Mallinckrodt Presents New TERLIVAZ® (terlipressin) for Injection Data on Hepatorenal Syndrome (HRS) Reversal at the Society of Critical Care Medicine (SCCM) 2023 Critical Care Congress

January 22, 2023

– Findings from a retrospective analysis suggest that patients with baseline acute-on-chronic liver failure (ACLF) grade ≤2 treated with TERLIVAZ® plus albumin had a higher incidence of HRS reversal than those treated with placebo plus albumin[1] –

DUBLIN, Jan. 22, 2023 /PRNewswire/ -- Mallinckrodt plc (NYSE American: MNK), a global specialty pharmaceutical company, today announced the presentation of results from a retrospective analysis of three North American-centric, Phase III, randomized, placebo-controlled studies comparing the incidence of hepatorenal syndrome (HRS) reversal with baseline acute-on-chronic liver failure (ACLF) grade in adults with rapid reduction in kidney function[2] treated with TERLIVAZ® plus albumin versus those treated with placebo plus albumin. Investigators will present the findings during an oral presentation at the SCCM 2023 Critical Care Congress on January 22, taking place in San Francisco, CA from January 21-24.

TERLIVAZ is the first and only FDA-approved product indicated for the treatment of adults with HRS involving rapid reduction in kidney function,[2] an acute and life-threatening condition requiring hospitalization.[3] Terlipressin is recommended by the American Association for the Study of Liver Diseases (AASLD) guidance[4] and the American College of Gastroenterology (ACG) guidelines.[5]

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

The retrospective analysis used pooled data from the OT-0401, REVERSE, and CONFIRM Phase III studies to compare the incidence of HRS reversal by baseline ACLF grade in patients treated with terlipressin plus albumin versus placebo plus albumin for up to 14 days. Severity of ACLF was graded according to the number of organ failures (ACLF grade 0-1, grade 2, and grade 3). The incidence of HRS reversal was defined as at least one serum creatinine value of ≤1.5 mg/dL while on treatment.[1]

"We're excited to share these data that not only provide valuable insight into the association between baseline patient ACLF grade and treatment response with TERLIVAZ, but also reinforce the importance of early treatment intervention to help improve outcomes for patients with HRS with rapid reduction in kidney function,[1,2]" said **Khurram Jamil, Vice President, Hepatology, Clinical Development & Critical Care**. "In light of the recent FDA approval of TERLIVAZ as the first and only treatment to improve kidney function in adults with HRS with rapid reduction in kidney function,[2] we remain committed to addressing the unmet needs of critically ill patient populations."

In the pooled analysis population (n=607), 278 patients had ACLF grade 0-1 (terlipressin: n=164; placebo: n=114), 208 patients had ACLF grade 2 (terlipressin: n=116; placebo: n=92), and 121 patients had ACLF grade 3 (terlipressin: n=72; placebo: n=49). The incidence of HRS reversal in terlipressin-treated patients decreased with increasing ACLF grade (ACLF grade 0-1: 43% (n=71/164); ACLF grade 2: 28% (n=32/116); ACLF grade 3: 19% (n=14/72)), whereas HRS reversal was similar across ACLF grades in placebo-treated patients (ACLF grade 0-1: 18% (n=21/114); ACLF grade 2: 15% (n=14/92); ACLF grade 3: 14% (n=7/49)).[1]

Additionally, a higher percentage of terlipressin-treated patients with ACLF grade 0-1 or grade 2 achieved HRS reversal compared with those in the respective placebo-treated groups (ACLF grade 0-1: terlipressin 43% (n=71/164) vs placebo 18% (n=21/114); ACLF grade 2: terlipressin 28% (n=32/116) vs placebo 15% (n=14/92)) ($p<0.0001$ and $p=0.02$, respectively). No differences in the incidence of HRS reversal were observed between terlipressin- (19%; n=14/72) and placebo- (14%; n=7/49) treated patients with ACLF grade 3 ($p=0.46$).[1]

This study was sponsored by Mallinckrodt Pharmaceuticals:

Baseline ACLF Grade and Treatment Response to Terlipressin in Patients with Hepatorenal Syndrome[1]

- **Presenter:** Ram Subramanian
- **Presentation Date:** January 22; 2:30PM PT
- **Location:** Exhibit Hall RST 8, Moscone Center South

Find more information on the Society of Critical Care Medicine's (SCCM) 2023 Critical Care Congress Meeting website.

About Hepatorenal Syndrome (HRS)

Hepatorenal syndrome (HRS) involving rapid reduction in kidney function[2] 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[2] is estimated to affect between 30,000 and 40,000 Americans annually.[6,7] If left untreated, HRS with rapid reduction in kidney function has a median survival time of approximately two weeks and greater than 80 percent mortality within three months.[8]

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 includes forward-looking statements, including with regard to TERLIVAZ, 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 Annual Report on Form 10-K for the fiscal year ended December 31, 2021, as updated by Mallinckrodt's Quarterly Reports on Form 10-Q for the quarterly periods ended April 1, July 1 and September 30, 2022 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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[2] TERLIVAZ® (terlipressin) for injection [Prescribing Information]. Mallinckrodt Hospital Products Inc.

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