Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the of the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) October 9, 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 committees discussed the efficacy, safety, and benefit-risk profile of new drug application (NDA) 213378, olanzapine/samidorphan oral tablets, submitted by Alkermes, Inc., for the proposed indications of schizophrenia and bipolar I disorder.

These summary minutes for the October 9, 2020 joint meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) were approved on January 4, 2021.

I certify that I attended the October 9, 2020 joint meeting of the PDAC and DSaRM of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
LaToya Bonner, PharmD	Rajesh Narendran, MD
Acting Designated Federal Officer, PDAC	Chairperson, PDAC

Final Summary Minutes of the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) October 9, 2020

The Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (DSaRM) of the Food and Drug Administration (FDA), Center for Drug Evaluation and Research, met on October 9, 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 and pre-recorded presentations 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 LaToya Bonner, PharmD (Acting Designated Federal Officer). There were approximately 400 people online. There were a total of 20 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 committees discussed the efficacy, safety, and benefit risk profile of new drug application (NDA) 213378, olanzapine/samidorphan oral tablets, submitted by Alkermes, Inc., for the proposed indications of schizophrenia and bipolar I disorder.

Attendance:

PDAC Members Present (Voting): Walter S. Dunn, MD, PhD; Jess G. Fiedorowicz, MD, PhD; Satish Iyengar, PhD; Felipe A. Jain, MD; Jessica J. Jeffrey, MD, MPH, MBA; Sonia L. Krishna, MD, FAPA, DFAACAP; Rajesh Narendran, MD (*Chairperson*); Patrick S. Thomas, Jr., MD, PhD; Kim O. Witczak (Consumer Representative)

PDAC Members Not Present (Voting): None

PDAC Member Not Present (Non-Voting): Robert W. Baker, MD (Industry Representative)

DSaRM Members (Voting): Denise M. Boudreau, PhD, RPh; Karim Anton Calis, PharmD, MPH, FASHP, FCCP; Steven B. Meisel, PharmD, CPPS

DSaRM Members Not Present (Voting): Marie R. Griffin, MD, MPH; Laurel A. Habel, MPH, PhD; Sonia Hernandez-Diaz, MD, MPH, DrPH; Collin A. Hovinga, PharmD, MS, FCCP; Martin Kulldorff, PhD; Lewis S. Nelson, MD; Soko Setoguchi, MD, DrPH

DSaRM Member (Non-Voting): Reema J. Mehta, PharmD, MPH (Industry Representative)

Temporary Members (Voting): Maryann Amirshahi, PharmD, MD, MPH, PhD; Amy S.B. Bohnert, PhD, MHS; Erin E. Krebs, MD, MDH; Matthew Racher, BA, CRPS (Patient Representative); Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP

FDA Participants (Non-Voting): Billy Dunn, MD; Eric Bastings, MD; Tiffany R. Farchione, MD; Bernard Fischer, MD; Judy Staffa, PhD, RPh; Cathy Southammakosane, MD; Jana McAninch, MD, MPH, MS

Acting Designated Federal Officer (Non-voting): LaToya Bonner, PharmD

Open Public Hearing Speakers: Phyllis Foxworth (Depression and Bipolar Support Alliance); Andrew Sperling (National Alliance on Mental Illness); Luke Kramer (The STARR Coalition); Kathy Bernstein; Linda Stalters, MSN, APRN (ret) (Schizophrenia And Related Disorders Alliance of America); Michelle Hammer (Schizophrenic.NYC); Meg Seymour, MD (National Center for Health Research); Ralph Aquila, MD; Alan L. Podawiltz, DO, MS, FAPA; Chris Bullard; Jason Wright (Oddball Magazine and the Oddball Foundation); Roger McIntyre, MD, FRCPC (Depression & Bipolar Support Alliance Scientific Advisory Board); Debbie F. Plotnick, MSS, MLSP; Jacob S. Ballon, MD, MPH; Michael T. Abrams, MPH, PhD (Health Research Group of Public Citizen); Andrew A. Nierenberg, MD; Joseph McEvoy, MD; Cecilia McGough; Thomas R. Kosten, MD; Christopher Correll, MD

The agenda was as follows:

Call to Order	**Rajesh Narendran, MD** Chairperson, PDAC
Introduction of Committee and Conflict of Interest Statement	**LaToya Bonner, PharmD** Acting Designated Federal Officer, PDAC
FDA Opening Remarks	**Bernard Fischer, MD** Deputy Director (Acting) Division of Psychiatry (DP) Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATION	**Alkermes, Inc.**
Summary Presentation	**Sarah Akerman, MD** Senior Medical Director, Medical Affairs Alkermes, Inc.
Clarifying Questions to Applicant	
Clarifying Questions to FDA	
LUNCH	
OPEN PUBLIC HEARING Questions to the Committee/Committee Discussion	

ADJOURNMENT

Questions to the Committee:

1. **VOTE:** Has the Applicant presented adequate evidence that samidorphan meaningfully mitigates olanzapine-associated weight gain?

   Vote Results: **Yes: 16** **No: 1** **Abstain: 0**

   Committee Discussion: *The majority of the committee members agreed that the Applicant presented adequate evidence that samidorphan meaningfully mitigates olanzapine-associated weight gain. The members were convinced by the data shown related to waist circumference reductions, lowered blood pressure measures, and overall weight gain mitigation (less weight gain in patients treated with ALKS 3831 than those administered olanzapine alone). Due to the low-risk population studied, some committee members suggested for the Applicant to broaden their studied population to reveal efficacy findings that can be applied to real-world settings. In addition, the members noted the need for further information on samidorphan, due to the safety concerns related to samidorphan's opioid antagonistic effect. The member that voted "No", stated that the overall weight gain mitigation was minimal, and the quality of life was non-impactful (minimum to none). Please see the transcript for details of the Committees' discussion.*

2. **VOTE:** Has the Applicant adequately characterized the safety profile of ALKS 3831 (olanzapine/samidorphan)?

   Vote Results: **Yes: 13** **No: 3** **Abstain: 1**

   Committee Discussion*: The majority of the committee members voted "Yes", agreeing that the Applicant adequately characterized the safety profile of olanzapine/samidorphan; however, some expressed the need for more post-marketing surveillance data on the safety of samidorphan. These members also suggested further data on the safety profile of samidorphan's metabolites in conjunction with other prescribed opioids. For those who voted, "No", they acknowledged the safety parameters of olanzapine but were not confident in the data shown regarding samidorphan's safe use. These panel members noted the potential of samidorphan to precipitate withdrawal in patients who are physically dependent on opioids, the possible ineffectiveness of analgesia when opioids are medically necessary, and the potential of opioid overdose due to possible efforts to overcome samidorphan's opioid receptor blocking effects. Overall, the committee members recommended additional safety data, specifically, pharmacokinetics (PK) studies of samidorphan's mu opioid affinity, metabolites and saturation data. Please see the transcript for details of the Committees' discussion.*

3. **VOTE:** Is labeling sufficient to mitigate the risks related to the opioid antagonist action of samidorphan?

Vote Result: **Yes: 11** **No: 6** **Abstain: 0**

Committee Discussion: *The majority of the committee members voted "Yes", agreeing that the labeling will be sufficient to mitigate risks associated with the opioid antagonist action of samidorphan. These members acknowledged the importance of labeling but agreed that other factors, such as post-marketing surveillance and responsible advertisement, are imperative to assure public safety. The committee members that voted "No", expressed that labeling was not enough to secure public safety, noting samidorphan is a new molecular enitity and its safety profile is unknown. In addition, these members conveyed their concerns about probable prescribing errors made by non-psychiatrists who would likely not be cognizant of the possible interactions with the patient's regimen.*

Collectively, the committee members expressed that more education is needed. The members recommended that targeted education towards opioid-prescribing healthcare providers should be considered and a comprehensive education plan should be established targeting psychiatric providers and patients. Please see the transcript for details of the Committees' discussion.

4. **DISCUSSION:** What, if any, additional data are needed to address outstanding issues of ALKS 3831 (olanzapine/samidorphan)?

   Committee Discussion*: The committee members provided several recommendations for additional data needed to address the outstanding issues of olanzapine/samidorphan. These include*
   - *positron emission tomography (PET) studies during and after therapy has been discontinued to assess samidorphan receptor occupancy*
   - *data showing the effects (i.e., weight and metabolic syndrome) of switching patients from olanzapine to olanzapine/samidorphan*
   - *data on non-compliant patients and their benefits/risks effects*
   - *opioid overdose data associated with olanzapine/samidorphan use*
   - *studies on other sub-populations (patients with higher BMI, bipolar disorder patients, and younger patients (18 – 25 y/o))*
   - *data on off-label use and long-term use*
   - *information on metabolic syndrome properties and adverse events*

   Please see the transcript for details of the Committees' discussion.

The meeting was adjourned at approximately 3:38 p.m.