Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
November 1, 2018

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 efficacy, safety and risk-benefit profile of new drug application (NDA) 210417 for buprenorphine and samidorphan sublingual tablets, submitted by Alkermes, Inc., for adjunctive treatment of major depressive disorder.

These summary minutes for the November 1, 2018 meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration were approved on December 10, 2018.

I certify that I attended the November 1, 2018 meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management 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 meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
November 1, 2018

The meeting of 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 November 1, 2018, 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 Alkermes, 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 225 people in attendance for the meeting. There were 13 Open Public Hearing speaker presentations.

Issue: The committees discussed efficacy, safety and risk-benefit profile of new drug application (NDA) 210417 for buprenorphine and samidorphan sublingual tablets, submitted by Alkermes, Inc., for adjunctive treatment of major depressive disorder.

Attendance:

Psychopharmacologic Drugs Advisory Committee Members Present (Voting): Walter S. Dunn, MD, PhD; Jess G. Fiedorowicz, MD, PhD; Satish Iyengar, PhD; Felipe A. Jain, MD; Rajesh Narendran, MD (Chairperson); Kim O. Wictzak (Consumer Representative)

Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting): Jessica J. Jeffrey, MD, MPH, MBA; Erick Turner, MD

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

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Kelly Besco, PharmD, FISMP**,** CPPS; Marie R. Griffin, MD, MPH; Laurel A. Habel, MPH, PhD; Sonia Hernandez-Diaz, MD, MPH, DrPH; Martin Kulldorff, PhD; Steven B. Meisel, PharmD; Anne-Michelle Ruha, MD, FACMT; Anne-Michelle Ruha, MD, FACMT; Terri L. Warholak, PhD, RPh, CPHQ, FAPhA

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Denise M. Boudreau, PhD, RPh; Suzanne B. Robotti (Consumer Representative); Soko Setoguchi, MD, DrPh

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

Temporary Members (Voting): Jane B. Acri, PhD; David Cella, PhD; Stephanie Y. Crawford, PhD, MPH; Harriet de Wit, PhD; Kathryn E. Flynn, PhD; Roxanne E. Jensen, PhD; Elizabeth Joniak-Grant (Patient Representative); Brandon D.L. Marshall, PhD; William T. Riley, PhD

FDA Participants (Non-Voting): Robert Temple, MD; Ellis Unger, MD; Mitchell Mathis, MD; Judy Staffa, PhD, RPh; Tiffany, Farchione, MD; Dominic Chiapperino, PhD; Daniel J. Lee, MD; Semhar Ogbagaber, PhD

Open Public Hearing Speakers: Maurizio Fava, MD (Massachusetts General Hospital and Harvard Medical School); Nathaniel Z. Counts, JD (Medical Health America); Ali Walker; Gordon Corsetti; J. Alexander Bodkin, MD (McLean Hospital); Kathryn Wichmann (Depression and Bipolar Support Alliance), Allen Sweatt (statement read by Eric Scharf) (Depression and Bipolar Support Alliance); Andrew Sperling (National Alliance on Mental Illness); Michael Pollock, (Depression and Bipolar Support Alliance); John H. Madigan, Jr.; Lauren Kenney; Angelo Sambunaris, MD; Stephanie Rawlings, PhD (National Center for Health Research)

The Agenda was as follows:

Call to Order and Introduction of Committee	**Raj Narendran, MD** Chairperson, PDAC
Conflict of Interest Statement	**Kalyani Bhatt, BS, MS** Designated Federal Officer, PDAC
FDA Opening Remarks	**Mitchell Mathis, MD** Director Division of Psychiatry Products (DPP) Office of Drug Evaluation I (ODE I) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Alkermes, Inc.**
Introduction	**Lisa von Moltke, MD** Senior Vice President, Clinical Development Alkermes, Inc.
The Unmet Need in MDD, and Challenges in MDD Clinical Trials	**George Papakostas, MD** Harvard Medical School Massachusetts General Hospital
Clinical Efficacy	**Jerald Schindler, DrPH** Vice President, Biostatistics Alkermes, Inc.

Clinical Safety, and Risk Mitigation Strategies	**Gary Bloomgren, MD** Vice President, Drug Safety and Pharmacovigilance Alkermes, Inc.
Clinical Perspective and Benefit-Risk Profile	**Sanjay Mathew, MD** Baylor College of Medicine
Conclusion	**Lisa von Moltke, MD**

Clarifying Questions to Applicant

BREAK

FDA PRESENTATIONS

Regulatory History	**Tiffany Farchione, MD** Deputy Director DPP, ODE I, OND, CDER, FDA
Clinical Efficacy and Safety Overview	**Semhar Ogbagaber, PhD** Statistician Division of Biometrics I Office of Biostatistics Office of Translational Sciences, CDER, FDA **Daniel J. Lee, MD** Clinical Reviewer DPP, ODE I, OND, CDER, FDA
Abuse Potential of Buprenorphine/Samidorphan (BUP/SAM)	**Edward Hawkins, PhD** Pharmacologist Controlled Substance Staff Office of the Center Director, CDER, FDA
FDA Review of the Epidemiologic and Surveillance Data	**Celeste Mallama, PhD, MPH** Epidemiologist Division of Epidemiology II Office of Surveillance and Epidemiology (OSE) CDER, FDA

UNIVERSITY OF WASHINGTON MEDICAL SCHOOL DEPARTMENT OF PSYCHIATRY & BEHAVIORAL SCIENCES PRESENTATION

Depression Effects On Long-Term Prescription Opioid Use, Abuse and Addiction	**Mark Sullivan, MD, PhD** Professor, Psychiatry and Behavioral Sciences University of Washington Medical Center

FDA PRESENTATIONS (cont.)

Risk Management for Buprenorphine/Samidorphan	**Somya Dunn, MD** Commander, United States Public Health Service Risk Management Analyst Division of Risk Management, OSE, CDER, FDA

Clarifying Questions to FDA and Dr. Sullivan

LUNCH

OPEN PUBLIC HEARING

Charge to Committee **Mitchell Mathis, MD**

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **VOTE**: Has substantial evidence been presented by the Applicant to support the effectiveness of buprenorphine/samidorphan for the adjunctive treatment of major depressive disorder?

Vote Result: ***Yes: 3*** ***No: 20*** ***Abstain: 0***

Committee Discussion*: The majority of the members voted "No" and agreed that there was not substantial evidence to support the effectiveness of buprenorphine/samidorphan for the adjunctive treatment of major depressive disorder. Those members who voted "Yes" were convinced that the analysis that was conducted was adequate with a restricted Risk Evaluation and Mitigation Strategy (REMS) program. Please see the transcript for details of the committee discussion.*

2. **VOTE**: Has the Applicant adequately characterized the safety profile of buprenorphine/samidorphan for the adjunctive treatment of major depressive disorder?

Vote Result: ***Yes: 13*** ***No: 10*** ***Abstain: 0***

Committee Discussion *The committee members who voted "Yes" agreed that the safety profile of buprenorphine/samidorphan was well characterized, and there seemed to be minimal withdrawal effects, and abuse liability. However, the committee members who voted, "No" had concerns that buprenorphine could be separated from samidorphan, some opioid-induced euphoria and withdrawal is still evident with the buprenorphine/samidorphan, and*

there are potential risks in using this compound to treat depression because of the established links between depression-pain-addictive disorders. Please see the transcript for details of the committee discussion.

3. **DISCUSSION:** Related to the potential risks associated with the use, misuse, and abuse of buprenorphine/samidorphan in post-market settings:
   1. Discuss any concerns you have about the risks of misuse, abuse, addiction, or overdose with buprenorphine/samidorphan in the intended patient population or in others who may access the drug.
   2. Discuss any concerns you have more generally about approving a product containing buprenorphine, an opioid, for the first time, for the treatment of depression.
   3. Discuss whether you are concerned about the risk of opioid overdose if other opioids are used, misused, or abused concurrently with buprenorphine/samidorphan, perhaps in higher doses intended to overcome buprenorphine/samidorphan's μ-opioid antagonist effects, with potential additive opioid agonist effects that have not been fully characterized.
   4. What risk reduction strategies could be implemented to decrease risks associated with buprenorphine/samidorphan use?

Committee Discussion: *Some committee members voiced concerns that family members may take the drugs, and this may increase the risk of abuse and overdose. However, some members were reassured that the 2mg/2mg dose was low enough to not be of a concern for serious overdose. Some members raised concerns about the long-term risks of using an opioid medication in a disorder that requires long duration of treatment. The committee members also voiced concerns with respect to prescribing an opioid medication because of the link between major depressive disorder-pain and addictive disorders. Few members had concerns about the risk of patients getting high dose narcotics for pain to override the effects of buprenorphine/samidorphan in acute emergency settings, and the risk of buprenorphine/samidorphan precipitating withdrawal in patients on medication assisted treatment (in case both are not prescribed by the same providers), etc. Some members endorsed a REMS that would include urine drug screens before initiation of the medication, monitoring individuals for abuse, advocated a formulation in which buprenorphine/samidorphan cannot be easily separated (to reduce risk of diversion), and making prescribing practices at least as restrictive (i.e., keeping track of number of scripts and patients written by providers, tracking patients receiving the medication, etc.) Please see the transcript for details of the committee discussion.*

4. **VOTE**: Do the available data support a favorable benefit-risk profile of buprenorphine/samidorphan to support approval?

Vote Result: ***Yes: 2*** ***No: 21*** ***Abstain:0***

Committee Discussion: *Most of the committee members agreed that the available data do not support a favorable benefit-risk profile of buprenorphine/samidorphan to support*

approval. The two members who voted "Yes" provided qualified support to approve it and recommended a strong REMS program. Please see the transcript for details of the committee discussion.

5. **DISCUSSION**: What, if any, additional data are needed pre- or post-approval to address outstanding issues with buprenorphine/samidorphan? Please be clear whether you believe these data should be required prior to approval.

Committee Discussion: *Committee members recommended studies: to get more clarity on responders (i.e., who are the super-responders who benefit the most from the drug); to get more data on long-term response and remission rates; consider studies in individuals with comorbid depression and pain; conduct an adequately powered study to measure the small effect; a medication discontinuation study to quantify the effects of opioid withdrawal with the medication; and in vivo receptor occupancy studies to understand it's mechanism of action of the 2mg/2mg dose. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 5:00 p.m.