Mallinckrodt Presents Clinical Data for TERLIVAZ® (terlipressin) for Injection in Adults with Hepatorenal Syndrome (HRS) at Digestive Disease Week (DDW) 2023

May 8, 2023

– Findings from two clinical study presentations in adults with HRS involving rapid reduction in kidney function[1] provide insight into the appropriate use of terlipressin for the care of critically ill patients[2,3] –

DUBLIN, May 8, 2023 /PRNewswire/ -- Mallinckrodt plc (NYSE American: MNK), a global specialty pharmaceutical company, today announced the presentation of results from two clinical studies for adults with hepatorenal syndrome (HRS) with rapid reduction in kidney function[1] treated with TERLIVAZ® (terlipressin) for injection at Digestive Disease Week® (DDW) 2023, taking place in Chicago, Ill. from May 6-9. Mallinckrodt's pooled analysis of three North American Phase III studies on the incidence of adverse events (AEs) related to bradycardia and arrhythmias in adults with HRS treated with terlipressin was awarded *Poster of Distinction* status from DDW, and was presented on Sunday, May 7, 2023, 12:30 – 1:30 p.m. CDT.[2] Additionally, Mallinckrodt's subgroup analysis of the CONFIRM Phase III study to assess terlipressin treatment outcomes in adults with HRS compounded by alcoholic hepatitis (AH) will be presented in an oral lecture session today, May 8, 2023, 10:30 – 10:45 a.m. CDT.[3]

TERLIVAZ is the first and only FDA-approved product indicated for the treatment of adults with HRS involving rapid reduction in kidney function,[1] an acute and life-threatening condition requiring hospitalization.[4] Terlipressin is recommended by the American Association for the Study of Liver Diseases (AASLD) guidance[5] and the American College of Gastroenterology (ACG) guidelines.[6]

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

Presented by Jasmohan S. Bajaj, School of Internal Medicine, Virginia Commonwealth University, Richmond, Va., the pooled analysis (*DDW Poster of Distinction: Su1535*) used the largest-to-date prospective database of three North American Phase III, randomized, placebo-controlled trials (OT-0401, REVERSE, CONFIRM) to evaluate the incidence of reported bradycardia and arrhythmias in adult patients with HRS treated with terlipressin vs. placebo. All three studies excluded patients with prior arrhythmias and significant cardiovascular disease, and statistical analysis was determined using a Fisher's Exact test.[2]

Khurram Jamil, Vice President & Head, Hepatology, Clinical Development & Critical Care at Mallinckrodt, said, "We are excited to share the results from this pooled analysis of the largest HRS patient data set to-date, selected as a *DDW 2023 Poster of Distinction*, which bolsters our overall understanding of TERLIVAZ® (terlipressin) for injection's risk-benefit profile and the significance of adverse events such as bradycardia and arrhythmias,[2] to ultimately provide continued support for the use of this treatment in appropriate patients with HRS with rapid reduction in kidney function.[1]"

The pooled safety population included 598 patients, of which 349 received terlipressin and 249 received placebo. The incidence of episodes of bradycardia was higher in terlipressin-treated patients (6.3%; n=22) compared with placebo-treated patients (0.8%; n=2; P<0.001), and none of these episodes were considered serious. Bradycardia was classified as severe per investigator assessment in 68.2% (n=15/22) of patients in the terlipressin group and in 100% (n=2/2) of patients in the placebo group, and most patients did not require a change in treatment dose (terlipressin: 72.7%; n=16/22 vs. placebo: 50%; n=1/2; P=0.507). One patient treated with terlipressin had a dose interruption, and there were no treatment discontinuations.[2]

Further, no differences were observed between treatment groups (terlipressin: arrhythmia [0%, n=0/349,]; nodal arrhythmia [0%, n=0/349]; ventricular fibrillation [0%, n=0/349] vs. placebo: arrhythmia [0.8%, n=2/249, P=0.173]; nodal arrhythmia [0.4%, n= 1/249, P=0.416]; ventricular fibrillation [0.4%, n=1/249, P=0.416]. Atrial fibrillation was the most reported arrhythmia across the pooled safety population (total: 4.0%, n=24/598; terlipressin: 3.7%, n=13/349; placebo: 4.4%, n=11/249; P=0.678).[2]

To be presented by Kevin Korenblat, Washington University School of Medicine, St. Louis, Mo., the key findings of a subgroup analysis (*DDW Oral Lecture: 651*) of the CONFIRM Phase III study aim to evaluate efficacy of terlipressin treatment in patients with HRS compounded by AH. Diagnosis of baseline AH was via investigator assessment, and data was retrospectively analyzed in patients with AH for verified HRS reversal (defined as the percentage of patients with 2 serum creatinine (SCr) values of ≤1.5 mg/dL ≥2 hours apart, while on treatment up to 72 hours after the last dose of study drug), admission to the intensive care unit (ICU), length of ICU stay, and incidence of renal replacement therapy (RRT) by Day 30.[3]

"The findings of this subgroup analysis of the CONFIRM Phase III study build upon the growing body of evidence supporting the use of TERLIVAZ® (terlipressin) for injection as a treatment option among critical care patients with HRS, including its therapeutic ability to drive meaningful

clinical outcomes for a significant population of patients with comorbid conditions, such as alcoholic hepatitis,[3]" added **Peter Richardson, MRCP (UK), Executive Vice President & Chief Scientific Officer at Mallinckrodt**. "As TERLIVAZ uptake and use among U.S. hospitals continues following FDA approval in 2022, our research at DDW 2023 reflects our ongoing commitment to critically ill patients by pursuing research that provides physicians with the most up-to-date treatment considerations to help inform patient care decisions."

In CONFIRM (n=300), 41% (81/199) of patients in the terlipressin group and 39% (39/101) of the patients in the placebo group had AH at baseline. In the subgroup of patients with AH (n=120), the median Maddrey discriminant function score was similar across treatment groups (terlipressin: 96.9 vs. placebo: 97.7; P=0.681). Verified HRS reversal was achieved in 30.9% (n=25/81) of patients in the terlipressin group vs. 7.7% (n=3/39) in the placebo group (P=0.005).[3]

Additionally, admission to the ICU was similar for patients in the terlipressin and placebo groups (17.3%, n=14 vs. 17.9%, n=7), whereas mean length of stay in the ICU was shorter for terlipressin (6.9 days) vs. the placebo group (12.4 days). There was a numerical decrease in RRT by Day 30 in the terlipressin group vs. the placebo group (21%, n=17 vs. 25.6%, n= 10).[3]

These studies were sponsored by Mallinckrodt Pharmaceuticals:

Presented Sunday, May 7, 2023; 12:30 – 1:30 p.m. CDT:

- **Poster Su1535*: Low Incidence of Clinically Significant Bradycardia and Arrhythmia in Patients with Hepatorenal Syndrome Following Terlipressin Treatment: A Pooled Analysis of 3 North American Phase III Clinical Studies**[2]
  - **Presenter:** Jasmohan S. Bajaj, School of Internal Medicine, Virginia Commonwealth University, Richmond, Va.

**Poster of Distinction*

To be presented Monday, May 8, 2023; 10:30 – 10:45 a.m. CDT; South Level, 402:

- **Oral Lecture 651: Clinical Responses to Terlipressin in the Subgroup of Patients with Hepatorenal Syndrome Further Compounded by Alcoholic Hepatitis: Analysis of the CONFIRM Phase III Study**[3]
  - **Presenter:** Kevin Korenblat, Washington University School of Medicine, St. Louis, Mo.

Find more information on the Digestive Disease Week (DDW) 2023 Meeting website.

About Digestive Disease Week®

Digestive Disease Week® (DDW) is the largest international gathering of physicians, researchers and academics in the fields of gastroenterology, hepatology, endoscopy and gastrointestinal surgery. Jointly sponsored by the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA) Institute, the American Society for Gastrointestinal Endoscopy (ASGE) and the Society for Surgery of the Alimentary Tract (SSAT), DDW is an in-person and online meeting from May 6-9, 2023. The meeting showcases more than 3,100 abstracts and hundreds of lectures on the latest advances in GI research, medicine and technology. More information can be found at www.ddw.org.

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.[4] 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.[4] HRS involving rapid reduction in kidney function[1] is estimated to affect between 30,000 and 40,000 Americans annually.[7,8] If left untreated, HRS with rapid reduction in kidney function[1] has a median survival time of approximately two weeks and greater than 80 percent mortality within three months.[9]

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 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.

Mallinckrodt uses its website as a channel of distribution of important company information, such as press releases, investor presentations and other financial information. It also uses its website to expedite public access to time-critical information regarding the company in advance of or in lieu of distributing a press release or a filing with the U.S. Securities and Exchange Commission (SEC) disclosing the same information. Therefore, investors should look to the Investor Relations page of the website for important and time-critical information. Visitors to the website can also register to receive automatic e-mail and other notifications alerting them when new information is made available on the Investor Relations page of the website.

CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS
This release contains forward-looking statements, including with regard to TERLIVAZ 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: satisfaction of 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; 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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of a Mallinckrodt company or their respective owners.

References

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

[2] Bajaj JS, et al. Low Incidence of Clinically Significant Bradycardia and Arrhythmia in Patients with Hepatorenal Syndrome Following Terlipressin Treatment: A Pooled Analysis of 3 North American Phase III Clinical Studies. *Abstract Presented at Digestive Disease Week (DDW) 2023.* May 2023.

[3] Korenblat, K et al. Clinical Responses to Terlipressin in the Subgroup of Patients with Hepatorenal Syndrome Further Compounded by Alcoholic Hepatitis: Analysis of the CONFIRM Phase III Study. *Abstract to be Presented at Digestive Disease Week (DDW) 2023.* May 2023.

[4] National Organization for Rare Disorders. Hepatorenal Syndrome. Available at: https://rarediseases.org/rare-diseases/hepatorenal-syndrome/. Accessed April 18, 2023.

[5] Biggins SW, Angeli P, Garcia-Tsao G, et al. Diagnosis, evaluation, and management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome: 2021 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021;74(2):1014-1048. doi:10.1002/HEP.31884.

[6] Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-chronic liver failure clinical guidelines. Am J Gastroenterol. 2022;1-28.

[7] C Pant, B S Jani, M Desai, A Deshpande, Prashant Pandya, Ryan Taylor, R Gilroy, M Olyaee. Heptorenal syndrome in hospitalized patients with chronic liver disease: results from the Nationwide Inpatient Sample 2002-2012. *J of Investig Med.* 2016; 64:33-38.

[8] United States Census Bureau: Quick Facts. Available at: https://www.census.gov/quickfacts/fact/table/US/PST045218. Accessed April 18, 2023.

[9] Flamm SL, Brown K, Wadei HM., 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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