NEW DRUG APPROVAL

Brand Name	Terlivaz®
Generic Name	terlipressin
Drug Manufacturer	Mallinckrodt Hospital Products Inc

New Drug Approval

FDA Approval Date: September 14, 2022

Review designation: Priority; Orphan

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 022231

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Hepatorenal syndrome (HRS) is a multiorgan condition affecting the kidneys and the liver. It is a cause of acute kidney injury that can be seen in those with acute or chronic liver disease. Research revealed that renal failure in liver cirrhosis was functional. This was demonstrated in patients with hepatorenal syndrome with normal kidney histology in addition to the absence of proteinuria. This was further demonstrated clinically when kidneys from patients with HRS were transplanted into those with chronic kidney disease as well as the improvement of renal function in liver cirrhosis patients who underwent a liver transplant. Further research investigating renal clearance established the association of renal vasoconstriction in HRS. Hepatorenal syndrome has two types. Type 1 is characterized by rapid and progressive decline in renal function defined by doubling of the serum creatinine to at least greater than 2.5 or a decrease in the creatinine clearance by half or more over a two-week period. This is usually associated with a urine output of less than 500mL/day, a normal urine sediment and a low urinary sodium excretion. Type 2 typically involves less severe kidney injury, and patients ordinarily present with diuretic-resistant ascites. Other apparent causes of acute kidney injury need to be excluded, including pre-renal, nephrotoxic drugs, obstructive nephropathy, and renal parenchymal disease.

The incidence of hepatorenal syndrome in patients with decompensated liver disease is approximately 4%. Most of these patients have portal hypertension from alcoholic hepatitis, cirrhosis, or metastatic cancers. The cumulative probability of developing HRS at 1 year is 18% and at 5 years is 39% in patients with decompensated liver disease. The highest risk patients were those with hyponatremia and high plasma renin activity. One third of patients that have spontenous bacterial pertionitis can go on to develop HRS.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Efficacy

The efficacy of Terlivaz® was assessed in a multicenter, double-blind, randomized, placebo-controlled study (CONFIRM) (NCT02770716). Patients with cirrhosis, ascites, and a diagnosis of HRS-1 with a rapidly progressive worsening in renal function to a serum creatinine (SCr) ≥2.25 mg/dL and meeting a trajectory for SCr to double over two weeks, and without sustained improvement in renal function (7.0 mg/dL, shock, sepsis, and/or uncontrolled bacterial infection were excluded from the study. Use of vasopressors was prohibited during the treatment period. A total of 300 patients were enrolled; the median age was 55 years (range: 23 to 82), 60% were

male, and 90% were White. At baseline, 40% had alcoholic hepatitis and 19% had ACLF Grade 3; the mean serum creatinine was 3.5 mg/dL, and the mean MELD score was 33.

Patients were randomized 2:1 to treatment with Terlivaz® (N=199) or placebo (N=101). Patients received 1 mg terlipressin acetate (equivalent to Terlivaz® 0.85 mg) or placebo every 6 hours administered as an IV bolus injection over 2 minutes for a maximum of 14 days. On Day 4 of therapy, if SCr decreased by less than 30% from the baseline value, the dose was increased to 2 mg terlipressin acetate (equivalent to Terlivaz® 1.7 mg) every 6 hours. If SCr was at or above the baseline value on Day 4, then treatment was discontinued. Both treatment groups received albumin therapy during the study (median dose 50 g/day). Concomitant diuretics were used in 26% of patients treated with Terlivaz® and 13% of patients treated with placebo. Median treatment duration was 5 days for Terlivaz®-treated patients and 4 days for placebo-treated patients. The primary efficacy endpoint was the incidence of Verified HRS Reversal, defined as the percentage of patients with 2 consecutive SCr values of ≤1.5 mg/dL, obtained at least 2 hours apart while on treatment by Day 14 or discharge. To be included in the primary efficacy endpoint analysis, patients had to be alive and without intervening renal replacement therapy (e.g., dialysis) at least 10 days after achieving Verified HRS Reversal.

Table 1: A greater proportion of patients achieved Verified HRS Reversal in the Terlivaz® arm compared to the placebo arm

Efficacy Analyses	Terlivaz® N = 199	Placebo N = 101	P value
Verified HRS Reversal[†], n (%) 95% CI	58 (29.1) (0.2, 0.4)	16 (15.8) (0.1, 0.2)	0.012
Durability of HRS Reversal[a,b], n (%) 95% CI	63 (31.7) (0.3, 0.4)	16 (15.8) (0.1, 0.2)	0.003
Incidence of HRS Reversal[a] in the Systemic Inflammatory Response Syndrome (SIRS) Subgroup, n (%) 95% CI	N=84 28 (33.3) (0.2, 0.4)	N=48 3 (6.3) (0.0, 0.1)	<0.001
Incidence of Verified HRS Reversal without HRS Recurrence by Day 30, n (%) 95% CI	48 (24.1) (0.2, 0.3)	16 (15.8) (0.1, 0.2)	0.092

†Primary endpoint
CI = confidence interval
[a] Patients with a SCr value of not more than 1.5 mg/dL while on treatment, by Day 14, or discharge.
[b] Patients with HRS Reversal without renal replacement therapy to Day 30.

Safety

ADVERSE EVENTS

The safety of Terlivaz® was evaluated in the CONFIRM trial. The average daily dose of Terlivaz® was 3.1 mg (range 0.8 to 5.8 mg), with a mean duration of exposure to Terlivaz® of 6.2 days (range 1 to 15 days). Treatment discontinuation due to adverse events occurred in 12.0% (24/200) of patients receiving Terlivaz® and 5.1% (5/99) of patients receiving placebo. The most common adverse reactions that led to Terlivaz® discontinuation were respiratory failure, abdominal pain, and intestinal ischemia/obstruction. The most commonly observed adverse reactions in Terlivaz® -treated patients (≥10%) were abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea.

Table 2: Adverse Reactions Reported by ≥4 % of Terlivaz® -Treated Patients

Patients, n (%)

	Terlivaz® (N=200)	Placebo (N=99)
Abdominal pain	39 (19.5)	6 (6.1)
Nausea	32 (16.0)	10 (10.1)
Respiratory failure	31 (15.5)	7 (7.1)
Diarrhea Patients, n (%)	26 (13.0)	7 (7.1)
Dyspnea	25 (12.5)	5 (5.1)
Fluid overload	17 (8.5)	3 (3.0)
Pleural effusion	11 (5.5)	0 (0.0)
Sepsis	11 (5.5)	1 (1.0)
Bradycardia	10 (5.0)	0 (0.0)
Ischemia-related events[a]	9 (4.5)	0 (0.0)

[a] Ischemia-related events include: skin discoloration, cyanosis, ischemia and intestinal ischemia.

WARNINGS & PRECAUTIONS

Serious or Fatal Respiratory Failure
It occurred in 14% of patients treated with Terlivaz® compared to 5% of patients on placebo. 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. Patients with fluid overload may be at increased risk of respiratory failure. Manage intravascular volume overload by reducing or discontinuing the administration of albumin and/or other fluids and 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.

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.

Ischemic Events
Terlivaz® may cause cardiac, cerebrovascular, peripheral, or mesenteric ischemia. Avoid use of Terlivaz® in patients with a history of severe cardiovascular conditions, cerebrovascular and 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 based on the mechanism of action and data from published literature. Terlipressin induces uterine contractions and endometrial ischemia in both humans and animals. If this drug is used during pregnancy, the patient should be apprised of the potential risk to the fetus.

CONTRAINDICATIONS

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

Clinical Pharmacology

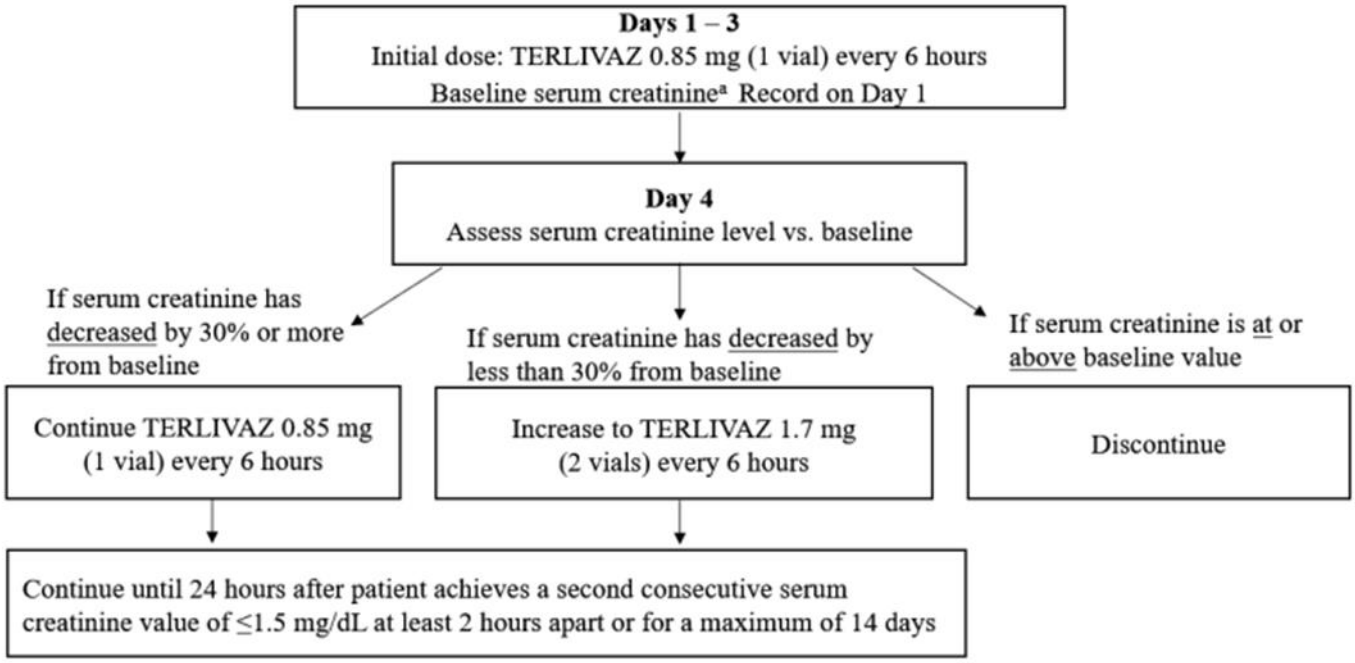
MECHANISMS OF ACTION

Terlipressin is a synthetic vasopressin analogue with twice the selectivity for vasopressin V1 receptors versus V2 receptors. Terlipressin acts as both a prodrug for lysine-vasopressin, as well as having pharmacologic activity on its own. Terlipressin is thought to increase renal blood flow in patients with hepatorenal syndrome by reducing portal hypertension and blood circulation in portal vessels and increasing effective arterial volume and mean arterial pressure (MAP).

Dose & Administration

ADULTS

Figure 1: Dosing Chart



[a] Baseline SCr is the last available serum creatinine before initiating treatment.

PEDIATRICS

None.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

For injection: Terlivaz® 0.85 mg is a white to off-white lyophilized powder in a single-dose vial for reconstitution.