October 20, 2020

Aliza Thompson, MD
Deputy Director Cardio-Renal Division

Dear Dr. Thompson:

Hepatorenal syndrome with acute kidney injury (HRS-AKI) is an uncommon complication of end stage liver disease, but it is NOT rare. HRS-AKI is associated with very high short-term mortality, and there are no approved safe and effective pharmacologic options for this condition. There is a significant unmet medical need for an improved, FDA-approved therapeutic option. Currently available off-label therapeutic options have limited efficacy and/or require ICU hospitalization. Liver transplantation is only a therapeutic option for a minority of patients due to contraindications for transplant and limited organ availability. Renal replacement therapy (RRT) is a temporary option, however RRT in this patient population is known to confer an extremely poor short prognosis and at best serve as a bridge to liver transplantation for the minority of patients who are transplantation candidates.

Terlipressin (Mallinckrodt Pharmaceuticals) is recommended in numerous academic guidelines as first-line therapy for HRS-AKI in dozens of countries, and there are significant data beyond the registration trials regarding its safety and efficacy. It is quite clear from the European experience that when terlipressin is used as early as possible in patients diagnosed with HRS-AKI that this drug saves lives that would otherwise be lost, especially as clinical experience with careful fluid management and titration of the dose of terlipressin to response is acquired. It is also clear from the CONFIRM data that the group most at risk from the predictable complications from terlipressin are those with the most advanced disease and who would easily be identifiable and excluded with a risk minimization strategy.

The CONFIRM study corroborated findings from previous pivotal trials demonstrating that terlipressin has efficacy in the HRS-AKI population. What may appear to be a modest benefit should not be underestimated given the current state of therapeutics. CONFIRM demonstrated that significantly more patients in the terlipressin group achieved the primary endpoint of verified HRS reversal compared to the placebo group (29.1% vs. 15.8%, respectively, p=0.012). In addition, there are a large number of patients that had a partial response (36.2% in the terlipressin group vs. 16.8% in the placebo group, p<0.001). From a clinical standpoint, this benefit is substantial. Furthermore, since patients in the trial were very advanced (baseline SCr$\geq$3 mg/dL in 60.3% of terlipressin and placebo groups), their prognosis was poor, thereby limiting favorable outcomes.[1,2] It is well known that starting terlipressin earlier in the process (if available) would improve efficacy outcomes and reduce adverse events and serious adverse events.

The modest adverse event profile should not preclude FDA-approval of terlipressin. The side effects are well known, and if patients are appropriately identified and managed, as they are in Europe and has been proposed by Mallinckrodt, tolerability will be acceptable given the benefits. Terlipressin has been used in

[1] Wong F, et al. The CONFIRM Study: A North American Randomized Controlled Trial of Terlipressin Plus Albumin for the Treatment of Hepatorenal Syndrome. *Hepatology.* 2019;60(Supplement 6): L05.
[2] Piano S, Schmidt HH, Ariza X et al. Association Between Grade of Acute on Chronic Liver Failure and Response to Terlipressin and Albumin in Patients with Hepatorenal Syndrome. Clin Gastroenterol Hepatol. 2018; 16:1792-1800.

Europe for decades and has been the subject of a large body of literature. There have been no new safety signals and no evidence of adverse events that make the risk vs. benefit profile problematic. Alternate effective therapies, e.g. norepinephrine, have similar or more severe side effects. These side effects would be expected for any effective vasoconstrictor.

In summary, HRS-AKI is not a rare problem and is associated with very high morbidity and mortality in patients with end stage liver disease. There are currently no FDA-approved options for pharmacologic therapy available to these patients in the US. Terlipressin therapy would add a beneficial option for the management of these patients and in the opinion of the undersigned specialists in the field, the adverse event profile is predictable and manageable. The Chronic Liver Disease Foundation and a consensus of experts who care for patients with HRS and who are familiar with this data, as well as with the long history of terlipressin, strongly urge the FDA to reconsider the decision on terlipressin and make this product available to clinicians, and more importantly, to our critically ill patients.

The Steering Committee who developed this statement include:
Kimberly Brown, MD
Robert S. Brown Jr, MD, MPH
Steven Flamm, MD
Marcelo Kugelmas, MD
Sammy Saab, MD, MPH
Hani Wadei, MD

Expert Physicians who agree with this statement include:

Nezam Afdhal, MD Boston, MA	Maliha Ahmad, MD Paterson, NJ	Aijaz Ahmed, MD Palo Alto, CA	Joseph Ahn, MD Portland, OR
Andrew Allegretti, MD Boston, MA	Walid Ayoub, MD Los Angeles, CA	Bruce Bacon, MD Saint Louis, MO	Justin Belcher, MD New Haven, CT
David Bernstein, MD Manhasset, NY	Brian Borg, MD Jackson, MS	Terry Box, MD Salt Lake City, UT	Andres Cardenas, MD Barcelona, Spain
Eddie Cheung, MD Oakland, CA	Raymond Chung, MD Boston, MA	Douglas Dieterich, MD New York, NY	Roberto Firpi-Morell, MD Gainesville, FL
Bradley Freilich, MD Kansas City, MO	Catherine Frenette, MD La Jolla, CA	Paul Gaglio, MD New York, NY	Yuri Genyk, MD Los Angeles, CA
Pierre Gholam, MD Cleveland, OH	Robert Gish, MD San Diego, CA	Aparna Goel, MD Redwood City, CA	Manuel Romero-Gomez, MD Seville, Spain
Stevan Gonzalez, MD Fort Worth, TX	Fredric Gordon, MD Burlington, MA	Jorge Herrera, MD Mobile, AL	Gideon Hirschfield, MD Toronto, ON
Ke-Qin Hu, MD Orange, CA	Prasun Jalal, MD Houston, TX	Sujit Janardhan, MD Chicago, IL	Donald Jensen, MD Chicago, IL

Arun B. Jesudian, MD New York, NY	Kris Kowdley, MD Seattle, WA	Paul Kwo, MD Palo Alto, CA	Marco A. Lacerda, MD Indianapolis, IN
Eric Lawitz, MD San Antonio, TX	Cynthia Levy, MD Miami, FL	Joseph Lim, MD New Haven, CT	Haripriya Maddur, MD Chicago, IL
Willis Maddrey, MD Dallas, TX	Richard Manch, MD Phoenix, AZ	Parvez Mantry, MD Dallas, TX	Paul Martin, MD Miami, FL
Albert Min, MD New York, NY	Mack Mitchell, MD Dallas, TX	Apurva A Modi, MD Fort Worth, TX	Andrew Muir, MD Durham, NC
Santiago Munoz, MD Pennington, NJ	Milton Mutchnick, MD Detroit, MI	Satheesh Nair, MD Memphis, TN	Christopher O'Brien, MD Miami, FL
Calvin Pan, MD New York, NY	George Papatheodoridis, MD Athens, Greece	Joykumar Patel, MD Oklahoma City, OK	Brian Pearlman, MD Atlanta, GA
Daniel S. Pratt, MD Boston, MA	Nikolaos Pyrsopolous, MD Newark, NJ	Vlad Ratziu, MD Paris, France	Natarajan Ravendhran, MD Catonsville, MD
Nancy Reau, MD Chicago, IL	Fredric Regenstein, MD New Orleans, LA	Kevin Regner, MD Milwaukee, WI	Justin Reynolds, MD Phoenix, AZ
Marina Roytman, MD Fresno, CA	Vinod Rustgi, MD New Brunswick, NJ	Eugene Schiff, MD Miami, FL	Neeral L. Shah, MD Charlottesville, VA
Obaid Shaikh, MD Pittsburgh, PA	Muhammad Sheikh, MD Fresno, CA	Samuel Sigal, MD New York, NY	Douglas Simonetto, MD Rochester, MN
Ashwani Singal, MD Sioux Falls, SD	Mitchell Shiffman, MD Richmond, VA	Coleman Smith, MD Washington, DC	Alex Thompson, MBBS, PhD Victoria, Australia
Hillel Tobias, MD New York, NY	James Trotter, MD Dallas, TX	Eugenia Tsai, MD San Antonio, TX	Naoky Tsai, MD Kailua, HI
Hugo Vargas, MD Phoenix, AZ	Mark Wong, MD Phoenix, AZ	Robert Wong, MD Palo Alto, CA	Vincent Wong, MD Hong Kong, China
Yousuf Yilmaz, MD Istanbul, Turkey	Zobair Younossi, MD Falls Church, VA		