Mallinckrodt Receives a Complete Response Letter from the U.S. Food and Drug Administration (FDA) for Terlipressin for the Treatment of Hepatorenal Syndrome Type 1 (HRS-1)

September 14, 2020

Company remains committed to working with FDA toward an approval for this important potential therapy

DUBLIN, Sept. 14, 2020 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a global biopharmaceutical company, today announced that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter (CRL) regarding the company's New Drug Application (NDA) seeking approval for the investigational agent terlipressin to treat adults with hepatorenal syndrome type 1 (HRS-1).

The CRL stated that, based on the available data, the agency cannot approve the terlipressin NDA in its current form and requires more information to support a positive risk-benefit profile for terlipressin for patients with HRS-1. HRS-1 is an acute and life-threatening syndrome involving acute kidney failure in people with cirrhosis[1] for which there is currently no FDA-approved treatment.[2] HRS-1 is estimated to affect between 30,000 and 40,000 Americans annually,[3,4] and often is a challenge to effectively diagnose in a timely manner due to its diagnosis of exclusion.[5] If left untreated, HRS-1 has a median survival time of approximately two weeks and greater than 80 percent mortality within three months.[5,6] U.S. discharge data in a recently published study indicated an in-hospital mortality rate of 34.2% (n=1,133), while an additional 14.4% (n=475) of patients were discharged to hospice.[7]

"While we are disappointed that the FDA issued a complete response letter for terlipressin, we remain confident in the strength of the data from our Phase 3 CONFIRM study, which is the largest clinical trial ever conducted in this rare condition," said **Steven Romano, M.D., Executive Vice President and Chief Scientific Officer at Mallinckrodt**. "HRS-1 is a complex disease that affects a critically ill patient population with no approved treatment in the U.S. at present. We are surprised by and disagree with the FDA's decision and remain committed to pursuing all available options as we continue working with the FDA toward approval of terlipressin in order to help address this difficult and life-threatening syndrome."

Terlipressin is an investigational agent being evaluated for the treatment of HRS-1 in the U.S., and its safety and effectiveness have not yet been established by the FDA.

Terlipressin is approved in many countries outside the United States, where it has been a standard of care for decades in the treatment of patients with HRS-1.[8,9] Terlipressin, together with albumin, is currently the standard of care for HRS-1 in countries where it is available.[10]

In 2005, terlipressin was granted Fast Track designation by the FDA, which provides for expedited review to facilitate development of drugs intended to treat serious or life-threatening conditions and fill an unmet medical need.[11] In 2016, Mallinckrodt and the FDA reached agreement on the Phase 3 CONFIRM trial protocol design and data analysis under the agency's special protocol assessment (SPA) process. A SPA is an advance agreement with the FDA for the acceptability of the clinical design, endpoints and statistical data analyses for a Phase 3 trial before the start of the trial.

On July 15, 2020, the company announced that the Cardiovascular and Renal Drugs Advisory Committee of the FDA voted to recommend approval of its investigational agent terlipressin to treat adults with HRS-1 based, in part, on results from the Phase 3 CONFIRM trial. The CONFIRM trial was the largest-ever prospective study (n=300) conducted to assess the safety and efficacy of terlipressin in patients with HRS-1 for potential use in the U.S. and Canada. Initial results were presented in a late-breaking session at The Liver Meeting® 2019, the annual meeting of the American Association for the Study of Liver Diseases (AASLD).

About Terlipressin
Terlipressin is a potent vasopressin analogue selective for V1 receptors being investigated for the treatment of HRS-1 in the U.S. and Canada. It is an investigational product in these countries as the safety and efficacy have not been established with, nor has approval been granted by, regulatory authorities in either country. Terlipressin is approved for use outside the U.S. and Canada.

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, nephrology, pulmonology and ophthalmology; 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.

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 terlipressin, including with regard to interactions with regulators as well as 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.

CONTACT

Media Inquiries
Caren Begun
Green Room Communications
201-396-8551
caren@greenroompr.com

Investor Relations
Daniel J. Speciale
Vice President, Finance and Investor Relations Officer
314-654-3638
daniel.speciale@mnk.com

References

[1] National Organization for Rare Disorders. Hepatorenal Syndrome. Available at: https://rarediseases.org/rare-diseases/hepatorenal-syndrome/. Accessed September 12, 2020.

[2] Boyer TD, Medicis JJ, Pappas SC, et al. A randomized, placebo-controlled, double-blind study to confirm the reversal of hepatorenal syndrome type 1 with terlipressin: the REVERSE trial design. *Open Access Journal of Clinical Trials*. 2012:4. https://www.dovepress.com/a-randomized-placebo-controlled-double-blind-study-to-confirm-the-reve-peer-reviewed-article-OAJCT.

[3] C Pant, B S Jani, M Desai, A Deshpande, Prashant Pandya, Ryan Taylor, R Gilroy, M Olyaee. Hepatorenal syndrome in hospitalized patients with chronic liver disease: results from the Nationwide Inpatient Sample 2002–2012. *Journal of Investigative Medicine*. 2016; 64:33–38.

[4] United States Census Bureau: Quick Facts. Available at: https://www.census.gov/quickfacts/fact/table/US/PST045218. Accessed September 12, 2020.

[5] Gines P, Sola E, Angeli P, et al. Hepatorenal syndrome. *Nature Reviews*. 2018;4:23.

[6] Colle I and Laterre PF. Hepatorenal syndrome: the clinical impact of vasoactive therapy. *Expert Review of Gastroenterology & Hepatology*. 2018;12(2):173-188. DOI: 10.1080/17474124.2018.1417034.

[7] Jamil K, Lodaya K, Tavares R, Huang X, Hayashida D. The hepatorenal syndrome patient journey: Portrait of an often-fatal path for those with liver disease. Presented at Digestive Disease Week® (DDW) Chicago, IL. May 2, 2020 – May 5, 2020.

[8] De Franchis R. Evolving Consensus in Portal Hypertension Report of the Baveno IV Consensus Workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol*. 2005;43:167-176.

[9] Ioannou GN, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database of Systematic Reviews*. 2003;1. doi: 10.1002/14651858.CD002147.

[10] European Association for the Study of the Liver (EASL). Clinical practice guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69(2):406-460.

[11] U.S. Food and Drug Administration (FDA). Fast Track. Available at https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track. Accessed September 12, 2020.

View original content to download multimedia:http://www.prnewswire.com/news-releases/mallinckrodt-receives-a-complete-response-letter-from-the-us-food-and-drug-administration-fda-for-terlipressin-for-the-treatment-of-hepatorenal-syndrome-type-1-hrs-1-301129813.html

SOURCE Mallinckrodt Pharmaceuticals