Mallinckrodt Receives U.S. FDA Approval for Terlivaz® (terlipressin) for injection for the Treatment of Hepatorenal Syndrome (HRS)

September 15, 2022

– Terlivaz is the first and only FDA-approved treatment for adults with HRS involving rapid reduction in kidney function[1] –

DUBLIN, Sept. 14, 2022 /PRNewswire/ -- Mallinckrodt plc (OTCMKTS: MNKPF), a global specialty pharmaceutical company, today announced that the U.S. Food and Drug Administration (FDA) approved Terlivaz® (terlipressin) for injection. Terlivaz is the first and only FDA-approved product indicated to improve kidney function in adults with hepatorenal syndrome (HRS) with rapid reduction in kidney function,[1] an acute and life-threatening condition requiring hospitalization.[2]

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

Siggi Olafsson, President and Chief Executive Officer, said, "The FDA approval of Terlivaz is a significant milestone for Mallinckrodt as it brings an important treatment option to these critically ill patients requiring hospitalization and to U.S. physicians who historically have had limited treatment interventions.[3] We're excited to bring Terlivaz to U.S. patients and physicians and plan to launch the product in the coming weeks. This approval reflects Mallinckrodt's continued commitment to underserved patients and their caregivers through our demonstrated expertise and dedication to developing therapeutics for critical conditions."

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] Terlipressin is one of the most studied pharmacological agents in HRS with more than 70 published manuscripts and presented abstracts on clinical data to date.[6] It has been approved outside the U.S. for more than 30 years and is available on five continents for its indications in the countries where it is approved.[7,8]

The FDA approval was based, in part, on results from the Phase 3 CONFIRM trial, the largest-ever prospective study (n=300) conducted to assess the safety and efficacy of terlipressin in patients with HRS type 1 (HRS-1) in the U.S. and Canada. The CONFIRM trial met its primary endpoint of Verified HRS Reversal, defined as renal function improvement, avoidance of dialysis and short-term survival (p=0.012).[1] To achieve Verified HRS Reversal, patients had to have two consecutive serum creatinine (SCr) values of ≤1.5 mg/dL, at least two hours apart by day 14 or hospital discharge. To be included in the primary efficacy endpoint analysis, patients had to be alive and without intervening renal replacement therapy (e.g., dialysis) at least 10 days after achieving Verified HRS Reversal.[1] Initial results were presented in a late-breaking session at The Liver Meeting® 2019, the annual meeting of AASLD. Results were also published in the *New England Journal of Medicine* in March of 2021. The CONFIRM trial was completed prior to the updated diagnostic criteria and terminology published in the 2021 AASLD guidance on hepatorenal syndrome.

Steven Romano, M.D., Executive Vice President and Chief Scientific Officer at Mallinckrodt said, "Diagnosing and treating HRS can be challenging, and every minute counts when managing patients who have it. Terlivaz gives U.S. physicians the first FDA-approved option for treating HRS patients with rapid reduction in kidney function[1] that may help them improve kidney function and lessen the associated need for renal replacement therapy, such as dialysis."

The most commonly observed adverse reactions in at least 4 percent of patients treated with Terlivaz compared to placebo were abdominal pain reported in 19.5 percent (n=39) of patients (vs. 6.1%; n=6), nausea reported in 16 percent (n=32) of patients (vs. 10.1%; n=10), respiratory failure reported in 15.5 percent (n=31) of patients (vs. 7.1%; n=7) diarrhea reported in 13 percent (n=26) of patients (vs. 7.1%; n=7) and dyspnea reported in 12.5 percent (n=25) of patients (vs. 5.1%; n=5).[1]

Terlivaz is expected to be available in the U.S. in the coming weeks.

* *Note, Terlivaz was not evaluated in comparison to other treatment options in a head-to-head clinical study.*

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 between 30,000 and 40,000 Americans annually.[9,10] 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.[11]

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 with regard to Terlivaz, including expectations with regard to its anticipated availability in the U.S 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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[8] FDA Cardiovascular and Renal Drugs Advisory Committee. Mallinckrodt Pharmaceuticals Terlipressin Advisory Committee Briefing Document NDA #022231. July 2020.

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