Treatment-Related Cost Analysis of Terlipressin for Adults with Hepatorenal Syndrome with Rapid Reduction in Kidney Function

Huang X, Bindra J, Chopra I, Niewoehner J, Wan G. Treatment-Related Cost Analysis of Terlipressin for Adults with Hepatorenal Syndrome with Rapid Reduction in Kidney Function. *Adv Ther.* 2023;40(12):5432-5446. doi:10.1007/s12325-023-02674-z.

Funding to support this study was provided by Mallinckrodt Pharmaceuticals.

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.

SELECT IMPORTANT SAFETY INFORMATION

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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Terlivaz®
terlipressin for injection

STUDY OBJECTIVE

The objective was to estimate the cost associated with TERLIVAZ® (terlipressin) + albumin and other unapproved treatments (including midodrine and octreotide + albumin and norepinephrine + albumin) for adult patients with hepatorenal syndrome (HRS) with rapid reduction in kidney function and the projected cost per HRS reversal or complete response from a US hospital perspective.

SELECT IMPORTANT SAFETY INFORMATION

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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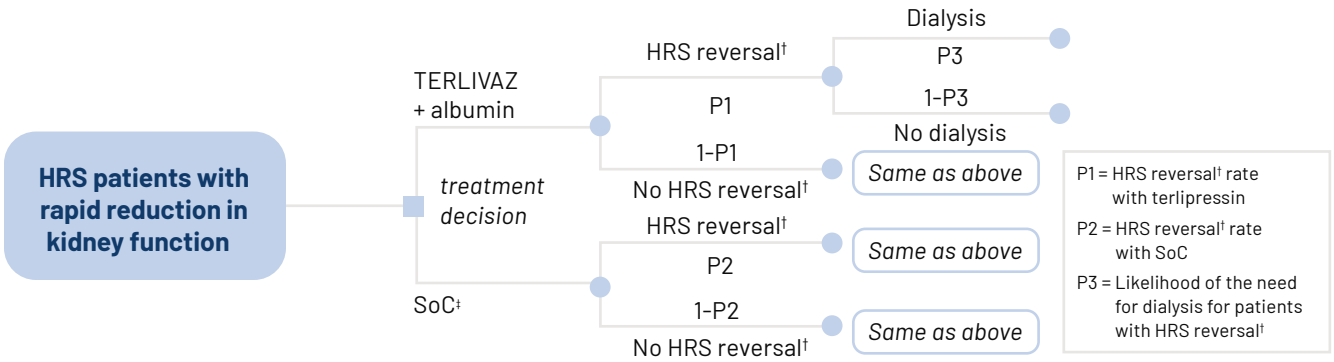
STUDY DESIGN

Study Design*:

- A decision-analytic model was developed to estimate the HRS treatment-related cost per response over an HRS hospitalization (assuming 14 days) from the US hospital perspective.
- Patients can experience either HRS reversal (complete response) or no HRS reversal (partial/no response) upon receipt of either TERLIVAZ® (terlipressin) + albumin vs. midodrine and octreotide + albumin or norepinephrine + albumin.
- Efficacy, safety, and treatment duration data were derived from published head-to-head randomized international trials.

Schematic of the Decision-Analytic Model for Cost of Care Analysis (CoCA)



*The study evaluated the estimated cost per response, defined as total treatment cost per HRS reversal.

†HRS reversal or complete response is defined as decrease in serum creatinine from baseline to ≤1.5 mg/dL on treatment (up to 24 hours after the last treatment dose). In the CONFIRM trial, complete response (other prespecified endpoint) was defined as a return of serum creatinine (SCr) ≤0.3 mg/dL of the baseline value.[1]

‡SoC, standard of care (midodrine and octreotide + albumin or norepinephrine + albumin).

Methods and Assumptions:

Factors used to determine estimated cost per response included*:

- **Efficacy or level of treatment response:** HRS reversal or complete response is defined as a decrease in serum creatinine from baseline to ≤1.5 mg/dL on treatment (up to 24 hours after last treatment dose) or no HRS reversal (partial/no response)
- **Cost per response:** Total treatment cost per HRS reversal was estimated for each treatment
- **Total treatment costs:** Costs related to drug acquisition, intensive care unit (ICU) stay, continuous pulse oximetry, dialysis, and adverse events
- **Number needed to treat (NNT):** Number of patients treated to achieve HRS reversal in 1 additional patient was estimated for each treatment

Cost components include:

- Drug acquisition costs (daily treatment cost x average number of treatment days)†
- ICU-related costs‡
- Dialysis-related costs
- Continuous pulse oximetry (for TERLIVAZ group only)§
- Adverse-event-related costs

Model assumptions based on analysis of previously performed clinical studies:

- 85% of TERLIVAZ + albumin patients treated on the general floor
- 85% of midodrine and octreotide + albumin patients treated on the general floor
- 0% of norepinephrine + albumin patients treated on the general floor

*Estimations made using clinical trial data, costs available in published literature, and healthcare databases.

†Assumed 8.2 and 9.1 days of treatment for TERLIVAZ vs. midodrine and octreotide, respectively; assumed 7.8 and 9.3 days of treatment for TERLIVAZ vs. norepinephrine, respectively.

‡Assumed % of patients treated in ICU: 15% of TERLIVAZ; 15% of midodrine and octreotide; 100% of norepinephrine.

§Continuous pulse oximetry monitoring is required during TERLIVAZ administration.

SELECT IMPORTANT SAFETY INFORMATION

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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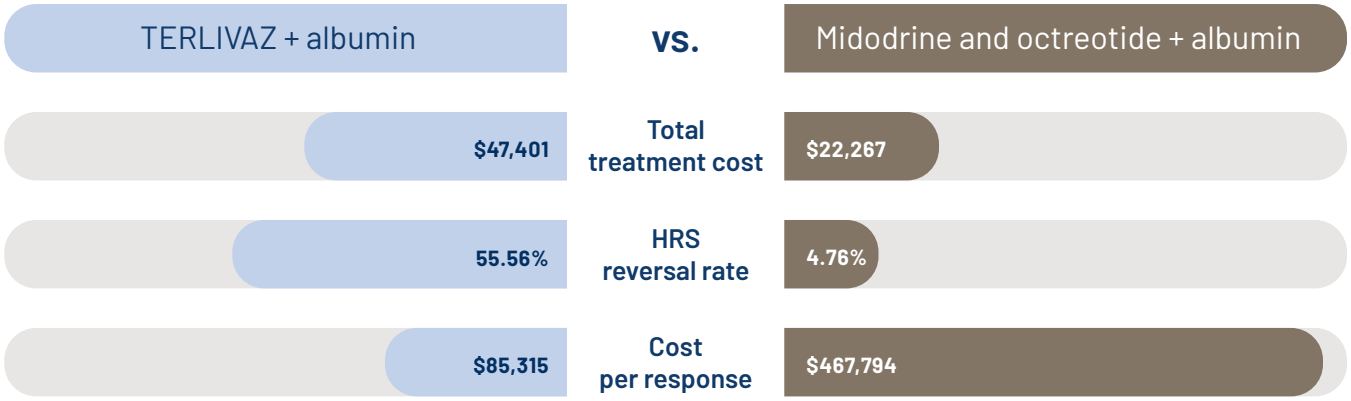
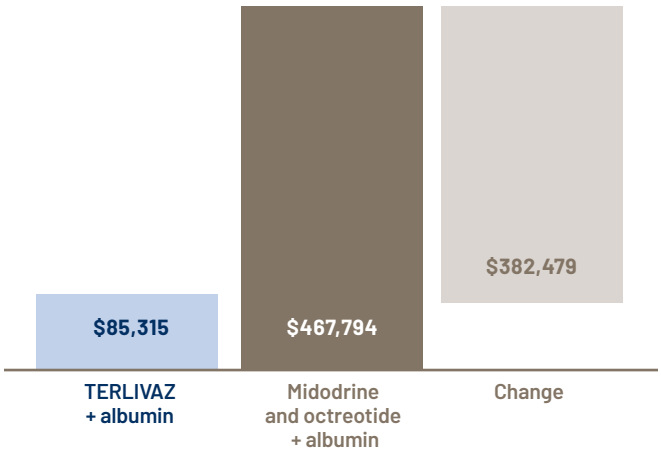
RESULTS

Estimated Cost Per Response: TERLIVAZ® (terlipressin) Regimen vs. Midodrine and Octreotide Regimen*



*Total treatment cost per response TERLIVAZ + albumin regimen vs. midodrine and octreotide regimen (albumin was included as part of treatment regimens).

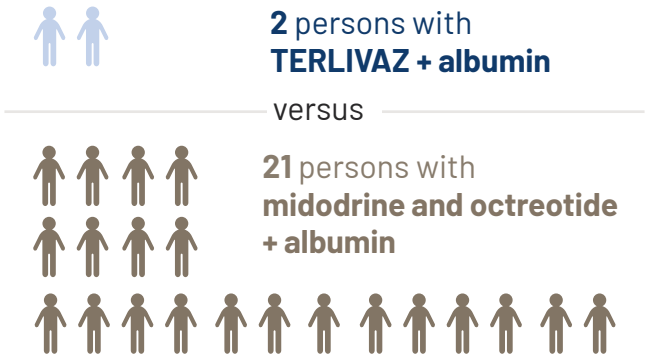
Estimated Cost Per Response: TERLIVAZ Regimen vs. Midodrine and Octreotide Regimen†



†Total treatment costs comprised costs related to drug acquisition, ICU stay, continuous pulse oximetry, dialysis, and adverse events.

Number Needed to Treat‡

Two patients needed to be treated with TERLIVAZ + albumin to achieve one additional HRS reversal vs. 21 patients who needed to be treated with midodrine and octreotide + albumin.



‡The number of patients treated to achieve HRS reversal in 1 additional patient (NNT) was estimated for each treatment.

SELECT IMPORTANT SAFETY INFORMATION

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.

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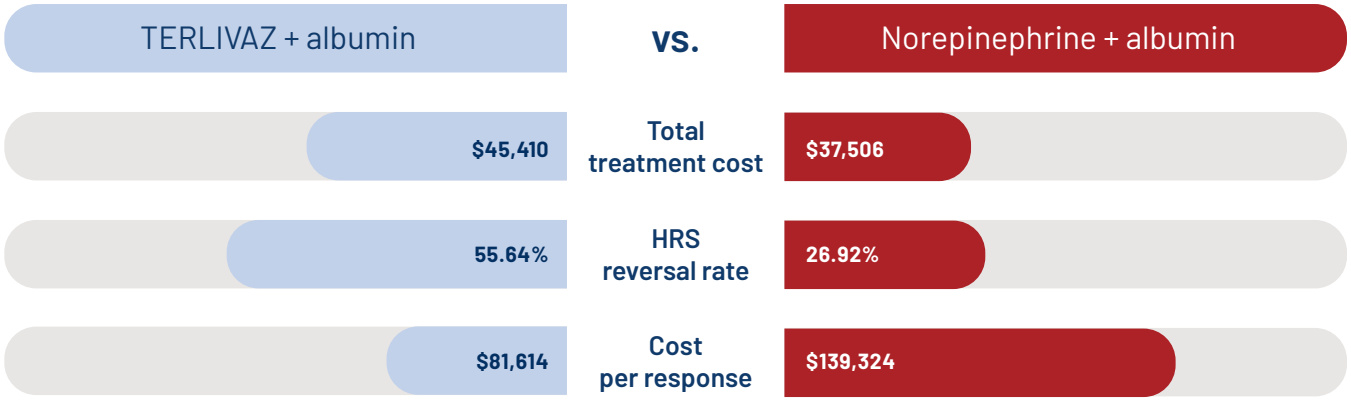
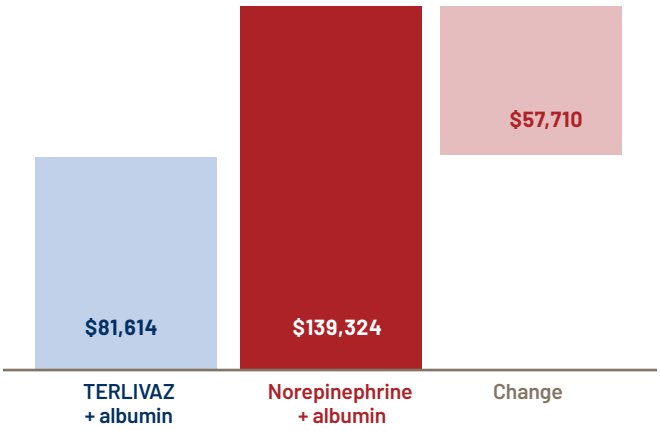
RESULTS

Estimated Cost Per Response: TERLIVAZ® (terlipressin) Regimen vs. Norepinephrine Regimen*



*Total treatment cost per response TERLIVAZ vs. norepinephrine regimen (albumin was included as part of treatment regimens).

Estimated Cost Per Response: TERLIVAZ Regimen vs. Norepinephrine Regimen†



†Total treatment costs comprised costs related to drug acquisition, ICU stay, continuous pulse oximetry, dialysis, and adverse events.

Number Needed to Treat‡

Two patients needed to be treated with TERLIVAZ + albumin to achieve one additional HRS reversal vs. four patients who needed to be treated with norepinephrine + albumin.

‡The number of patients treated to achieve HRS reversal in 1 additional patient (NNT) was estimated for each treatment.

SELECT IMPORTANT SAFETY INFORMATION

Warnings and Precautions (cont'd)

- **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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STUDY LIMITATIONS

- Efficacy and treatment-related adverse event data are from published head-to-head randomized clinical trials (terlipressin + albumin vs. midodrine and octreotide + albumin or terlipressin + albumin vs. norepinephrine + albumin), which may not be generalizable to the adult HRS population in the US.
  - Furthermore, verified HRS reversal,* primary endpoint of the CONFIRM trial, was not used in this analysis.
- Treatment-related adverse event data used in this analysis are also from the aforementioned published randomized clinical trials, which are different from the adverse events in the FDA-approved TERLIVAZ® (terlipressin) label. The estimated cost for each adverse event is based on the MarketScan database and may be different from a hospital's/institution's experience.
- Several assumptions were used in the analysis, including the number of patients treated on a general floor with midodrine and octreotide + albumin or norepinephrine + albumin.
- Cost data from public sources (Micromedex Solutions, Medicare payment schedule, and literature) may be different from the actual costs of a hospital/institution. Drug costs do not reflect discounts and/or rebates offered by manufacturers.
- Analysis focuses on treatment-related cost of care over 14 days, however, the cost of kidney transplantation, transjugular intrahepatic portosystemic shunt (TIPS), or liver transplantation during the initial hospitalization (from hospital admission to discharge) is not considered.
- Due to the short time horizon, other mid- and long-term benefits of HRS reversal are not captured, including the reduced need for dialysis, kidney transplantation, and better outcomes post-liver transplantation.
- The requirement of dialysis by treatment response (HRS reversal vs. no HRS reversal) estimated based on pooled data of three randomized clinical trials (CONFIRM, REVERSE, and OT0401) may be different from a hospital's/institution's experience.
- The duration of ICU stays by treatment response generated based on the CONFIRM trial may be different from a hospital's/institution's experience.
- The average treatment dose and duration were based on the clinical practice; no sensitivity analyses were performed for the maximum dose and duration. However, considerable changes in costs are not anticipated.

*Two consecutive serum creatinine measurements of 1.5 mg/dL or less at least 2 hours apart up to day 14 and survival without renal-replacement therapy for at least an additional 10 days.[1]

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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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THE AUTHORS CONCLUDED

- **Based on this CoCA, TERLIVAZ® (terlipressin) + albumin was associated with a lower cost per HRS reversal than midodrine and octreotide + albumin or norepinephrine + albumin.**
- **These findings suggest that TERLIVAZ is a cost-effective treatment due to its higher efficacy and administration in the non-ICU setting.**
- **In this CoCA study, TERLIVAZ was shown to be a cost-effective, value-based treatment option for appropriate adults with HRS with rapid reduction in kidney function.**

Reference:

1. Wong F, Pappas SC, Curry MP, et al. Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome. *N Engl J Med*. 2021;384(9):818-828. doi:10.1056/NEJMoa2008290.

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Mallinckrodt Pharmaceuticals