
Mean baseline SCr, mg/dL (SD)	3.5 (±1.0)	3.5 (±1.1)
Mean baseline MAP, mm Hg (SD)	78.7 (±12.1)	77.5 (±9.4)
Mean total bilirubin, mg/dL (SD)	13.1 (±13.5)	15.0 (±15.6)
Mean baseline MELD score (SD)	32.7 (±6.6)	33.1 (±6.2)
Mean baseline Child-Pugh score (SD)	10.0 (±1.85)	10.2 (±1.89)

MAP, mean arterial pressure; MELD, Model for End-stage Liver Disease.

[a]Concomitant albumin was recommended at a dose of 1 g/kg of body weight up to 100 g on day 1 followed by 20 to 40 g/day.
[b]One hundred one patients underwent randomization to placebo, but 1 did not receive a first dose.

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Warnings and Precautions (cont'd)

- **Ineligibility for Liver Transplant:** TERLIVAZ-related adverse reactions (respiratory failure, ischemia) may make a patient ineligible for liver transplantation, if listed. For patients with high prioritization for liver transplantation (e.g., MELD ≥35), the benefits of TERLIVAZ may not outweigh its risks.

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EFFICACY

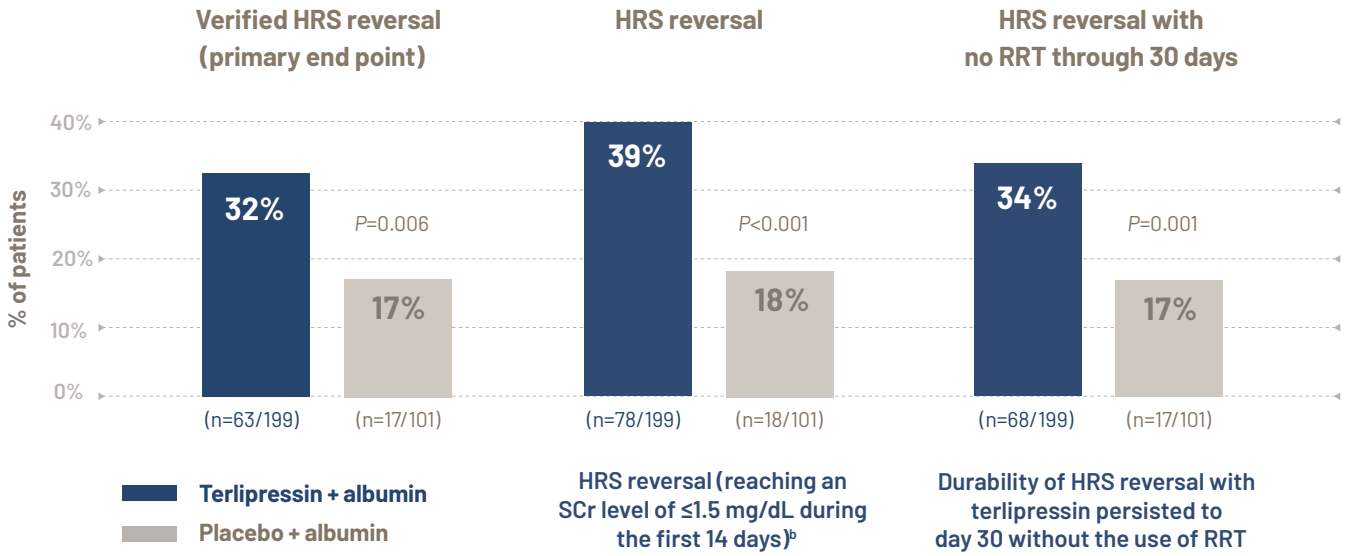
CONFIRM evaluated a variety of efficacy end points, including 1 primary and 4 secondary

A rigorous primary end point was assessed[a]

The primary end point, verified HRS reversal, consisted of 3 components:

- 2 consecutive SCr measurements of ≤1.5 mg/dL at least 2 hours apart by day 14
- Absence of renal-replacement therapy (RRT) for at least 10 days
- Survival without renal replacement therapy for at least 10 days

More patients achieved the primary and secondary end points with terlipressin than placebo



[a]A multicomponent end point was selected to demonstrate a clinically meaningful outcome beyond a surrogate marker of renal function.
[b]Limitation of analysis: HRS reversal is a surrogate end point using a single SCr measurement of ≤1.5 mg/dL. Conclusions based on these data may be limited.

Overall, the results of the CONFIRM study are consistent with the data from previous clinical trials, which provided evidence that terlipressin improves kidney function in patients with HRS-1.

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Warnings and Precautions (cont'd)

- **Ischemic Events:** TERLIVAZ may cause cardiac, cerebrovascular, peripheral, or mesenteric ischemia. Avoid use of TERLIVAZ in patients with a history of severe cardiovascular conditions or cerebrovascular or ischemic disease. Discontinue TERLIVAZ in patients who experience signs or symptoms suggestive of ischemic adverse reactions.
- **Embryo-Fetal Toxicity:** TERLIVAZ may cause fetal harm when administered to a pregnant woman. If TERLIVAZ is used during pregnancy, the patient should be informed of the potential risk to the fetus.

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SAFETY

Adverse events (AEs) in the safety population[a]

	Terlipressin arm (N=200)	Placebo arm (N=99)
AEs of any grade,[b] n (%)	176 (88)	88 (89)
AEs leading to discontinuation of the trial regimen, n (%)	24 (12)	5 (5)
Serious AEs with an incidence of ≥3% in either group,[c] n (%)		
Any, n (%)	130 (65)	60 (61)
Cardiac disorders, n (%)	8 (4)	6 (6)
Gastrointestinal disorders, n (%)	30 (15)	6 (6)
General disorders and administration-site conditions, n (%)	11 (6)	6 (6)
Hepatobiliary disorders, n (%)	37 (18)	29 (29)
Worsening of HRS, n (%)	3 (2)	3 (3)
Infections and infestations, n (%)	19 (10)	5 (5)
Nervous system disorders, n (%)	13 (6)	3 (3)
Respiratory, thoracic, and mediastinal disorders,[d] n (%)	33 (16)	8 (8)
Acute respiratory failure, n (%)	8 (4)	2 (2)
Respiratory failure, n (%)	20 (10)	3 (3)
Vascular disorders, n (%)	10 (5)	4 (4)

Please review the article for a more complete summary of AEs reported.

[a]The safety population included all patients who underwent randomization and received at least 1 dose of terlipressin or placebo. For each event category, the patients were counted once even if they had multiple events in that category. One patient in the placebo group did not receive a first dose, and 1 patient who had been assigned to receive placebo inadvertently received 1 dose of terlipressin and was therefore assigned to the terlipressin group in the safety analysis.
[b]The numbers of events include those that occurred up to 7 days after the end of the treatment period.
[c]The numbers of events include those that occurred up to 30 days after the end of the treatment period.
[d]The numbers reported for acute respiratory failure or respiratory failure are for patients with the condition as coded by the investigator; there is no overlap.

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Adverse Reactions

- The most common adverse reactions (≥10%) include abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea.

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Click here to download and review your own copy of the "Terlipressin Plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome" publication.

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