

# Request for Unique ICD-10-PCS Codes for the Administration of Terlipressin, an Investigational New Drug for the Treatment of Hepatorenal Syndrome Type 1

Khurram Jamil, MD  
*Executive Director, Clinical Affairs*  
*Mallinckrodt Pharmaceuticals*

ICD-10 Coordination and Maintenance Committee  
Centers for Medicare & Medicaid Services  
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# Terlipressin is an Investigational New Drug for the Treatment of Hepatorenal Syndrome Type 1 (HRS-1)\*



- ▶ **Potent V1-selective vasoconstrictor** and the only one that can be **administered outside of the ICU**<sup>1,2</sup>
- ▶ **Most studied pharmacological therapy for HRS-1**, approved since the 1980s across 60 countries in E.U., Asia, Latin America, and Australia<sup>3</sup>
- ▶ **Standard of care for HRS-1 wherever available, per global treatment guidelines**<sup>4†</sup>
- ▶ **Significantly more effective than the current U.S. off-label standard of care (*i.e.*, combination of midodrine, octreotide, and albumin) in improving renal function in HRS-1 patients**<sup>5</sup>

\*Terlipressin is an investigational new drug, and its safety and effectiveness have not yet been established by the FDA.

†Referred in International (IAC, International Ascites Club), European (EASL, European Association for the Study of the Liver), Asia Pacific (APASL, Asian Pacific Association for the Study of the Liver), and U.S. (AASLD, American Association for the Study of Liver Diseases) guidelines.

E.U. – European Union; FDA – Food and Drug Administration; HRS-1 – Hepatorenal Syndrome Type 1; ICU – Intensive Care Unit; V1 – Vasopressin Receptor 1

1. Jamil K, Pappas SC, Devarakonda K. In vitro binding and receptor-mediated activity of terlipressin at vasopressin receptors V1 and V2. J. Exp. Pharmacol. 2017;Volume 101-7. doi:10.2147/jep.s146034.

2. Mallinckrodt Pharmaceuticals. Australian PI - GLYPRESSIN® (terlipressin) Solution for Injection. Accessed January 15, 2020.




3. Mindikoglu AL, Pappas SC. New Developments in Hepatorenal Syndrome. Clin. Gastroenterol. Hepatol. 2017;16(2):162-177.e1. doi:10.1016/j.cgh.2017.05.041.

4. Angeli P, Bernardi M, Villanueva C, et al. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J. Hepatol. 2018;69(2):406-460. doi:10.1016/j.jhep.2018.03.024.

5. Cavallin M, Kamath PS, Merli M, et al. Terlipressin plus albumin versus midodrine and octreotide plus albumin in the treatment of hepatorenal syndrome: A randomized trial. Hepatology 2015;62(2):567-574. doi:10.1002/hep.27709.

# Current ICD-10-PCS Codes Do Not Adequately Describe the Administration of Terlipressin for the Anticipated HRS-1 Indication<sup>1</sup>



-  **Terlipressin represents a substantial clinical improvement over existing therapies.** To that end, Mallinckrodt Pharmaceuticals submitted an **NTAP** application for **terlipressin** to CMS for FY2021 implementation
-  Mallinckrodt Pharmaceuticals requests **unique ICD-10-PCS “X” codes** for the **administration of terlipressin**
-  **Without unique ICD-10-PCS codes, the inpatient administration of terlipressin to HRS-1 patients cannot be identified and tracked**

# HRS-1 is Associated with a Poor Prognosis and a High Rate of Hospitalizations

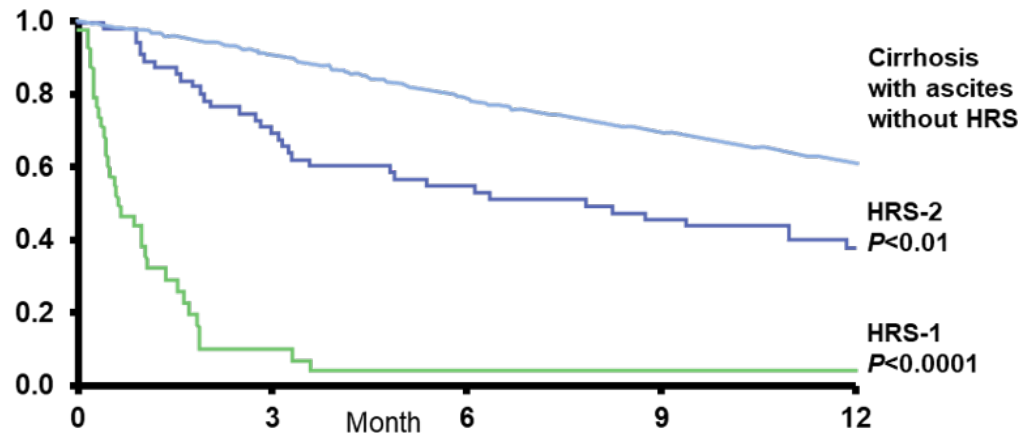


- **Serious, life-threatening condition** characterized by development of acute or sub-acute renal failure in patients with advanced chronic liver disease<sup>1</sup>



**Median survival time of <2 weeks and >80% mortality within 3 months if left untreated<sup>2,3</sup>**

## Actuarial Probability to Survive in Cirrhotic Patients with Different Renal Impairments<sup>4</sup>



Affects **30,000–40,000** patients in the U.S. annually<sup>5,6</sup>



Most patients are **60–70 years old** (mean age: **62 ± 1.2** years)<sup>7</sup>



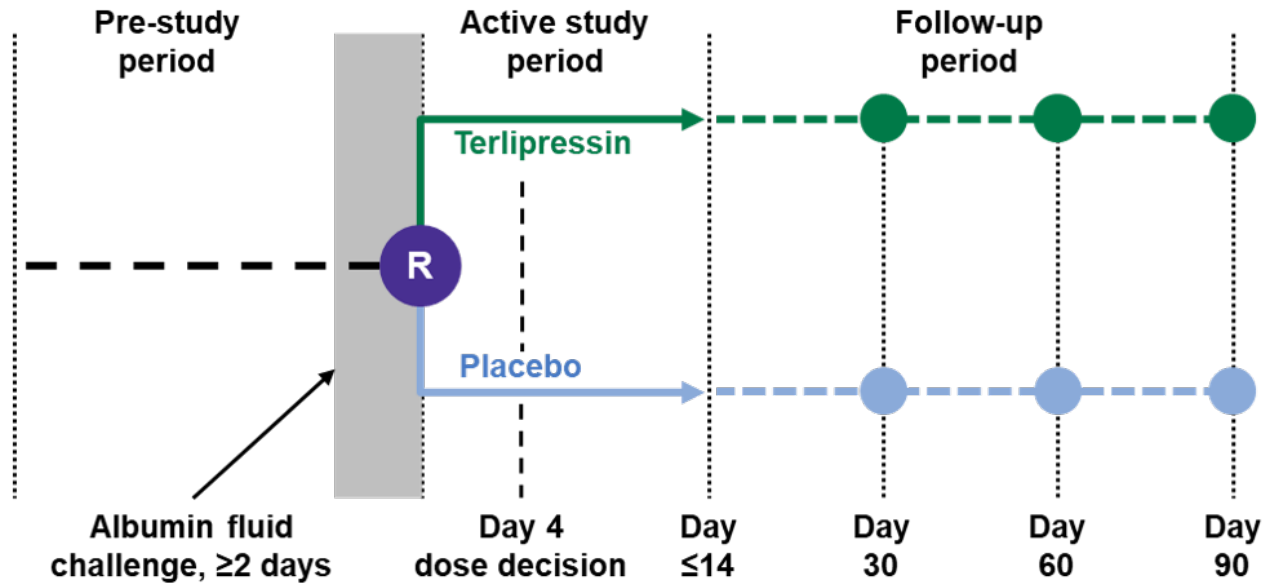
**Leading cause of hospitalizations** among all patients with advanced chronic liver disease (**~12%** of all hospitalized patients with cirrhosis and ascites)<sup>8</sup>



**36.9% in-hospital mortality**  
When accounting for an **8.9%** discharged to hospice, mortality rate increases to **45.8%**<sup>9</sup>

1. Mindikoglu AL, Pappas SC. New Developments in Hepatorenal Syndrome. Clin. Gastroenterol. Hepatol. 2017;16(2):162-177.e1. doi:10.1016/j.cgh.2017.05.041.
2. Colle I, Laterre P. Hepatorenal syndrome: the clinical impact of vasoactive therapy. Expert Rev. Gastroenterol. Hepatol. 2017;12(2):173-188. doi:10.1080/17474124.2018.1417034
3. Ginès P, Solà E, Angeli P, et al. Hepatorenal syndrome. Nat. Rev. Dis. Primers 2018;4(1) doi:10.1038/s41572-018-0022-7.
4. Salerno F, Cazzaniga M, Merli M, et al. Diagnosis, treatment and survival of patients with hepatorenal syndrome: A survey on daily medical practice. J. Hepatol. 2011;55(6):1241-1248. doi:10.1016/j.jhep.2011.03.012.
5. Pant C, Jani BS, Desai M, et al. Hepatorenal syndrome in hospitalized patients with chronic liver disease: results from the Nationwide Inpatient Sample 2002–2012. J. Investig. Med. 2016;64(1):33-38. doi:10.1136/jim-d-15-00181.
6. United States - 2019 Population Estimates. The United States Census Bureau. Accessed January 15, 2020.
7. Salerno F, Cazzaniga M, Merli M, et al. Diagnosis, treatment and survival of patients with hepatorenal syndrome: A survey on daily medical practice. J. Hepatol. 2011;55(6):1241-1248. doi:10.1016/j.jhep.2011.03.012.
8. Allegretti AS, Ortiz G, Wenger J, et al. Prognosis of Acute Kidney Injury and Hepatorenal Syndrome in Patients with Cirrhosis: A Prospective Cohort Study. Int. J. Nephrol. 2015;2015:1-9. doi:10.1155/2015/108139.
9. Jamil K, Huang X, Lovelace B, et al. The burden of illness of hepatorenal syndrome (HRS) in the United States: a retrospective analysis of electronic health records. J. Med. Econ. 2019;22(5):421-429. doi:10.1080/13696998.2019.1580201

# CONFIRM is the Largest Prospective Study Ever Conducted to Evaluate the Efficacy and Safety of Terlipressin for the Treatment of HRS-1<sup>1</sup>



- ▶ Terlipressin (1 mg IV q6h) or placebo, plus albumin in both groups; 2:1 randomization ratio
- ▶ Study drug dose increase to 2 mg IV q6h, if SCr has decreased, but by <30% from the baseline value on Day 4
- ▶ Recommended albumin doses were per ICA guidelines, 1 g/kg (to a maximum of 100 g) on the first day and 20–40 g/day thereafter as clinically indicated



**300 patients**  
(89% in U.S. and 11% in Canada)



**17%** of patients age **65 or older**



Patients were critically ill at baseline:

- ▶ mean MELD score of 33
- ▶ mean SCr level of 3.5 mg/dL
- ▶ 61% were categorized as Child-Pugh Class C

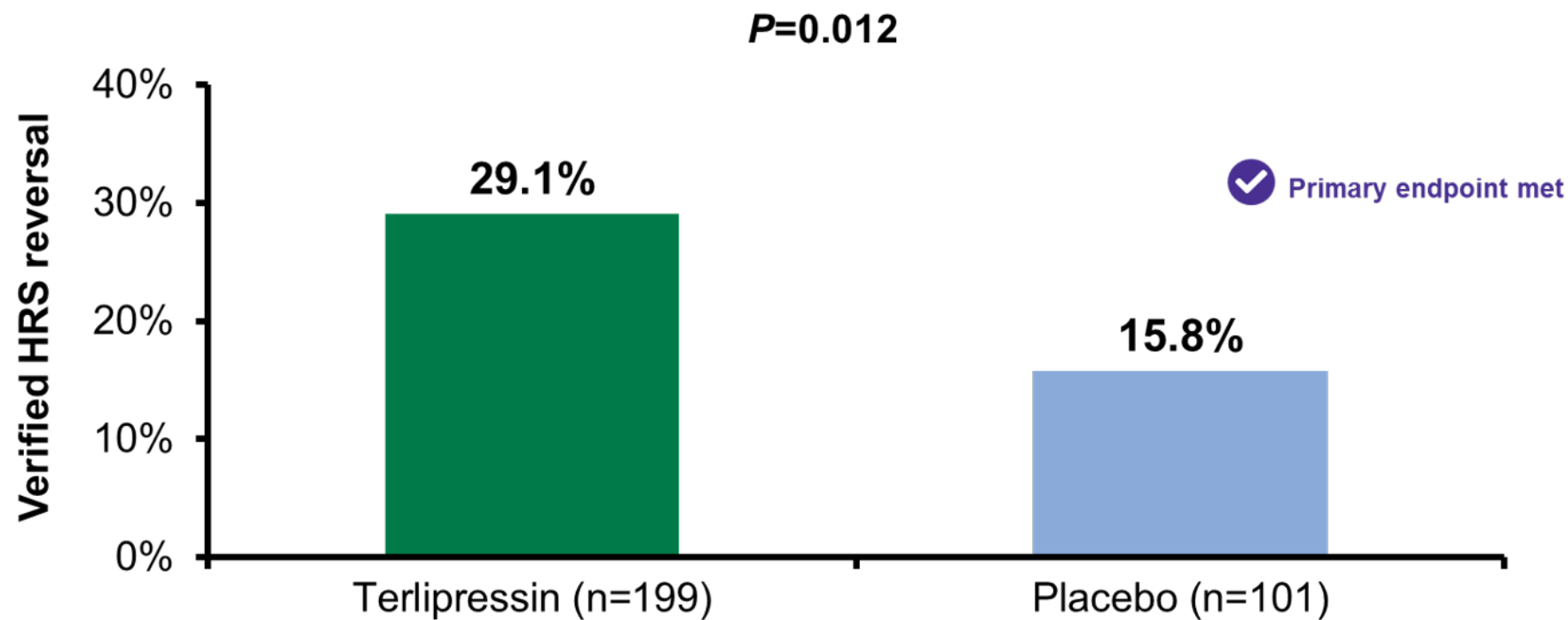


**40%** of patients were transferred to trial sites and **60%** had failed to respond to off-label SOC treatment (combination of midodrine, octreotide, and albumin)

ICA – International Club Of Ascites; IV – Intravenous; MELD – Model for End-stage Liver Disease; SCr – Serum Creatinine; SOC – Standard of Care; q6h – Every 6 Hours

1. Wong F, Curry MP, Reddy KR, et al, on behalf of the CONFIRM Study Investigators. The CONFIRM Study: A North American Randomized Controlled Trial (RCT) of Terlipressin plus Albumin for the Treatment of Hepatorenal Syndrome Type 1 (HRS-1). Presented at: The American Association for the Study of Liver Diseases (AASLD) meeting; November 8-12, 2019; Boston, MA.

# The CONFIRM Trial Demonstrated the Substantial Clinical Improvement of Terlipressin When Compared With Placebo<sup>1</sup>



## What is *verified HRS reversal*?

- ▶ Two SCr values  $\leq 1.5$  mg/dL while on treatment by Day 14 or discharge
- ▶ Dialysis-free for at least 10 days after achieving the second SCr
- ▶ Survived at least 10 days after achieving the second SCr

1. Wong F, Curry MP, Reddy KR, et al, on behalf of the CONFIRM Study Investigators. The CONFIRM Study: A North American Randomized Controlled Trial (RCT) of Terlipressin plus Albumin for the Treatment of Hepatorenal Syndrome Type 1 (HRS-1). Presented at: The American Association for the Study of Liver Diseases (AASLD) meeting; November 8-12, 2019; Boston, MA.

# The CONFIRM Trial Met the Majority of its Pre-specified Secondary Endpoints<sup>1</sup>



1

## HRS reversal<sup>a</sup>

**36.2%** (n=72) of patients in the terlipressin group demonstrated HRS reversal vs. **16.8%** (n=17) on placebo (***P*<0.001**)

2

## Durability of maintaining HRS reversal<sup>b</sup>

**31.7%** of patients receiving terlipressin (n=63) maintained HRS reversal without RRT/dialysis up to Day 30 vs. **15.8%** (n=16) in the placebo group (***P*<0.003**)

3

## HRS reversal in the SIRS subgroup

**33.3%** (28/84) of patients with SIRS in the terlipressin arm achieved HRS reversal vs. **6.3%** (3/48) in the placebo arm (***P*<0.001**)

4

## Verified HRS reversal without HRS recurrence by Day 30<sup>c</sup>

**24.1%** (n=48) of patients on terlipressin and **15.8%** (n=16) of patients in the placebo group (***P*=0.092**) achieved Verified HRS reversal without recurrence by Day 30

<sup>a</sup>The incidence of HRS reversal is defined as the percentage of subjects with a SCr value  $\leq 1.5$  mg/dL while on treatment (on treatment defined as up to 24 hours after the final dose of study drug) by Day 14 or discharge. SCr values after RRT, TIPS, liver transplant, or open-label vasopressor use are excluded.

<sup>b</sup>Durability of HRS reversal was defined in the protocol as the percentage of subjects with HRS reversal (as defined above) without RRT to Day 30.

<sup>c</sup>Verified HRS reversal without HRS recurrence by Day 30 was defined in the protocol as the percentage of subjects with verified HRS reversal who did not experience a recurrence of HRS by Day 30. Verified HRS reversal was defined as described for the primary efficacy endpoint and SCr values after RRT, TIPS placement, liver transplant, or open-label vasopressor treatment were excluded from the analysis.

RRT – Renal Replacement Therapy; SIRS – Systemic Inflammatory Response Syndrome

1. Wong F, Curry MP, Reddy KR, et al, on behalf of the CONFIRM Study Investigators. The CONFIRM Study: A North American Randomized Controlled Trial (RCT) of Terlipressin plus Albumin for the Treatment of Hepatorenal Syndrome Type 1 (HRS-1). Presented at: The American Association for the Study of Liver Diseases (AASLD) meeting; November 8-12, 2019; Boston, MA.



# Reversal of HRS with Terlipressin Treatment Significantly Improved Clinical Outcomes for HRS-1 Patients<sup>1,2</sup>



## Achieving HRS reversal led to greater overall survival

Overall survival up to Day 90 was **higher in responders** (subjects who achieved verified HRS reversal or HRS reversal while receiving treatment) than in non-responders ( $P<0.001$ )



## Decreased cumulative incidence of renal replacement therapy through treatment period and after liver transplant

**23.1%** (n=46) of patients in the terlipressin group vs. **34.7%** (n=35) on placebo ( $P=0.03$ ) through Day 14

**19.6%** (n=46) of liver transplant patients in the terlipressin group vs. **44.8%** (n=29) in the placebo group ( $P=0.04$ )



## Shorter length of ICU stay without increased rate of ICU admission due to treatment

Patients on terlipressin stayed an average of **6.4 days** in the ICU vs. **13.2 days** for patients on placebo




1. Data on file. CONFIRM Study Report. Mallinckrodt Pharmaceuticals; November 2019.

2. Wong F, Curry MP, Reddy KR, et al, on behalf of the CONFIRM Study Investigators. The CONFIRM Study: A North American Randomized Controlled Trial (RCT) of Terlipressin plus Albumin for the Treatment of Hepatorenal Syndrome Type 1 (HRS-1). Presented at: The American Association for the Study of Liver Diseases (AASLD) meeting; November 8-12, 2019; Boston, MA.



# Unique ICD-10-PCS “X” Codes Are Needed to Describe the Administration of Terlipressin to HRS-1 Patients



-  Terlipressin represents a substantial clinical improvement compared to the current off-label standard of care in U.S. for HRS-1 patients
-  HRS-1 is a life-threatening form of advanced liver disease and a significant burden to the Medicare population
-  Current ICD-10-PCS codes do not adequately describe the administration of terlipressin for HRS-1 treatment