Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting
March 27, 2018

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland

Topic: The committee discussed the new drug application (NDA) 209229, lofexidine hydrochloride, submitted by US WorldMeds, LLC, for mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment.

These summary minutes for the March 27, 2018 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration were approved on May 10, 2018.

I certify that I attended the March 27, 2018 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/
Kalyani Bhatt, BS, MS
Designated Federal Officer
Psychopharmacologic Drugs AC

/S/
Rajesh Narendran, MD
Chairperson
Psychopharmacologic Drugs AC

Summary Minutes of the Psychopharmacologic Drugs Advisory Committee Meeting
March 27, 2018

The Psychopharmacologic Drugs Advisory Committee (PDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on March 27, 2018 at the Tommy Douglas Conference Center, 10000 New Hampshire Ave, Silver Spring, Maryland 20903. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and US World Meds, LLC. The meeting was called to order by Rajesh Narendran, MD (Chairperson). The conflict of interest statement was read into the record by Kalyani Bhatt, BS, MS (Designated Federal Officer). There were approximately eighty (80) people in attendance. There were six (6) Open Public Hearing 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 the new drug application (NDA) 209229, lofexidine hydrochloride, submitted by US WorldMeds, LLC, for mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment.

Attendance:
Psychopharmacologic Drugs Advisory Committee Members Present (Voting):
Walter S. Dunn, MD, PhD; Jess G. Fiedorowicz, MD, PhD; Felipe A. Jain, MD; Jessica J. Jeffrey, MD, MPH, MBA (via phone); Rajesh Narendran, MD (Chairperson); David Pickar, MD; Erick H. Turner, MD; Kim O. Witczak (Consumer Representative)

Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting):
Satish Iyengar, PhD

Psychopharmacologic Drugs Advisory Committee Members Present (Non- Voting):
Robert R. Conley, MD (Industry Representative)

Temporary Members (Voting): Kathleen T. Brady, MD, PhD; Kathleen M. Carroll, PhD; Sabrina Numann (Patient Representative); Michael Proschan, PhD

FDA Participants (Non-Voting): Mary Thanh-Hai, MD; Sharon Hertz, MD; Celia Winchell, MD; Pamela Horn, MD; David Petullo, MS; Yi Ren, PhD

Designated Federal Officer (Non-Voting): Kalyani Bhatt, BS, MS

Open Public Hearing Speakers: Laura Parrish; Travis N. Reider, PhD; Maureen Elias (The Veterans Health Council, Vietnam Veterans of America); Sidney Wolfe, MD (Public Citizen); Megan Polanin, PhD (National Center for Health Research; Pat Bielecki

The agenda was as follows:

Call to Order and Introduction of Committee	**Rajesh Narendran, MD** Chairperson, PDAC
Conflict of Interest Statement	**Kalyani Bhatt, MS** Designated Federal Officer, PDAC
FDA Opening Remarks	**Celia Winchell, MD** Clinical Team Leader Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) Office of Drug Evaluation II (ODE II) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**US WorldMeds, LLC.**
Opening Remarks	**Kristen Gullo** Vice President Development & Regulatory Affairs, US WorldMeds
Medical Landscape	**Louis Baxter, MD, DFASAM, DABAM** Executive Medical Director, Professional Assistance Program of NJ, Inc.
Introduction to LUCEMYRA (lofexidine) Development	**Kristen Gullo**
Lofexidine Trial Program	**Marc Fishman, MD** Medical Director, Maryland Treatment Centers Assistant Professor Johns Hopkins University School of Medicine
Efficacy	**Charles Gorodetzky, MD, PhD** Former Medical Officer, US WorldMeds Principal Investigator, Lofexidine Clinical Trials Consultant, Pharmaceutical Medicine
Safety	**Mark Pirner, MD, PhD** Senior Medical Director US WorldMeds, LLC
Clinical Perspective	**Thomas Kosten, MD** Waggoner Chair and Professor of Psychiatry and Pharmacology Baylor College of Medicine

Clarifying Questions

BREAK

FDA PRESENTATIONS

Clinical and Statistical Review of Lofexidine	**Pamela Horn, MD** Clinical Reviewer DAAAP, ODE II, OND, CDER, FDA
	Yi Ren, PhD Statistical Reviewer Division of Biometrics II Office of Biostatistics Office of Translational Sciences, CDER, FDA

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Two concepts are under consideration, a) mitigation of symptoms associated with opioid withdrawal and b) facilitation of completion of abrupt opioid discontinuation treatment in patients with opioid use disorders (OUD).

   Discuss whether an effect on completion rates of abrupt discontinuation treatment is necessary to establish the clinical relevance of the efficacy data for mitigation of symptoms associated with opioid withdrawal. Could a finding of efficacy be made without data supporting both?

   Committee Discussion: *A couple of committee members noted it is important to demonstrate clinical relevance, such as an effect on completion rates of opioid withdrawal treatment. Most members were reassured that the data presented by the Applicant had established an*

effect on both symptomatic relief and study completion rates. Several of the committee members voiced opinions that an effect on withdrawal symptoms in itself has public health relevance. These members noted that one can make a connection based on pathophysiology and clinical experience that patients who are past the physical withdrawal symptoms are more likely to be able to abstain from opioids (at least in the short-term). One member stated that even small changes in withdrawal symptoms can improve the likelihood of a patient successfully completing detoxification from opioids.

Please see the transcript for details of the committee discussion.

2. **VOTE:** Do the data provide substantial evidence of effectiveness of lofexidine for the mitigation of symptoms associated with opioid withdrawal?

Vote Result: ***Yes:*** *12* ***No:*** *0* ***Abstain:*** *0*

Committee Discussion: *After clarifying that the question should refer to effectiveness in mitigation of symptoms of withdrawal in the context of abrupt discontinuation of opioids (and not in the context of taper), the panel members unanimously agreed that the data did provide substantial evidence of effectiveness of lofexidine for the mitigation of symptoms associated with opioid withdrawal. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** Discuss the appropriateness of including facilitation of completion of abrupt opioid discontinuation treatment as a second indication. Is this supported by the data provided?

Committee Discussion: *One member stated that there was no harm in including facilitation of abrupt opioid discontinuation treatment as a second indication. Another member mentioned the data shown supports inclusion of this as a second indication. However, many of the committee members opined that the available data do not support this indication. These members noted that the time-point for completion of opioid withdrawal treatment (5-7 days) is a bit arbitrary and including this as a second indication based on these data would send the wrong message to a patient with respect to the need to be engaged in long term treatment. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** Discuss which dosing regimen is best supported by the data, given the similarity in efficacy results and differences in toxicity between the 3.2 mg and 2.4 mg per day doses.

Committee Discussion: *Most of the members agreed that there were negligible differences with respect to efficacy between the two doses. They also agreed that the higher dose (3.2 mg) carries significantly increased risk to patients. One member noted concerns about bradycardia, hypotension, the lack of data to support use beyond 7-14 days, and rebound hypertension. Some members noted it would be useful to communicate to clinicians the need to consider lower and flexible dosing strategies to reduce the risks. Please see the transcript for details of the committee discussion.*

5. **DISSCUSION:** Discuss the adequacy of the available safety data to support use between 7 and 14 consecutive days.

   Committee Discussion: *Most members of the committee agreed that the available safety data support use between 7-14 days. However, two members raised concerns with respect to opioid abusers having to repeatedly go back on the medication based on limited exposure data (due to multiple relapses and detoxification treatments they would undergo during the course of their disorder). Please see the transcript for details of the committee discussion.*

6. **VOTE:** Do you recommend approval of this application?

   Vote Result: ***Yes: 11*** ***No: 1*** ***Abstain: 0***

   Committee Discussion: *The majority of the panel members recommended approving this NDA application for mitigation of symptoms associated with opioid withdrawal but not for facilitation of completion of opioid discontinuation treatment. Additionally, most of the panel members agreed to the use of the 2.4 mg per day dose but not the 3.2 mg per day dose. One member voted "No" based on increased risks at the higher dose and limited safety data (with respect to duration of exposure) based on the trials. Please see the transcript for details of the committee discussion.*

7. **DISCUSSION:** Discuss any issues that should be evaluated using postmarketing requirements.

   Committee Discussion: *The panel members recommended postmarketing studies to examine: the risks of rebound hypertension; QTc prolongation when combined with psychotropic medications; use of the medication to treat withdrawal symptoms when opioids (both illegal and prescription opioids, including methadone) are gradually tapered as opposed to abruptly discontinued; and its use in adolescent and child opioid use disorders who may be on concurrent Attention-Deficit/Hyperactivity Disorder (ADHD) medications. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 3:10 p.m.