Terlipressin (TERLIVAZ)
in Hepatorenal Syndrome with Acute Kidney Injury
Criteria for Use
March 2023

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at the *PBM INTRAnet* site for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive terlipressin.

- ☐ Acute-on-chronic liver failure grade 3 (any 3 of bilirubin > 12 mg/dL, SCr ≥ 3.5 or renal replacement, encephalopathy grade 3–4, INR ≥ 2.5, vasopressor for MAP < 70 mm Hg; or PaO_2/FiO_2 ratio ≤ 200, SpO_2/FiO_2 ratio ≤ 214 or intubated)
- ☐ SCr > 5 mg/dL
- ☐ Listed for liver transplant with MELD ≥ 35
- ☐ Hypoxia (e.g., SpO_2 < 90%) or worsening respiratory symptoms. May use terlipressin once oxygenation improves.
- ☐ Ongoing signs or symptoms of coronary, peripheral, or mesenteric ischemia
- ☐ History of severe cardiovascular conditions, cerebrovascular and ischemic disease

Inclusion Criteria

All of the following criteria must be met.

- ☐ Hospitalized inpatient
- ☐ Documented initial nonresponse to volume expansion (e.g., albumin)
- ☐ Documented diagnosis of hepatorenal syndrome with acute kidney injury made by a VA expert in GI / hepatology, nephrology, intensive care, or liver transplant surgery

Other Justification

- ☐ _____

Supplemental Information

This supplemental information is provided to assist in adjudication of requests for terlipressin.

Orders for terlipressin must be processed as urgent requests and the drug dispensed within 3 hours.

Section	Criterion	Issues for Consideration
Exclusion Criteria	Acute-on-chronic liver failure grade 3 (any 3 of bilirubin > 12 mg/dL, SCr ≥ 3.5 or renal replacement, encephalopathy grade 3–4, INR ≥ 2.5, vasopressor for MAP < 70 mm Hg; or PaO_2/FiO_2 ratio ≤ 200, SpO_2/FiO_2 ratio ≤ 214 or intubated)	Based on the CLIF-C Organ Failure Score, consistent with the CONFIRM trial protocol.
Inclusion Criteria	Documented diagnosis of hepatorenal syndrome with acute kidney injury made by a VA expert in GI / hepatology, nephrology, intensive care, or liver transplant surgery Documented initial nonresponse to volume expansion (e.g., albumin)	Diagnosis of hepatorenal syndrome with acute kidney injury (HRS-AKI) can be complex. It is reasonable to allow some latitude in the use of terlipressin for a *potential* or working diagnosis of HRS-AKI. Albumin volume challenge is recommended as part of the diagnostic workup for HRS-AKI to distinguish between volume-responsive and volume unresponsive acute renal failure (ARF) / AKI. HRS-AKI is a type of volume unresponsive ARF / AKI. A typical presentation of HRS-AKI includes ascites, hyponatremia, and low mean arterial pressure (MAP < 70). Use of terlipressin for an atypical presentation of HRS-AKI may be considered if any of the listed specialists considers HRS to be the most likely diagnosis. Use of terlipressin for an uncertain diagnosis of hepatorenal syndrome (HRS) or as a "therapeutic trial" cannot be recommended.
	Hospitalized inpatient	Terlipressin administered at home as a continuous IV infusion has been used as a bridge to liver transplant in lieu of renal replacement therapy. There is insufficient evidence to support its routine use at this time. Requests for outpatient use of terlipressin should be adjudicated case by case. Unlike norepinephrine, which requires placement of a central venous catheter and admission to an ICU, terlipressin may be given via a peripheral line in non-ICU settings.
Miscellaneous Information	If concomitant albumin is used as an adjunct to terlipressin therapy, VHA experts advise that albumin doses should preferably not exceed 50 g/d. Co-use of albumin for volume expansion is NOT a requirement for use of terlipressin.	In the CONFIRM trial, concomitant albumin was only strongly recommended if clinically indicated, not absolutely required. Only 87% of patients received concomitant albumin. Virtually all patients (>=99%) had received the pre-treatment albumin challenge. Larger cumulative amounts of albumin were a risk factor for respiratory failure. VHA experts were concerned that requiring concomitant daily albumin with terlipressin may increase the risk of fluid overload and respiratory complications. Therefore, concomitant albumin is NOT a requirement to use terlipressin. The optimal dose of albumin in HRS-AKI has not been established. For reference, the albumin dosage used in the CONFIRM trial was 1 g/kg/d to a maximum of 100 g/d on Day 1 then 20 to 40 g/d until terlipressin is discontinued. However, because of the probable contribution of IV albumin in the development of pulmonary edema / respiratory failure in this trial, **doses of albumin should preferably not exceed 50 g/day and should be held if there is evidence of volume overload, hypoxemia and/or serum albumin levels >3.5 g/dL**.
	Adequate Therapeutic Trial	Terlipressin should be discontinued if there is no response by Day 4. No response means the SCr is at or above the baseline value. Maximum 14 days of therapy.

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