Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the
Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
October 31, 2017

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

Topic: The committees discussed new drug application (NDA) 210136, buprenorphine subcutaneous injection, submitted by Braeburn Pharmaceuticals, Inc., for treatment of opioid dependence.

These summary minutes for the October 31, 2017 joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting of the Food and Drug Administration were approved on December 4, 2017.

I certify that I attended the October 31, 2017 Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/S/

Kalyani Bhatt,
Designated Federal Officer, PDAC

/S/

Rajesh Narendran, MD,
Chairperson, PDAC

Summary Minutes

Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

October 31, 2017

The following is a final report of the joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee held on October 31, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Division of Anesthesia, Analgesic, and Addiction Products and the Office of Safety and Epidemiology and posted on the FDA website at:
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/ucm535446.htm and
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm536632.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met jointly on October 31, 2017, at the FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA, and from Indivior Inc. 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 130 people in attendance for the meeting. There were 8 Open Public Hearing speakers.

Issue: The committees discussed new drug application (NDA) 209819, buprenorphine subcutaneous injection, submitted by Indivior, Inc., for treatment of opioid dependence.

Attendance:

Psychopharmacologic Drugs Advisory Committee Members Present (Voting): Satish Iyengar, PhD; Rajesh Narendran, MD (Chairperson)**;** David Pickar, MD; Erick H. Turner, MD; Kim O. Witczak (Consumer Representative)

Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting): Walter S. Dunn, MD, PhD; Jess G. Fiedorowicz, MD, PhD; Felipe A. Jain, MD; Jessica J. Jeffrey, MD, MPH, MBA

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

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Denise M. Boudreau, PhD, RPh; Laurel A. Habel, MPH, PhD; Steven B. Meisel, PharmD;

Suzanne B. Robotti (Consumer Representative); Anne-Michelle Ruha, MD, FACMT; Almut Winterstein, RPh, PhD, FISPE

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Kelly Besco, PharmD, FISMP, CPPS; Niteesh K. Choudhry, MD, PhD; Christopher H. Schmid, PhD; Soko Setoguchi, MD, DrPh; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

Drug Safety and Risk Management Advisory Committee Members Not Present (Non-Voting):
Linda Scarazzini, MD, RPh (Industry Representative)

Temporary Members (Voting): G. Caleb Alexander, MD, PhD; Kathleen T. Brady, MD, PhD; Chester Buckenmaier, II, MD; Kathleen M. Carroll, PhD; Daniel Ciccarone, MD, MPH; Adam J. Gordon, MD, MPH, FACP, FASAM; Daniel L. Krinsky, MS, RPh; Sabrina Numann (Patient Representative)

FDA Participants (Non-Voting): Sharon Hertz, MD; Rigoberto Roca, MD; Celia Winchell, MD; Judy Staffa, PhD, RPh; Cynthia LaCivita, PharmD; Dominic Chiapperino, PhD

Open Public Hearing Speakers: Amit Vijapura, MD; Ayeisha A. Cox (Center for Lawful Access and Abuse Deterrence (CLAAD); statement read by Patty McCarthy Metcalf); Dr. Danielle Shapiro (National Center for Health Research); Susan Awad (American Society of Addiction Medicine); General Arthur T. Dean (Community Anti-Drug Coalitions of America); Victoria Wilson; Patty McCarthy Metcalf (Faces and Voices of Recovery); James L. Andersen, M.D. FASAM

The agenda was as follows:

Call to Order and Introduction of Committee	**Raj 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	**Indivior, Inc.**
Introduction	**Susan Learned, MD, PharmD, PhD**

Medicines Development Program RBP-6000	Senior Vice-President of Global Medicines Development, Indivior Inc.
Need for Improvements In the Treatment of Opioid Use Disorder	**Brent Boyett, DO, DMD** Boyett Health Services Inc.
Clinical Pharmacology, RBP-6000	**Celine Laffont, PhD** Director, Quantitative Clinical Pharmacology Indivior Inc.
Clinical Efficacy, RBP-6000	**Barbara Haight, PharmD** Medicines Development Lead and Senior Director RBP-6000, Indivior Inc.
Clinical Safety, RBP-6000	**Anne Andorn, MD** Head Late Stage Clinical Development Indivior Inc
Clinical Perspective	**Eric C. Strain, MD** Director, John Hopkins Center for Substance Abuse Treatment and Research, John Hopkins University
Clarifying Questions	

BREAK

FDA PRESENTATIONS

Clinical Overview	**Emily Deng, MD, MPH** Clinical Reviewer DAAAP, ODEII, OND, CDER, FDA
Blockade Study: Analyses and Issues	**Alan Trachtenberg, MD, MPH** Clinical Reviewer Controlled Substance Staff Office of Center Director, CDER, FDA
	Qianyu Dang, PhD Lead Statistician Division of Biostatistics VI, Office of Biostatistics (OB), Office of Translational Sciences (OTS) CDER, FDA

Blockade Study: Pharmacokinetic-Pharmacodynamic Analyses of Drug Liking	**Michael Bewernitz, PhD** Pharmacometrics Reviewer Division of Pharmacometrics Office of Clinical Pharmacology, OTS, CDER, FDA
Clinical and Statistical Review	**Feng Li, PhD** Statistics Reviewer Division of Biostatistics II, OB, OTS, CDER, FDA **Emily Deng, MD, MPH**
Proposed Risk Evaluation and Mitigation Strategies (REMS) for RBP-6000	**Somya Dunn, MD** Commander, United States Public Health Service RISK Management Analyst Division of Risk Management Office of Surveillance and Epidemiology CDER, FDA
Clarifying Questions	

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee	**Sharon Hertz, MD** Director DAAAP, ODEII, OND, CDER, FDA

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **VOTE:** Do the data from the clinical trial, taken together with the results of the blockade study, provide substantial evidence of effectiveness of RBP-6000 for the treatment of opioid use disorder in patients who had undergone induction with a transmucosal buprenorphine product?

***YES**: 17* **NO**: *2* ***Abstain:** 0*

Committee Discussion: *The majority of the committee members agreed that the data from the clinical trial, taken together with the results of the blockade study, provide substantial evidence of effectiveness of RBP-6000 for the treatment of opioid use disorder in patients who had undergone induction with a transmucosal buprenorphine. Those voting "Yes", stated that they view the data from the clinical trial and results of the blockade study to suggest that RBP-6000 is comparable to sublingual buprenorphine. Some members stated that the results seen in the clinical trial may be less generalizable in the real world, because the study did not examine the use of fentanyl and other synthetic opioids. Those committee members voting "No", expressed concerns over the limited amount of clinical trial data and concerns of liver toxicity at the highest doses examined. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Do the provided safety data sufficiently support the use of the proposed RBP 300 mg/300 mg dose regimen, given that the steady-state plasma exposures associated with RBP-6000 300 mg exceed those associated with the highest labeled dose of the reference product, Subutex?

***YES**: 13* ***NO:** 6* ***Abstain:** 0*

Committee Discussion: *The majority of the committee members agreed that the safety data sufficiently supported the use of the proposed RBP 300 mg/300 mg dose regimen, even though the steady-state plasma exposures associated with RBP-6000 300 mg exceed those associated with the highest labeled dose of the reference product, Subutex. Those voting "Yes", stated that it is necessary in clinical practice to go up on the dose of buprenorphine for effectiveness; the higher dose is needed for some patients with more severe opioid use disorders and it is good to keep the higher dose option for some patients who may be in need; the risks with hepato-toxicity do not seem inconsistent with what we already know/have seen with sublingual buprenorphine; and it is good to have some flexibility in dosing patients. Those committee members voting "No", expressed concerns that they were unconvinced completely about the higher dose's added efficacy; they need to see more clinical safety data*

for the highest dose; and more toxicology studies are warranted. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Discuss the role of the RBP-6000 300/300 mg regimen, given the similarity in efficacy results between the RBP-6000 300/300 mg and RBP-6000 300/100 mg.

Committee Discussion: *The majority of the committee members agreed that both the RBP-6000 300/300 mg and 300/100 mg regimen are efficacious. Committee members stated they mostly see no significant difference in the doses with respect to efficacy given that there is no good evidence against it. The members further stated that the higher doses should include liver function monitoring. Some members commented it would be useful to see a clinical trial to determine whether the maintenance dose of sublingual buprenorphine is predictive of the need for higher RBP-6000 doses. The members also wanted to see more clinical trial data on the characteristics of patients (severity, frequency, intravenous users, etc.,) that exactly benefit by the higher 300/300 mg dose regimen. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** Discuss the pros and cons of the restricted distribution under a Risk Evaluation and Mitigation Strategy (REMS), as proposed by the Applicant, to mitigate the risks that might ensue from direct distribution of RBP-6000 to patients.

    a. What barriers to access may arise from implementing a restricted distribution system?

    b. What systemic or institutional barriers might be anticipated for a restricted distribution system?

    c. What modifications might address barriers to access while mitigating risk?

    d. Is the proposed REMS sufficient, or are other measures needed?

Committee Discussion: *The majority of the committee members agreed with the need for the FDA proposed addition to the applicant's proposed REMS to include a one-time certification of health care settings that order and dispense RBP-6000 to put systems in place from being dispensed directly to the patient. Some committee members wanted to ensure this certification process is not extremely burdensome and attainable by smaller health care settings so that it could reach individuals who are most in need of RBP-6000 (example, rural settings, criminal justice system, for all States to be able to accept and implement this within their own laws, etc.,). Some members favored a registry to keep track of individuals who are being prescribed RBP-6000. Some members wanted community pharmacies to somehow be notified that the patients' current medication list that includes RBP-6000 to avoid prescribing/dispensing drugs with interactions with it. Please see the transcript for details of the committee discussion.*

5. VOTE: Do you recommend approval of this application?

YES: 18 NO: 1 Abstain: 0

Committee Discussion: *The majority of the committee stated that the benefit and safety profile of buprenorphine was favorable for approval. The committee member voting "No", expressed concerns over need for more data for safety. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 4:20 p.m.