Mallinckrodt Announces Journal Publication of Economic Evidence for TERLIVAZ® (terlipressin) for Injection in Adults with Hepatorenal Syndrome (HRS)

December 21, 2023

– Analysis indicates treatment with TERLIVAZ plus albumin in adults with HRS with rapid reduction in kidney function[1] can help improve kidney function with lower HRS treatment-related healthcare utilization costs[2] –

– Journal manuscript with full data results now published in the December issue of *Advances in Therapy* –

DUBLIN, Dec. 21, 2023 /PRNewswire/ -- Mallinckrodt plc, a global specialty pharmaceutical company, recently announced the publication of findings from a cost analysis of TERLIVAZ® (terlipressin) for injection for adults with hepatorenal syndrome (HRS) with rapid reduction in kidney function.[1,2] This analysis assessed the treatment-related cost per patient response with TERLIVAZ plus albumin from a U.S. hospital perspective.[2]

The manuscript was published in the December 2023 print issue of *Advances in Therapy* and is also available on the *Advances in Therapy* website.

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.[3] HRS involving rapid reduction in kidney function[1] is estimated to affect more than 42,000 Americans annually and rates of HRS hospitalizations are increasing.[4]

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

The publication, titled "Treatment-Related Cost Analysis of Terlipressin for Adults with Hepatorenal Syndrome with Rapid Reduction in Kidney Function," used a decision analytic model to estimate the treatment-related cost associated with TERLIVAZ plus albumin and other non-FDA approved treatments, such as midodrine and octreotide plus albumin and norepinephrine plus albumin, for adult patients with HRS with rapid reduction in kidney function.[1,2] HRS treatment-related utilization of healthcare resources from the U.S. hospital perspective, including the incremental cost of intensive care unit (ICU) bed, dialysis, pulse oximetry monitoring and adverse events, was estimated based on the level of response.[2] HRS reversal (or complete response) was defined as a decrease in serum creatinine (SCr) from baseline to ≤ 1.5 mg/dL on treatment (up to 24 hours after the last treatment dose).[2]

"Continued research on the real-world clinical and economic impact of TERLIVAZ is critical to further our understanding of the relationship between HRS treatment choice and patient outcomes, and the related healthcare costs," said **George Wan, Ph.D., M.P.H., Vice President, Evidence Generation & Data Sciences**. "These findings suggest that TERLIVAZ may help to improve kidney function with lower ICU, dialysis, and other HRS treatment-related healthcare utilization costs when compared to other non-FDA approved treatments used in the U.S. hospital setting.[2]"

Key Findings[2]:

- The cost per response of TERLIVAZ plus albumin was lower than midodrine and octreotide plus albumin ($85,315 vs. $467,794) and norepinephrine plus albumin ($81,614 vs. $139,324).
- Midodrine and octreotide plus albumin resulted in higher ICU- and dialysis-related costs (ICU: $9,039; dialysis: $8,266) vs. TERLIVAZ plus albumin (ICU: $6,712; dialysis: $5,073). Similarly, norepinephrine plus albumin resulted in higher ICU- and dialysis-related costs (ICU: $22,656; dialysis: $6,873) vs. TERLIVAZ plus albumin (ICU: $6,382; dialysis: $5,068).
- The HRS reversal rate for those treated with TERLIVAZ plus albumin was higher than those treated with midodrine and octreotide plus albumin (55.56%; n=15/27 vs. 4.76%; n=1/21), and those treated with norepinephrine plus albumin (55.64%; n=74/133 vs. 26.92%; n=35/130).
- For every two patients treated with TERLIVAZ plus albumin instead of midodrine and octreotide plus albumin, one additional patient was estimated to achieve HRS reversal. For every four patients treated with TERLIVAZ plus albumin instead of norepinephrine plus albumin, one additional patient was estimated to achieve HRS reversal.
- Collectively, these findings suggest that TERLIVAZ can be considered a cost-effective, value-based treatment option for appropriate patients with HRS with rapid reduction in kidney function.[1,2]

Limitations[2]:

- Efficacy, safety, and treatment-related adverse event data were sourced from published head-to-head randomized clinical trials, which may not be generalizable to the entire adult HRS population and differed from the adverse events in the FDA-approved TERLIVAZ label.
- Verified HRS reversal, the primary endpoint of the CONFIRM trial for TERLIVAZ (NCT02770716), was not used in this analysis.
- Several assumptions for the model were made, including the proportion of patients treated on the general floor with

midodrine and octreotide plus albumin, and norepinephrine plus albumin.
- Cost data from public sources may be different from the actual costs of a hospital/institution and may not reflect discounts or rebates offered by manufacturers.
- The analysis focuses on the treatment-related cost of care over 14 days of the initial hospitalization and due to the short time horizon, other mid- and long-term benefits of HRS reversal post-initial hospitalization are not captured, including the reduced need for dialysis, kidney transplantation, and better outcomes post-liver transplantation.

This study was funded 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.

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.[3] 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.[3] HRS involving rapid reduction in kidney function[1] is estimated to affect more than 42,000 Americans annually 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.[5]

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; cultured skin substitutes 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" section of Mallinckrodt's most recent Annual Report on Form 10-K 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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