Terlipressin (TERLIVAZ) in Hepatorenal Syndrome
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description / Mechanism of Action

- Terlipressin was introduced as a safer synthetic analogue of vasopressin in 1975 and was subsequently approved outside the US for the treatment of hepatorenal syndrome (HRS) and acute variceal bleed (AVB).[1] It is considered standard of care for the treatment of HRS outside the US including Europe.[2]
- Terlipressin is an active prodrug that is metabolized by exopeptidases, resulting in sustained production of an active moiety, lysine vasopressin, which remains active for 3 to 4 hours. Terlipressin produces more selective and longer-acting effects than vasopressin. It is a vasopressin agonist with twice the selectivity for V1 receptors than V2 receptors and exerts vasoconstrictor effects in the splanchnic and systemic vasculature.[3,4] It reverses splanchnic arterial vasodilation, reduces portal hypertension, and increases the effective arterial blood volume and mean arterial pressure.

Indication Under Review in This Document

- To improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function.
- Limitation of Use: Patients with a serum creatinine (SCr) > 5 mg/dL are unlikely to experience benefit.

Dosage and Administration

Assessments prior to initiating and during therapy

- Oxygen saturation (SpO_2). Do not use terlipressin in patients with hypoxia until it resolves.
- Acute-on-Chronic Liver Failure (ACLF) Grade and volume status. Assess before initiating therapy.

Recommended Dosage

- Record the last available SCr value prior to initiating treatment.
- **Initial Dose, Days 1–3**: 0.85 mg every 6 hours by slow intravenous bolus injection (over 2 minutes).
- **Subsequent Dosage, Day 4**: Assess SCr vs baseline.
    - If SCr has decreased by ≥ 30% from baseline: Continue 0.85 mg every 6 hours.
    - If SCr has decreased by less than 30% from baseline: Increase to 1.7 mg every 6 hours.
    - If SCr is at or above the baseline value: Discontinue terlipressin.
- Continue terlipressin (if not discontinued) 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.

Administration

- Terlipressin can be administered through a peripheral or central line. A dedicated central line is not required.

Dosage Form Under Review

- For injection: Single-dose vial containing 0.85 mg of terlipressin (equivalent to 1 mg terlipressin acetate) for reconstitution.

Clinical Evidence Summary

Efficacy Considerations

- The first two marketing applications for terlipressin in 2009 and 2015 were not approved because the two submitted studies involving patients in North America (OT-0401 and REVERSE) showed numerically better but statistically nonsignificant benefits in their primary endpoints (percentage of patients alive with a SCr of ≤ 1.5 mg/dL on at least 2 measurements 48 hours apart by the end of 14 days).[5] Furthermore, there were no survival benefits.
- The FDA approval of terlipressin in September 2022 was mainly supported by the CONFIRM trial, a double-blind, placebo-controlled randomized clinical trial (RCT) that compared terlipressin IV with placebo in adult patients with type 1 HRS.[5,6] The aim of this trial was to confirm the efficacy and safety of terlipressin relative to placebo in a North American population, with all patients receiving albumin. The FDA authorized priority review, fast-track status, and orphan drug designation for the terlipressin marketing application.[7]
- The primary efficacy measure used in the CONFIRM trial was HRS reversal, a putative surrogate endpoint.[6] Exploratory efficacy analyses assessed improvement in renal replacement treatment (RRT)-free survival and mortality.
- An independent Data Safety Monitoring Board identified an increased incidence of deaths and fatal or serious respiratory failure, both of which had not been observed in previous trials. The manufacturer proposed risk mitigation criteria that were assessed in a retrospective risk-benefit analysis to determine their effects on the efficacy and safety of terlipressin vs placebo. Hence, in the FDA Integrated Review, results were analyzed using the Intent-to-treat (ITT) Population and a post hoc Mitigated Population. The Mitigated Population consisted of a subgroup of patients not excluded by the mitigation criteria and were thereby considered to be at lower risk of serious or fatal respiratory failure than the overall study population (see explanation under Safety Considerations, page 6).

Pivotal Randomized Clinical Trial

Table 1 Methods of Phase 3 RCT

Topic	CONFIRM Trial	
Study Design	MC DB PC RCT involving hospitalized patients; used 2:1 randomization and followed patients to Day 90 Stratified randomization by qualifying SCr (< 3.4 mg/dL or ≥ 3.4 mg/dL) and large volume paracentesis Hochberg procedure to control for type 1 error	
Major Entry Criteria	Inclusions Age ≥ 18 y Type 1 HRS with rapidly progressive kidney failure (doubling of SCr to ≥ 2.25 mg/dL within 14 d before randomization or on a nomogram-predicted trajectory to develop doubling of SCr) Cirrhosis, ascites	Exclusions Sustained improvement in renal function (≥ 20% decrease in SCr or SCr < 2.25 mg/dL) at least 48 hours after diuretic withdrawal and the beginning of plasma volume expansion with albumin SCr > 7.0 mg/dL Clinical evidence suggesting parenchymal renal disease Severe cardiovascular disease

Topic	CONFIRM Trial	
		Sepsis or uncontrolled bacterial infection treated with antibiotics for < 2 d
		Use of vasopressors other than midodrine or octreotide of ≥ 3 consecutive days within the prior 14-d screening period
		Large volume (≥ 4 L) paracenteses within previous 2 days
		Transjugular intrahepatic portosystemic shunt within 30 days of randomization
		Current or recent (within 4 wks) renal replacement therapy
Interventions	Albumin fluid challenge for ≥ 2 days prior to randomization was strongly recommended and received by ≥ 99% of patients. Concomitant use of albumin was strongly recommended if clinically indicated as per current standard of care. Dosage was 1 g/kg to maximum of 100 g on D1, then a constant dose of 20–40 g/d. SCr was measured within 8 hours before the first dose of study drug. • Terlipressin 1 mg (one vial) IV bolus Q6H + Albumin. If, on D4 after a minimum of 10 doses, SCr decreased by < 30% from baseline, dose was increased to 2 mg Q6H. • Placebo + Albumin Doses were not increased in patients with coronary artery disease, circulatory overload, pulmonary edema, or bronchospasm. Study treatment was continued until 24 hours after two consecutive SCr values of ≤ 1.5 mg/dL were achieved or up to 14 d. Study treatment was discontinued if the SCr was at or above the baseline value or if the patient received renal replacement therapy, another vasopressor, a transjugular intrahepatic portosystemic shunt, or a liver transplant.	
Primary Efficacy Measure(s)	Verified HRS reversal, defined as two consecutive SCr values ≤ 1.5 mg/dL at least 2 hours apart while on treatment by D14 or discharge. In addition, patients had to be alive without need for renal replacement therapy for ≥ 10 d after achieving verified HRS reversal.	
Baseline Patient Characteristics	Male 59% Mean age 54 y White / African American or Black / Asian: 91% / 6% / 2% US / Canada 89% / 12% Listed for liver transplant 24% Alcoholic hepatitis 40%	Mean MELD score 33 ACLF Grade 0 / 1 / 2 / 3: 0% / 46% / 36% / 19% Child-Pugh Class A / B / C: 2% / 33% / 61% Any vasopressor use 75% Diuretic use pre-randomization 56% ≥ 1 LVP up to 14 d before randomization 40%

ACLF, Acute-on-chronic liver failure; **LVP**, Large volume paracentesis; **MELD**, Model for end-stage liver disease

Results

- Overall, 87% of patients received concomitant albumin: 83% (mean total dose 199.4 ± 146.8 g over a median of 5.0 days) in the terlipressin group vs 91% (239.5 ± 183.6 g over 5.5 days) in the placebo group.
- The publication of the CONFIRM trial reported rates of Clinical Success,[6] an outcome not defined in the protocol and not covered in the FDA Integrated Review.[6] Relative to the treatment difference of 13.3% for the protocolled primary efficacy outcome of verified HRS reversal (see Table 2), the Clinical Success rates showed a slightly larger treatment difference of 15% (terlipressin 63/199 [32%] vs placebo 17/101 [17%]).
- Efficacy data from the FDA Integrated Review are summarized in Table 2.

Table 2 Selected efficacy results from the CONFIRM trial, FDA Integrated Review

Outcome	Analysis Population	Terlipressin	Placebo	Relative Risk (95% CI)	Absolute Difference, %p (95% CI)
Primary Efficacy					
Verified HRS reversal to D14, n/N (%)	ITT	58/199 (29)	16/101 (16)	1.8 (1.1, 3.0)	13.3 (3.1, 22.2)
	Mitigated	48/132 (36)	13/71 (18)	2.0 (1.2, 3.4)	18.1 (5.0, 29.3)
Secondary Efficacy					
Verified HRS reversal without RRT to D30 (Durability of HRS reversal), n/N (%)	ITT	63/199 (32)	16/101 (16)	2.0 (1.2, 3.3)	15.9 (5.6, 24.8)
	Mitigated	51/132 (39)	13/71 (18)	2.1 (1.2, 3.6)	20.3 (7.1, 31.5)
Verified HRS reversal without HRS recurrence by D30, n/N (%)	ITT	48/199 (24)	16/101 (16)	1.5 (0.9, 2.5)	8.3 (–1.6, 17.0)
	Mitigated	38/132 (29)	13/71 (18)	1.6 (0.9, 2.8)	10.5 (–2.2, 21.5)
Exploratory Outcomes					
RRT-free survival to D90, n/N (%)	ITT	67/199 (34)	28/101 (28)	1.2 (0.8, 1.8)	6.0 (–5.3, 16.4)
	Mitigated	51/132 (39)	22/71 (31)	1.2 (0.8, 1.9)	7.6 (–6.3, 20.4)
All-cause Death to D90, n/N (%)	ITT	103/199 (52)	47/101 (47)	1.1 (0.9, 1.4)	5.3 (–6.6, 16.9)
	Mitigated	59/132 (45)	33/71 (46)	1.0 (0.7, 1.3)	1.8 (–12.2, 15.9)

Source: 6
%p, Percentage points; **CFB**, Change from baseline; **HRS**, Hepatorenal syndrome; **RRT**, Renal replacement therapy

- The anticipated absolute effects for achieving verified HRS reversal and verified HRS reversal without RRT are presented in Table 3.

Table 3 Absolute Effects for Achieving HRS Reversal

	Population	AAE, per 1000 pts (95% CI)	NNT (95% CI)	Q
Verified HRS reversal to D14	ITT	127 (16, 317) more	8 (5, 33)	M$^{\alpha\beta}$
	Mitigated	183 (37, 439) more	6 (4, 20)	L$^{\alpha\beta}$
Verified HRS reversal without RRT to D30	ITT	158 (32, 364) more	7 (4, 19)	M$^{\alpha}$
	Mitigated	201 (37, 476) more	5 (3, 14)	L$^{\alpha\beta}$

AAE, Anticipated absolute effect for achieving the outcome; **NNT**, Number needed to treat for one additional patient to benefit; **Q**, GRADE quality of evidence (M = Moderate; L = Low)
$^{\alpha}$ Downgraded for imprecision (wide CIs, optimal information size not met).
$^{\beta}$ Downgraded for risk of bias (the Mitigated Population was identified post hoc)

- Other Analyses
  - The terlipressin group had a numerically lower percentage of patients who underwent liver transplant within 90 days compared with the placebo group (23% vs 29%, respectively).[6]
- Subgroup Analyses
  - Terlipressin was significantly better (by 95% CIs) than placebo in patient subgroups with alcoholic hepatitis, baseline SCr ≥ 3.0 and < 5.0 mg/dL, and patients with systemic inflammatory response syndrome (SIRS).[6]
  - Terlipressin was ineffective in patient subgroups with absence of alcoholic hepatitis at baseline, baseline SCr < 3.0, baseline SCr ≥ 5.0, and baseline mean arterial pressure of < 70 mm Hg.[6]

Durability of Response

- Of 58 terlipressin patients who achieved verified HRS reversal, as many as 13 patients (22%), 10 of whom met HRS recurrence criteria and 3 of whom could not be excluded, may have experienced HRS recurrence by Day 30. None of 16 placebo patients were considered to have HRS recurrence.
- HRS recurrence was defined as "rapidly progressive worsening in renal function to a SCr of ≥ 2.25 mg/dL and meeting a trajectory for SCr to double over 2 weeks and without 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."[6]

Studies Comparing Off-label Continuous IV Infusions With IV Boluses

- Continuous IV infusions of terlipressin were originally explored by independent researchers because the reduction in portal pressure lasted only 3 to 4 hours after IV bolus dosing,[8,9] and early studies suggested that the total effective dose could be lower with continuous IV infusions than IV boluses, which could potentially reduce adverse effects.[10,11]
- The 2018 EASL guidelines on the management of decompensated cirrhosis states that continuous infusion of terlipressin can reduce the total dose of drug and the rate of adverse effects.[23]
- RCTs evaluating terlipressin continuous infusion relative to bolus doses are summarized in Table 4.

Table 4 Randomized clinical trials comparing terlipressin continuous infusions with bolus doses

Reference	Population / Design / Primary Objective	Terlipressin Regimens (N)	Results (CIVI vs IV bolus)
Cavallin, et al. (2016)[8]	• Cirrhosis, type 1 HRS • MC RCT • Assess safety	• 2 mg/d CIVI by pump; dose was progressively increased to 12 mg/d if SCr decreased by < 25% of baseline value. Dose was dissolved in 50 mL D5W. (N=39) • 0.5 mg Q4H IV bolus; progressively increased to 2 mg Q4H if SCr decreased by < 25%. (N=39) • Duration: Max. 15 d	• Rate of AEs was significantly lower with CIVI than IV bolus (20.6% of 34 pts vs 43.2% of 37 pts, respectively) • Treatment Response (total + partial response) was nonsignificantly higher with CIVI vs IV bolus • NSD in probability of 90-d LTP-free survival • Mean daily effective dose was lower with CIVI than IV bolus (2.23 vs 3.51 mg/d, respectively).
Ding, et al. (2013)[12]	• Portal HTN, TIPS • RCT • Assess hepatic and systemic hemodynamics	• 1 mg/d IV bolus then 4 mg/d CIVI (N=10) • 2 mg/d IV bolus then 1 mg Q6H (N=10)	• Portal venous pressure decreased in both groups, stabilized with CIVI vs rebounded with IV bolus. • HR at 1 h decreased by 9.6 vs 10.3 bpm ($p < 0.005$) • MAP increased (NSD)
Jha, et al. (2018)[13]	• EVH / AVB, portal HTN • RCT • Assess treatment failure (rebleeding or death) within 5 days of admission	• 1 mg IV bolus then 4 mg/d CIVI (N=43) • 2 mg/d IV bolus then 1 mg Q6H (N=43)	• Significantly lower rates of treatment failure (4.7% vs 20.7%), fresh hematemesis after endosocopic therapy, and death due to exsanguination with CIVI • WDAEs: Sinus bradycardia, persistent chest pain, systolic HTN
Guta, et al. (2020, abstract)[14]	• ACLF-AKI with no improvement in SCr after albumin x 48 h • OL RCT • Assess regression (full or partial response), stable/no response, and progression of AKI	• 2 mg/d CIVI (N=50) • 1 mg Q6H IV bolus (N=50) • Dose was increased to 12 mg/d if SCr decreased by < 25%	• NSD in regression of AKI and mortality • Mean dose (4 mg vs 8.5 mg) and AEs (0% vs 30%) were lower with CIVI • WDAEs: Lower rates with CIVI (abdominal pain, diarrhea, dyspnea, myocardial ischemia)

ACLF, Acute-on-chronic liver failure; AE, Adverse event; AKI, Acute kidney injury; AVB, Acute variceal bleeding; CIVI, Continuous IV infusion; EVH, Esophageal variceal hemorrhage; HRS, Hepatorenal syndrome; HTN, Hypertension; LTP, Liver transplant; MAP, Mean arterial pressure; NSD, No significant difference; OL, Open-label; TIPS, Transjugular intrahepatic portosystemic shunt; WDAE, Withdrawal due to adverse event

- Outpatient continuous terlipressin infusion as bridging therapy while awaiting liver transplant has shown promising benefits in observational studies.[15,16,17,18] There is insufficient evidence to inform appropriate use.

- Recommended off-label dose for terlipressin infusions: Initiate at 2 mg/d, increase dose in a step-wise manner (every 24–48 h) up to 12 mg/d if SCr decreases by < 25% from the peak value.[23,8]
- Dilution of terlipressin in 50–500 mL of 0.9% NaCl (normal saline [NS]), 5% dextrose (D5W) or 3.3% dextrose / 0.3% saline (DS) retains pH stability.[19]
- Mallinkrodt has no stability data for continuous infusions (Medical Information e-mail communication 14 Nov 2022).

Evidence Gaps

- Survival / Mortality: Further data are needed to verify the exploratory results suggesting potential benefit in RRT-free survival and lack of mortality benefit in the CONFIRM trial.

Safety Considerations

Respiratory Failure and Mitigation Criteria

- Terlipressin was associated with a higher incidence of the serious adverse event respiratory failure vs placebo (14% vs 5%, respectively).[6] Of the 28 events of respiratory failure SAEs, 17 (61%) resulted in death as compared with 1 death (20%) among 5 such SAE cases in placebo-treated patients.[6] Although plasma volume expansion with the pre-treatment use of albumin (albumin challenge) may be a contributing factor, the underlying mechanism is unclear.
- **Mitigation Criteria**. The manufacturer proposed a mitigation strategy to reduce the risk of serious or fatal respiratory failure. The strategy consisted of excluding patients who
    (1) have acute-on-chronic liver failure (ACLF) Grade 3,
    (2) have a SCr ≥ 5 mg/dL, and
    (3) are listed for liver transplant with a MELD score ≥ 35.[6]
- The rationale for these criteria are described below.
    - In CONFIRM, among patients with ACLF Grade 3 liver failure at baseline, terlipressin was worse than placebo in the risk of SAEs (30% vs 0%, respectively) and death due to respiratory failure (23% vs 0%, respectively).[6] Patients with ACLF Grade 3 liver failure also did not seem to benefit from terlipressin therapy vs placebo in terms of verified HRS reversal (18% vs 17%, respectively).
    - Among patients treated with terlipressin, the predicted probability of HRS reversal was lower in those with SCr ≥ 5 mg/dL at baseline than those with SCr < 5 mg/dL (9% vs 32%, respectively), although terlipressin still showed benefit vs placebo in the subgroup with most advanced renal failure (9% vs 0%, respectively).[6] Mortality up to Day 90 was also numerically higher in the terlipressin group than the placebo group among patients with SCr ≥ 5 mg/dL (61% vs 43%, respectively).
    - Patients listed for transplant with a MELD score ≥ 35 are most likely to receive an imminent liver transplant (the definitive treatment for type 1 HRS) and stand to be most at risk of losing transplant eligibility because of terlipressin adverse effects.
- In post hoc analyses, the Mitigated Population (i.e., randomized patients who did not meet the mitigation criteria) obtained benefits in HRS reversal and a lower risk of serious or fatal respiratory failure relative to the intent-to-treat population. Of the three criteria, exclusion of patients with ACLF Grade 3 contributed the most to the reduction in risk.[6] Further exclusion of patients using the other two criteria (SCr ≥ 5 mg/dL and listed for transplant with MELD ≥ 35) were expected to improve the benefit-risk profile of terlipressin therapy.
- The mitigation strategy was incorporated into the US Prescribing Information for terlipressin as follows:
    - In the Boxed Warning, patients with ACLF Grade 3 (or volume overload) are identified as being at increased risk for serious or fatal respiratory failure.

- A Limitation of Use advisory states that patients with SCr > 5 mg/dL are unlikely to benefit from terlipressin.
- There is a Warning / Precaution which states that the benefit-risk profile of terlipressin may not be favorable in patients at high priority for liver transplant, such as those with MELD scores ≥ 35.

Safety Profile from US Prescribing Information

- **Boxed Warnings**: Serious or fatal respiratory failure
- **Contraindications**: Hypoxia or worsening respiratory symptoms; ongoing coronary, peripheral, or mesenteric ischemia
- **Other Warnings / Precautions**:
  - Terlipressin-related adverse reactions may make a patient ineligible for liver transplantation if patient is listed for liver transplant.
  - Ischemic events
  - Embryofetal toxicity
- **Common Adverse Events (≥ 10%)**: Abdominal pain, nausea, respiratory failure, diarrhea, dyspnea.

Selected Safety Findings from the CONFIRM Trial

Deaths

- The incidence of total deaths up to Day 90 in the Safety Population were numerically higher in the terlipressin group than the placebo group (102/200, 51.0% vs 44/99, 44.4%).[6] Rates of deaths were similar between the two treatment groups in the Mitigated Population (61/132, 46.2% vs 32/71, 45.1% for terlipressin vs placebo, respectively).[6]
- The most common cause of death was hepatic disorder. Acute respiratory failure / respiratory failure was reported as the cause of death in more terlipressin-treated patients than placebo patients in the Safety Population (9.0% vs 1.0%) and the Mitigated Population (6.1% vs 1.4%). A similar pattern was seen for acute renal failure in the Safety Population (2.0% vs 0.0%) and the Mitigated Population (3.0% vs 0.0%).
- The mean time from start of the study to death was 3 days longer in the terlipressin group vs placebo group (22 vs 19 days, respectively) of the Safety Population and was 6 days longer in the Mitigated Population (26 vs 20 days, respectively).

Serious Adverse Events (SAEs)

- The incidence of SAEs up to Day 30 was slightly higher in the terlipressin group than the placebo group in both the Safety Population (65.0% vs. 60.6%, respectively) and the Mitigated Population (61.4% vs 59.2%, respectively).
- The most common SAE was hepatic disorders, which occurred at a lower rate in the terlipressin group than the placebo group in both the Safety Population (25.0% vs 33.3%, respectively) and the Mitigated Population (23.5% vs 32.4%, respectively).
- All other SAEs up to Day 30 occurred numerically more frequently on terlipressin than placebo in both the Safety Population and the Mitigated Population. These SAEs were acute respiratory failure / respiratory failure, sepsis / septic shock, gastrointestinal hemorrhage, abdominal pain / vomiting, hemodynamic edema / effusions and fluid overload, and intestinal ischemia.

Fluid Overload-related Adverse Events

- Hemodynamic edema, effusions, and fluid overload occurred more frequently on terlipressin than placebo: 55/200 (27.5%) vs 16/99 (16.2%), respectively.[5]

Withdrawals Due to Adverse Events

- The rate of withdrawals due to adverse events excluding death was numerically higher in the terlipressin group than the placebo group: 19/199 (10%) vs 4/101 (4%).

- In a network meta-analysis (NMA), a median of 8% (range, 4–22) of patients discontinued terlipressin because of serious adverse events.[20]

Other Therapeutic Options

- The pharmacologic treatment to reverse hepatorenal syndrome acute kidney injury (HRS AKI) consists of combined use of colloidal albumin for volume expansion and a vasoconstrictor to counteract splanchnic vasodilation. Vasoconstrictors improve kidney function in 20%–80% (average ~50%) of patients with HRS AKI.[21] In one meta-analysis, any vasoconstrictor reduced the relative risk of mortality by 27% for every 1 mg/dL decrease in SCr.[22] Patients who fail medical therapy may be considered for transjugular intrahepatic portosystemic shunt (TIPS) or continuous renal replacement therapy (RRT) / dialysis as a bridge to liver transplantation or liver recovery if the liver injury is reversible.
- According to the European Association for the Study of the Liver (EASL) practice guidelines, terlipressin should be considered as the first-line therapy of HRS acute kidney injury (AKI).[23]
- In 2021, the American Association for the Study of Liver Diseases (AASLD) published a practice guidance developed by expert consensus and a comprehensive literature review on topics. The practice guidance replaced the 2012 AASLD *Guidelines* which were developed through systemic literature reviews, rating of evidence quality, and strength of recommendations. The general steps in systemic drug therapy of acute kidney injury in patients with hepatorenal syndrome according to the 2021 Practice Guidance by the AASLD[21] are shown in Table 5.

Table 5 Systemic Pharmacotherapies for Hepatorenal Syndrome Acute Kidney Injury: Evidence Summary and 2021 Practice Guidance by the American Association for the Study of Liver Diseases (AASLD)

Drug Class	Treatment Alternative	AASLD Place in Therapy	Comparative Efficacy / Safety	Issues for Consideration
Colloids	Albumin 1 g/kg (maximum of 100 g) on D1 then 20–40 g/d for the duration of terlipressin therapy	Infuse concomitantly with terlipressin.		Used for volume expansion and antioxidant, immunomodulating, and endothelial stabilizing effects. Dosage in HRS is not well established.
Vasoconstrictors	**Terlipressin** 0.85 mg slow IV push Q6H on D1–D3. If < 30% reduction in SCr occurs by D4, increase to 1.7 mg Q6H. Refer to US PI for details.	Considered the preferred vasoconstrictor, given either as an IV bolus or continuous IV infusion, in combination with albumin.	Similar to **norepinephrine** in reversing HRS,[21,24,25] and reducing mortality,[20,25,26] and was associated with either more adverse effects[26] or a similar rate of adverse effects.[20] Better than[20] or similar to[25] **norepinephrine** in reducing HRS recurrence after discontinuation of therapy. Significantly better than **octreotide** in reversing HRS (55% vs 20%).[26] Similar to **dopamine** in 24-h urine output and plasma renin	V1 and V2 receptor agonist; systemic and splanchnic vasoconstrictor. An NMA trial-sequential analysis showed that only the comparison between terlipressin / albumin and albumin was robust against error, whereas norepinephrine / albumin vs albumin could represent a type I error.[28] In an NMA, terlipressin increased HRS reversal vs placebo in patients with HRS type 1 (absolute risk difference 142 more per 1,000; 95% CI 87.7 to 210.9 more; high quality evidence).[29] Terlipressin

Drug Class	Treatment Alternative	AASLD Place in Therapy	Comparative Efficacy / Safety	Issues for Consideration
			activity and 1-month mortality.[26] Significantly more effective than **midodrine + octreotide** in reversing HRS / renal failure[20] and improving renal function.[27] Similar in adverse effects.[20] In **type 1 HRS** patients, similar to **norepinephrine** in reversing HRS.[25,26] In **type 2 HRS** patients, **terlipressin / albumin** was not significantly different from albumin.[28]	reduced mortality (–93.7; –168.7, –12.5; low quality evidence) and had a nonsignificant increase in serious adverse events (20.4; –5.1 to 51; low quality evidence).[29] *Advantages*: Unlike norepinephrine, use of terlipressin does not require a central line or ICU admission. Terlipressin has more robust data than norepinephrine.
	Norepinephrine 0.5–3 mg/h continuous infusion	Should be given if terlipressin is not available. Requires placement of a central line and cardiac monitoring in an ICU. Give in combination with albumin.	Seems to be similar to **terlipressin** in HRS reversal.[26,30] More effective than[20] or similar to[25] **midodrine + octreotide**.	Alpha-1 adrenergic agonist; systemic vasoconstrictor.[31] No placebo-controlled RCTs[31] but norepinephrine / albumin was shown to be more effective than albumin in mixed treatment comparisons.[28] In HRS type 1, norepinephrine trials are small and nonblinded.[32] In an NMA of studies in patients with HRS type 1, norepinephrine had low quality evidence of improving HRS reversal, very low quality evidence of having a nonsignificant effect on mortality, and very low quality evidence of reducing serious adverse effects relative to placebo.[29]
	Midodrine 7.5–12.5 mg PO TID + Octreotide 100–200 mcg SC Q8H or 50 mcg/h continuous IV infusion	Consider midodrine + octreotide if neither terlipressin nor norepinephrine is available. Give in combination with albumin.	Inferior to terlipressin.	Midodrine is a systemic vasoconstrictor and octreotide is a splanchnic vasoconstrictor.[31] Slow onset; may take weeks for onset of renal response. An SRMA showed no significant differences between midodrine + octreotide vs placebo in HRS reversal, mortality, and serious adverse events

Drug Class	Treatment Alternative	AASLD Place in Therapy	Comparative Efficacy / Safety	Issues for Consideration
				in patients with HRS type 1 (very low quality of evidence for each outcome).[29]
	Vasopressin	Not mentioned.		Retrospective cohort studies. No RCTs.[29] Similar mechanism, shorter acting vs terlipressin.[29]
	Dopamine + Furosemide	Not mentioned.		

Source: 21
NMA, Network meta-analysis; SRMA, Systematic review / Meta-analysis

Other Potential Off-label Uses of Terlipressin

- **Acute variceal bleed**: Terlipressin is approved outside the US for this indication and is reportedly the only vasoactive drug shown to reduce mortality, rebleeding rate, and need for blood transfusions.[1,33] Terlipressin was shown to be better than vasopressin in controlling variceal bleeding,[34,35] better than placebo in reducing mortality,[36,37] and similar to somatostatin[38,39,40] and octreotide[40,41] in controlling bleeding. A network meta-analysis of 50 RCTs (37 RCTs and 4628 patients for primary analysis) showed that terlipressin was the only vasoconstrictor to reduce mortality vs placebo (OR 0.2; 95% CI 0.1, 0.8 in direct treatment comparison) and the only treatment to significantly reduce the risk of re-bleeding vs placebo (0.36; 0.13, 0.99).[33] The quality of evidence was very low. The authors concluded that terlipressin may be the best vasoconstrictor to control acute variceal bleeding, and somatostatin and vasopressin could be used as alternatives if terlipressin is unavailable; however, further studies are needed for confirmation.
- **Septic shock** (open-label RCT, N = 84)[42]
- **Paracentesis-induced circulatory dysfunction** (two pilot RCTs, N = 20 and 40)[43,44]
- **AKI in living donor liver transplant** (6 RCTs, range of N: 30–80)[45,46,47,48,49] and a retrospective case-control study (N = 303)[50]
- **Liver transplant outcomes** (1 retrospective cohort study, N = 82)
- **ACLF HRS**: One RCT (N = 120) showed terlipressin was better than norepinephrine in rates of HRS reversal and 28-day survival and reduced need for RRT.[51]

Projected Place in Therapy

- **Epidemiology and Prevalence of Hepatorenal Syndrome in Veterans**. Hepatorenal syndrome is a serious type of acute kidney injury conventionally considered to be functional kidney failure associated with liver disease without kidney abnormality or intrinsic kidney disease. Its causes include severe peripheral vasodilation, which triggers renal vasoconstriction, reduction in renal blood flow, low urine output and sodium retention. Newer theories suggest that hepatorenal syndrome may also be due to inflammation, which can cause direct tubular injury. Traditionally there were two types of hepatorenal syndrome. Type 1 hepatorenal syndrome referred to a more rapid reduction in kidney function; i.e., the serum creatinine increased at least twofold to greater than 2.5 mg/dL in less than 2 weeks. Type 2 hepatorenal syndrome was characterized by less rapid progression of kidney injury. The classification was revised to diagnose and initiate treatment at an earlier stage of renal impairment. Type 1 hepatorenal syndrome currently compares to hepatorenal syndrome acute kidney injury (HRS AKI) and type 2 hepatorenal syndrome now corresponds to renal impairment meeting criteria for HRS but not AKI (non-AKI-HRS or NAKI), and only

HRS-chronic kidney disease (HRS-CKD).[23] The International Club of Ascites (ICA) redefined AKI in patients with cirrhosis as an increase in SCr of ≥ 0.3 mg/dL within 2 days or an increase in SCr by ≥ 50% that was known or presumed to have occurred in the previous 7 days.[23] HRS is the subset of AKI characterized by no response to volume resuscitation alone. HRS-AKI affects about 30,000 to 40,000 Americans per year. Patients with cirrhosis and ascites have been estimated to have an 18% probability of developing HRS-AKI at 1 year.[52] Untreated HRS-AKI has a poor prognosis, with a median survival of 2 to 4 weeks[53,54] and more than 80% mortality within 3 months.[55] In VHA, 845 patients had an ICD-10 diagnosis of hepatorenal syndrome in FY22.

- **Potential Place in Therapy Based on the Evidence**. The results of the CONFIRM trial, other RCTs (including head-to-head trials) evaluated in network meta-analyses, more than 30 years of clinical experience in non-US countries, and clinical practice guidelines[23,21] support the use of terlipressin (in combination with albumin) as the preferred treatment in patients with type 1 HRS / HRS AKI. The CONFIRM trial results affirmed that, in patients with type 1 HRS, terlipressin significantly improved the rates of verified HRS reversal and verified HRS reversal without RRT to 1 month after initiation of therapy. While the CONFIRM trial did not show that terlipressin improved clinical outcomes of survival or reduced mortality, the FDA noted that the data trends suggested that terlipressin could reduce resources needed to care for HRS patients, namely ICU time, renal replacement therapy, and liver transplantation, although the FDA Advisory Committee found these data difficult to interpret for various reasons.[5] A network meta-analysis of the CONFIRM trial and other terlipressin RCTs showed therapy reduced mortality (low quality evidence). The survival and mortality effects and a numerically lower percentage of liver transplant with terlipressin need confirmation. In CONFIRM, terlipressin increased the risk of all-cause death and serious or fatal respiratory failure. In a retrospective analysis, these risks were reduced to placebo-comparable rates in patients without certain risk factors for respiratory failure (i.e., the Mitigated Population). The profile of patients considered most likely to experience greater benefit than harm are those identified in the US Prescribing Information; specifically, patients who (1) do NOT have an ACLF Grade of 3; (2) do NOT have a SCr ≥ 5 mg/dL; and (3) are NOT listed for liver transplant with a MELD score ≥ 35. Based on network meta-analyses, terlipressin is similar to norepinephrine in reversing HRS and reducing mortality but inconsistent findings suggest that terlipressin might be better than or similar to norepinephrine in reducing HRS recurrence and might be associated with a higher or similar rate of adverse effects. Continuous IV infusion of terlipression reduces the rate of adverse effects; however, it is unclear how terlipressin continuous infusions compare with norepinephrine infusions in safety in HRS. One of the major disadvantages of terlipressin therapy is that response to terlipressin may decrease the MELD score and disadvantage patients waiting for liver transplant, which is definitive treatment for cirrhosis. On the other hand, nonresponse to terlipressin may increase the risk of severe AKI and need for RRT and increase progression to CKD following liver transplant. Although the CONFIRM trial patients met the former criteria for type 1 HRS and it is unclear what percentage of the study patients meet the current definition of HRS AKI, the prescribing information profiles the type of patients appropriate for terlipressin as those with HRS with “rapid reduction in kidney function” and does not specify a timeframe or magnitude of SCr changes.
- **Potential Place in Therapy in VHA**. Terlipressin offers the option of administration via a peripheral line and a greater certainty of hepatorenal syndrome reversal relative to norepinephrine. Terlipressin administered by IV bolus or continuous IV infusion may be used in conjunction with albumin for the treatment of patients with hepatorenal syndrome with rapid reduction in kidney function. The use of terlipressin should follow the recommended guidance described in the US prescribing information. A continuous IV infusion of norepinephrine is an acceptable and less costly alternative but often requires that patients have a central line and be admitted to an intensive care unit for monitoring.

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