Mallinckrodt Presents Data on TERLIVAZ® (terlipressin) for Injection in Patients with Hepatorenal Syndrome (HRS) at Kidney Week 2024

October 26, 2024

– Pooled analysis from Phase 3 clinical trials highlights liver transplant rates in adult patients with HRS with rapid reduction in kidney function treated with TERLIVAZ[1] –

DUBLIN, Oct. 26, 2024 /PRNewswire/ -- Mallinckrodt plc, a global specialty pharmaceutical company, today announced a poster presentation on TERLIVAZ® (terlipressin) for injection in patients with hepatorenal syndrome (HRS) with rapid reduction in kidney function[1] at Kidney Week 2024, the annual meeting of the American Society of Nephrology (ASN) taking place in San Diego from October 23-27, 2024.

TERLIVAZ is the first and only FDA-approved product indicated to improve kidney function in adults with HRS with rapid reduction in kidney function,[1] an acute and life-threatening condition requiring hospitalization.[2] HRS involving rapid reduction in kidney function[1] is estimated to affect more than 42,000 Americans annually, approximately 0.01% of the U.S. population,[3] making it a very rare condition; and rates of hospitalizations are increasing.[4]

Please see Limitation of Use and Important Safety Information, including Boxed Warning, below.

The poster presentation highlights a pooled analysis of data from the CONFIRM and REVERSE Phase 3 placebo-controlled trials of TERLIVAZ.[5] The analysis examined the rates of hepatorenal syndrome-acute kidney injury (HRS-AKI) reversal, renal replacement therapy (RRT), and liver transplant (LT) among a subpopulation of patients listed for LT at baseline who met FDA label guidelines for treatment with TERLIVAZ (SCr <5 mg/dL, ACLF grade 0–2, and MELD score <35).[5] In this patient subpopulation, treatment with TERLIVAZ increased the rate of HRS-AKI reversal and reduced the need for RRT at all time points assessed.[5] The increase in HRS-AKI reversal with TERLIVAZ did not negatively impact the LT rate in patients listed for LT at baseline.[5]

- The rate of HRS-AKI reversal was 43% in the TERLIVAZ group (n=53) and 20% in the placebo group (n=35).[5]
- The rate of RRT in the TERLIVAZ and placebo groups was 28% and 46% by Day 30; 32% and 54% by Day 60; and 36% and 54% by Day 90, respectively.[5]
- The LT rate was similar in the TERLIVAZ and placebo groups at all time points assessed: 53% and 51% by Day 30; 66% and 57% by Day 60; and 66% and 63% by Day 90, respectively.[5]

The limitations of this study include, but are not limited to, small sample sizes, variables in methodology, and possible errors and omissions within the data sets.[5]

"This analysis of data from our Phase 3 trials furthers our understanding of the appropriate patient subpopulations and the potential impact of treatment on liver transplantation rates," said **Peter Richardson, MRCP (UK), Executive Vice President & Chief Scientific Officer**. "For these critically ill patients with HRS-AKI, a liver transplant is the definitive treatment, and we know there are significant challenges associated with RRT; which makes continued research important."

This study was sponsored by Mallinckrodt Pharmaceuticals. Presentation details can be found below:

Poster #PO0102-2: Hepatorenal syndrome-acute kidney injury reversal and liver transplant rates in patients treated with terlipressin[5]

- **Presenter:** Justin Belcher
- **Session Type:** Poster Presentation
- **Session Title:** AKI: Clinical, Outcomes, and Trials - Management
- **Session Date and Time:** Saturday, October 26, 2024; 10:00 a.m. – 12:00 p.m. PT

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.

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%.**

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.

- **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 or cerebrovascular or 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. If TERLIVAZ is used during pregnancy, the patient should be informed of the potential risk to the fetus.

Adverse Reactions

- The most common adverse reactions (≥10%) include abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea.

Please click here to see full Prescribing Information, including Boxed Warning.

ABOUT HEPATORENAL SYNDROME (HRS)

Hepatorenal syndrome (HRS) involving rapid reduction in kidney function[1] is an acute and life-threatening condition that occurs in people with advanced liver disease.[2] HRS is classified into two distinct types – a rapidly progressive type that leads to acute renal failure where patients are typically hospitalized for their care and a more chronic type that progresses over weeks to months.[2] HRS involving rapid reduction in kidney function[1] is estimated to affect more than 42,000 Americans annually, approximately 0.01% of the U.S. population,[3] making it a very rare condition; and rates of HRS hospitalizations are increasing.[4] If left untreated, HRS with rapid reduction in kidney function[1] has a median survival time of less than two weeks and greater than 80 percent mortality within three months.[6]

ABOUT MALLINCKRODT

Mallinckrodt is a global business consisting of multiple wholly owned subsidiaries that develop, manufacture, market and distribute specialty pharmaceutical products and therapies. The company's Specialty Brands reportable segment's areas of focus include autoimmune and rare diseases in specialty areas like neurology, rheumatology, hepatology, nephrology, pulmonology, ophthalmology, and oncology; immunotherapy and neonatal respiratory critical care therapies; analgesics; and gastrointestinal products. Its Specialty Generics reportable segment includes specialty generic drugs and active pharmaceutical ingredients. To learn more about Mallinckrodt, visit www.mallinckrodt.com.

CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS

This release contains forward-looking statements, including with regard to TERLIVAZ®, its potential to improve health and treatment outcomes, and its potential impact on patients. The statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those in the forward-looking statements: the effects of Mallinckrodt's recent emergence from bankruptcy; satisfaction of, and compliance with, regulatory and other requirements; actions of regulatory bodies and other governmental authorities; changes in laws and regulations; issues with product quality, manufacturing or supply, or patient safety issues or adverse side effects or adverse reactions associated with TERLIVAZ; and other risks identified and described in more detail in the "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of Mallinckrodt's most recent Annual Report on Form 10-K, Quarterly Reports on Form

10-Q, and other filings with the SEC, all of which are available on its website. The forward-looking statements made herein speak only as of the date hereof and Mallinckrodt does not assume any obligation to update or revise any forward-looking statement, whether as a result of new information, future events and developments or otherwise, except as required by law.

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References

[1] TERLIVAZ® (terlipressin) for Injection. Prescribing Information. Mallinckrodt Hospital Products Inc. 2023.

[2] National Organization for Rare Disorders. Hepatorenal Syndrome. Available at: https://rarediseases.org/rare-diseases/hepatorenal-syndrome/. Accessed October 2024.

[3] United States Census Bureau: Quick Facts. Available at: https://www.census.gov/quickfacts/fact/table/US/PST045218. Accessed October 2024.

[4] Singh J., Dahiya D.S., Kichloo A., et al. Hepatorenal Syndrome: A Nationwide Trend Analysis from 2008 to 2018. *Annals of Med*. 2021;53:1. 2018-2024 doi.org/10/1080/07853890.

[5] Belcher J.M., Regner K.R., Mujtaba M.A., et al. Hepatorenal syndrome-acute kidney injury reversal and liver transplant rates in patients treated with terlipressin. *Abstract to be presented at the American Society of Nephrology (ASN) 2024 Annual meeting.* October 2024.

[6] Flamm, S.L., Brown, K., Wadei, H.M., et al. The Current Management of Hepatorenal Syndrome–Acute Kidney Injury in the United States and the Potential of Terlipressin. *Liver Transpl*. 2021;27:1191-1202. https://doi.org/10.1002/lt.26072.

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