# Real-World Data of Terlipressin in Hospitalized Patients in U.K. with Hepatorenal Syndrome Type 1 (HRS-1) Published in Alimentary Pharmacology and Therapeutics

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**- U.K. medical chart study showed an association between patients treated with terlipressin and an improvement in kidney function in 73 percent of hospitalized adult patients with HRS-1 -**

STAINES-UPON-THAMES, United Kingdom, June 11, 2020 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a global biopharmaceutical company, today announced publication of findings from a medical chart study to assess the real-world use of terlipressin and other vasopressors in hospitalized patients with hepatorenal syndrome type 1 (HRS-1), an acute and life-threatening syndrome involving acute kidney failure in people with cirrhosis.[1] The study, funded by Mallinckrodt, found that terlipressin was associated with an improvement in kidney function among HRS-1 patients as measured by a reduction in serum creatinine (SCr). The results of the study were published in the peer-reviewed journal *Alimentary Pharmacology and Therapeutics*.

Mallinckrodt is investigating terlipressin for the treatment of HRS-1 in the U.S. Its safety and effectiveness have not yet been established by the U.S. Food and Drug Administration (FDA).

Medical records of 250 adult patients with HRS-1 from 26 centers in the U.K. were reviewed, 225 of whom were treated with vasopressor therapy. The majority of patients were treated with terlipressin (n=203, 90 percent) with a median duration of therapy of six days, in line with European Association for the Study of the Liver (EASL) guidelines recommending terlipressin for first-line use in patients with HRS-1.[2] A complete response (SCr reduction of ≤1.5 mg/dL) was observed in 50 percent of patients treated with terlipressin and 23 percent of those treated with other vasopressors. Overall response, as measured by a complete response or partial response (SCr reduction of at least 20 percent from baseline but SCr >1.5 mg/dL), was demonstrated in 73 percent of patients treated with terlipressin and 59 percent treated with other vasopressors. In addition, lower SCr at the time of treatment initiation was associated with higher complete response rates.[3]

"While there are limitations to medical chart study, the findings from this real-world data are encouraging for patients with HRS-1 who have limited treatment options and are often facing a poor prognosis," said lead author **Kevin Moore, M.D., UCL Institute of Liver and Digestive Health, Royal Free Hospital, University College London**.

HRS-1 has a median survival time of approximately two weeks and greater than 80 percent mortality within three months if left untreated.[4,5] At present, there are no approved drug therapies for HRS-1 in the U.S. or Canada.[6] HRS-1 is estimated to affect between 30,000 and 40,000 patients in the U.S. annually.[7,8] The company announced in April the U.S. FDA accepted its New Drug Application for review of terlipressin to treat HRS-1.

"This retrospective analysis of the use of terlipressin in HRS-1 patients, where it is approved and available, provides important insight into the real-world treatment patterns and outcomes in this rare, acute syndrome," said **Tunde Otulana, M.D., Senior Vice President and Chief Medical Officer at Mallinckrodt**. "Mallinckrodt is committed to advancing the science to benefit patients with this devastating and rapidly progressing syndrome for which effective treatment options are limited."

**About the Study**[3]
The study, titled **Real-World Treatment Patterns and Outcomes Using Terlipressin in 203 Patients with the Hepatorenal Syndrome**, was a medical chart study to assess treatment and outcomes of terlipressin and other vasopressors in 250 adult patients with HRS-1 hospitalized in 26 centers in the U.K. between January 2013 and December 2017. Ninety percent of patients were treated with terlipressin monotherapy (72 percent in combination with albumin) with an average treatment duration of six days.

- Results:
  - Terlipressin was associated with improved kidney function: the overall response rate was 73 percent and the complete response rate (SCr <1.5 mg/dL) was 50 percent of patients treated with terlipressin.
  - Lower SCr at the time of treatment initiation was associated with higher complete response rates. Mild, moderate and severe acute kidney injury (AKI) were defined by baseline SCr:
    - Mild AKI (SCr <2.25 mg/dL): 79 percent complete response.
    - Moderate AKI (SCr ≥2.25 mg/dL and <3.5 mg/dL): 55 percent complete response.
    - Severe AKI (SCr ≥3.5 mg/dL): 14 percent complete response.
  - The 90-day survival was 86 percent for all patients (93 percent for overall responders and 66 percent for treatment non-responders, $P<0.0001$).
  - Adverse events were attributed to terlipressin in 25 percent of patients and 41 percent in those treated with other vasopressors.
  - Fluid overload/pulmonary edema and multi-organ failure were the most commonly reported adverse events. Severe

AKI was associated with higher rates of adverse events (41 percent severe AKI versus 25 percent moderate AKI versus 9 percent mild AKI, *P*<0.001).

- Study Limitations:
  - Patients in the retrospective chart study likely represented a more heterogeneous population than that included in randomized controlled trials of HRS-1 patients.
  - All patients may not have met the full criteria for HRS-1 diagnosis, as diagnosis relies on clinical judgement rather than an objective diagnostic test.
  - Robustness of between treatment difference is uncertain due to lack of randomization and small number of patients on other vasopressors.
  - Changes to the 2015 International Club of Ascites Hepatorenal Syndrome (ICA-HRS) guidelines, which occurred during the study, may have altered clinicians' judgement on when to initiate treatment.
  - The study's sampling strategy may have led to higher survival and treatment response rates than seen in other settings, leading to a selection bias towards surviving patients.

**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.

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**CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS**
This release includes forward-looking statements with regard to terlipressin and the study described in this release, including 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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