Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
July 15, 2020

Location: Please note that due to the impact of the COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed new drug application (NDA) 22231, terlipressin, lyophilized powder for solution for injection, submitted by Mallinckrodt Pharmaceuticals, for the proposed indication of treatment of hepatorenal syndrome Type 1.

These summary minutes for the July 15, 2020 meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration were approved on August 27, 2020.

I certify that I attended the July 15, 2020 meeting of the CRDAC meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Joyce Yu, PharmD
Designated Federal Officer, CRDAC

/s/
Julia Lewis, MD
Chairperson, CRDAC

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
July 15, 2020

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 15, 2020. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Mallinckrodt Pharmaceuticals. The meeting was called to order by Julia B. Lewis, MD (Chairperson). The conflict of interest statement was read into the record by Joyce Yu, PharmD (Designated Federal Officer). There were approximately 450 people online. There were eight Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed new drug application (NDA) 22231, terlipressin, lyophilized powder for solution for injection, submitted by Mallinckrodt Pharmaceuticals, for the proposed indication of treatment of hepatorenal syndrome Type 1.

Attendance:
Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting): Jacquline D. Alikhaani, BA (Consumer Representative); C. Noel Bairey Merz, MD, FACC, FAHA, FESC; Thomas D. Cook, PhD, MS, MA; C. Michael Gibson, MD, MS; Edward K. Kasper, MD, FACC, FAHA; Julia B. Lewis, MD (Chairperson); David J. Moliterno, MD; Paul M. Ridker, MD, MPH, FACC, FAHA; Ravi I. Thadhani, MD, MPH

Cardiovascular and Renal Drugs Advisory Committee Member Not Present (Voting): Peter E. Carson, MD

Cardiovascular and Renal Drugs Advisory Committee Member Present (Non-Voting): David G. Soergel, MD (Industry Representative)

Temporary Members (Voting): David N. Assis, MD; Daniel Bonner, MBA, PMP (Patient Representative); Javed Butler, MD, MPH, MBA; Barry R. Davis, MD, PhD; Patrick H. Nachman, MD, FASN; Steven F. Solga, MD

FDA Participants (Non-Voting): Ellis F. Unger, MD; Norman Stockbridge, MD, PhD; Aliza Thompson, MD, MS; Rekha Kambhampati, MD, MHS; Tzu-Yun McDowell, PhD

Designated Federal Officer (Non-Voting): Joyce Yu, PharmD

Open Public Hearing Speakers: Catherine Nelson; Jay Beyer-Kropuenske; Lynn Seim (American Liver Foundation); K. Rajender Reddy, MD (University of Pennsylvania); Khalid Mumtaz, MBBS, MSc (Ohio State University); Hussein Elsiesy, MD (Baylor Scott & White All Saints Medical Center); Donna Cryer, JD (Global Liver Institute); Suzanna Masartis (Community Liver Alliance)

The agenda was as follows:

Call to Order and Introduction of Committee	**Julia B. Lewis, MD** Chairperson, CRDAC
Conflict of Interest Statement	**Joyce Yu, PharmD** Designated Federal Officer, CRDAC
FDA Opening Remarks	**Aliza Thompson, MD, MS** Deputy Director Division of Cardiology and Nephrology (DCN) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Mallinckrodt Pharmaceuticals**
Introduction	**Khurram Jamil, MD** Vice President, Clinical Research in Hepatology Critical Care Division, Mallinckrodt
Pathophysiology of HRS-1 and Rationale for Terlipressin	**Michael P. Curry, MD** Section Chief of Hepatology Beth Israel Deaconess Medical Center Harvard Medical School
Efficacy	**Khurram Jamil, MD**
Safety	**Chris Pappas, MD, JD, FAASLD** Clinical Hepatologist Consultant, Mallinckrodt
Risk Management	**Khurram Jamil, MD**
Benefit/Risk and Clinical Considerations	**Arun Sanyal, MD** Professor, Department of Internal Medicine Division of Gastroenterology, Hepatology and Nutrition Virginia Commonwealth University School of Medicine
Clarifying Questions	
BREAK	
FDA PRESENTATIONS	
Terlipressin for the Treatment of Hepatorenal Syndrome Type 1	**Rekha Kambhampati, MD, MHS** Medical Officer DCN, OCHEN, OND, CDER, FDA
	Tzu-Yun McDowell, PhD Clinical Analyst

DCN, OCHEN, OND, CDER, FDA

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Although FDA prospectively agreed to "HRS reversal" as the primary endpoint in CONFIRM, FDA also noted that the primary endpoint captured treatment effects on a laboratory parameter (serum creatinine) and, as such, FDA considered the endpoint to be a surrogate endpoint (as opposed to a clinical outcome). Acknowledging the challenges of designing a trial to assess effects on clinically significant outcomes in hepatorenal syndrome Type 1 (HRS-1), FDA expressed the view that, along with success on the primary endpoint, FDA expected to observe favorable trends in clinical outcomes thought to be important in the treatment of HRS-1.

   Discuss whether the trial findings provide reassurance that terlipressin's effect on verified HRS reversal is accompanied by treatment effects on clinical outcomes thought to be important in HRS-1, such as renal replacement therapy-free survival, post-transplant outcomes, and length of intensive care unit stay.

   Committee Discussion: *Committee members generally agreed that the CONFIRM trial met its primary endpoint. There were, however, different views on whether terlipressin's effect on verified HRS reversal was accompanied by favorable trends in treatment effects on clinical outcomes. Most members noted that there was a trend in improvement for renal replacement therapy-free survival, a clinically important outcome, in the terlipression arm. Members noted that treatment effects on outcomes after liver transplant were challenging to interpret, mainly because the analyses were based on post-randomization variables. Members also thought that treatment effects on length of intensive care unit stay were difficult to interpret for a variety of reasons (see transcript for details). One member thought that the data supported efficacy in patients with alcoholic hepatitis at baseline, but questioned whether terlipressin provided benefit in patients without alcoholic hepatitis at baseline. Some also voiced concern that the proportion of patients on terlipressin who received liver transplants,*

the definitive therapy for HRS-1, was lower in the terlipressin arm than on placebo. Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION:** Discuss the safety findings in CONFIRM, including the serious adverse events of respiratory failure and sepsis.

   a) What are the serious risks of terlipressin?

   b) Do the available data indicate that the serious risks of terlipressin can be adequately mitigated, and, if so, how (e.g., by appropriate patient selection, monitoring)?

   Committee Discussion: *Committee members agreed that respiratory failure and fluid overload were serious risks associated with use of terlipressin and that a clear and effective risk mitigation strategy would be needed to ensure the product's benefits outweighed its risks. Some observed that the currently proposed mitigation strategy included factors that might be difficult for hepatologists to implement because of their subjective nature (e.g., hepatologists may interpret the proposed instructions in different ways). Some voiced concern that the devised strategy was based on "slicing and dicing" the CONFIRM data and thought that the mitigation strategy should be prospectively tested and/or validated in a separate dataset. Please see the transcript for details of the Committee's discussion.*

3. VOTE: Do you recommend approval of terlipressin for the treatment of HRS-1?

   Vote Result: Yes: 8 No: 7 Abstain: 0

   Committee Discussion: *In general, members who voted for approval cited the unmet need for treatments for HRS-1, a condition associated with a high mortality rate. Members further noted that there were no approved treatments for the condition and that there were more data on the efficacy and safety of terlipressin than for other therpaies that are commonly used off-label to treat HRS-1. These members noted that CONFIRM met its primary endpoint of verified HRS reversal and that treatment with terlipressin was associated with favorable trends in renal replacement therapy-free survival. Some members noted the potential for terlipressin to be used as a "temporizing measure" to stabilize patients until liver transplant. There was general consensus that an adequate risk mitigation strategy would be needed. Proposals included a REMS (details not specified), patient consent (that patients would need to be educated on and understand risks), and/or a postmarketing study.*

   Committee members who voted "No" voiced concern about safety and the ability of the proposed strategy to mitigate risk adequately because of difficulty with implementation and/or because the strategy had not been prospectively tested. These members did not believe that the benefits of terlipressin outweighted its risks. Some members also questioned the clinical significance of the efficacy findings. Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 4:13 p.m.