Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
February 12, 2019

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) 211243, esketamine 28 mg single-use nasal spray device, submitted by Janssen Pharmaceuticals, Inc., for the treatment of treatment-resistant depression.

These summary minutes for the February 12, 2019 joint meeting of the Psychopharmacologic Drugs Advisory Committee of the Food and Drug Administration were approved on March 14, 2019.

I certify that I attended the February 12, 2019 joint 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

Final Summary Minutes of the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
February 12, 2019

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 February 12, 2019, at the FDA White Oak Campus, 10903 New Hampshire Avenue, Building 31 Conference Center, the Great Room (Rm. 1503) Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and Janssen Pharmaceuticals, 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.. There were seven (7) Open Public Hearing speaker presentations.

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

Issue: The committees discussed efficacy, safety and risk-benefit profile of new drug application (NDA) 211243, esketamine 28 mg single-use nasal spray device, submitted by Janssen Pharmaceuticals, Inc., for the treatment of treatment-resistant depression.

Attendance:

Psychopharmacologic Drugs Advisory Committee Members Present (Voting): Walter S. Dunn, MD, PhD; Jess G. Fiedorowicz, MD, PhD (via phone); Rajesh Narendran, MD (Chairperson); Kim O. Witczak (Consumer Representative)

Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting): Satish Iyengar, PhD; Felipe A. Jain, MD**,** Jessica J. Jeffrey, MD, MPH, MBA; Erick Turner, MD

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

Drug Safety and Risk Management Advisory Committee Members Present (Voting): Kelly Besco, PharmD, FISMP**,** CPPS; Sonia Hernandez-Diaz, MD, MPH, DrPH; Steven B. Meisel, PharmD, CPPS; Anne-Michelle Ruha, MD, FACMT

Drug Safety and Risk Management Advisory Committee Members Not Present (Voting): Denise M. Boudreau, PhD, RPh; Marie R. Griffin, MD, MPH; Laurel A. Habel, MPH, PhD; Martin Kulldorff, PhD; Suzanne B. Robotti (Consumer Representative); 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): Warren B. Bilker, PhD; Wilson Compton, MD, MPE; Anita Everett MD, DFAPA; Mi Hillefors, MD, PhD; Lee Hoffer, PhD, MPE; Terrence Kungel (Patient Representative); Daniel Pine, MD; Matthew V. Rudorfer, MD; Julie M. Zito, PhD

FDA Participants (Non-Voting): Robert Temple, MD; Judy Staffa, PhD, RPh; Tiffany, Farchione, MD; Cynthia LaCivita, PharmD; Jean Kim, MD, MA; Andrew Potter, PhD

Open Public Hearing Speakers: Stephanie Fox-Rawlings, PhD (National Center for Health Research); Joy Cohen; Eric Scharf (Depression and Bipolar Support Alliance (DBSA); Madeline Reinert, MPH (Mental Health America); Andrew Sperling (National Alliance on Mental Health Illness); Collen Kelley; Susan Gurley (Anxiety and Depression Association of America)

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	**Tiffany R. Farchione, MD** Director (Acting) Division of Psychiatry Products (DPP) Office of Drug Evaluation I (ODE I) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Janssen Pharmaceuticals, Inc.**
Introduction	**David Hough, MD** Esketamine Compound Development Team Leader Janssen Research and Development, LLC
Unmet Medical Need	**A. John Rush, MD** CEO Curbstone Consultant LLC Professor Emeritus Duke NUS Santa Fe, New Mexico
Clinical Development Program Efficacy	**Jaskaran Singh, MD** Senior Director, Clinical Development Janssen Research and Development, LLC
Clinical Safety	**Vanina Popova, MD** Director, Clinical Development Janssen Research and Development, LLC
Abuse Potential	**Andrew Krystal, MD** Ray and Dagmar Dolby Distinguished Professor of Psychiatry University of California San Francisco

Risk Mitigation	**David Hough, MD** Esketamine Compound Development Team Leader Janssen Research and Development, LLC
Benefit Risk Assessment	**David Hough, MD** Esketamine Compound Development Team Leader Janssen Research and Development, LLC
Clinician's Perspective	**Madhukar Trivedi, MD** Professor of Psychiatry University of Texas Southwestern Medical Center
Clarifying Questions to Applicant	

BREAK

FDA PRESENTATIONS

Clinical Overview: Efficacy	**Jean Kim, MD, MA** Clinical Reviewer DPP, ODE I, OND, CDER, FDA **Andrew Potter, PhD** Statistical Reviewer Division of Biometrics I Office of Biostatistics Office of Translational Sciences, CDER, FDA
Clinical Overview: Safety	**Qi Chen, MD, MPH** Safety Reviewer DPP, ODE I, OND, CDER, FDA
Risk Management for Esketamine	**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 to FDA	

LUNCH

OPEN PUBLIC HEARING

Charge to Committee	**Tiffany R. Farchione, MD**

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **VOTE**: Has the Applicant provided substantial evidence of the effectiveness of esketamine for the treatment of treatment-resistant depression?

   Vote Result: ***Yes: 14*** ***No: 2*** ***Abstain: 1***

   Committee Discussion*: The majority of the members voted "Yes" and agreed that there was substantial evidence to support the effectiveness of esketamine for the treatment of -resistant depression. Those members who voted "No" were convinced that the evidence supporting its efficacy was not adequate. The one member who abstained was concerned about blinding of esketamine with such immediate and recognizable effects. Please see the transcript for details of the committee discussion.*

2. **VOTE**: Has the Applicant adequately characterized the safety profile of esketamine for the treatment of treatment-resistant depression?

   Vote Result: ***Yes: 15*** ***No: 2*** ***Abstain: 0***

   Committee Discussion *The majority of the committee members voted "Yes" that the safety profile of esketamine was well characterized for the treatment of treatment-resistant depression. The panel members noted concerns about the long term cognitive deficit, high blood pressure and suicidal ideation. The panel members agreed that the safety profile appeared to be characterized well enough and importantly beyond the short-term and with repeated administrations. However, the committee members who voted, "No" had concerns regarding death with esketamine use and about the long-term safety of the drug. Please see the transcript for details of the committee discussion.*

3. Vote: Given the effectiveness and safety of esketamine and the FDA's proposed risk evaluation and mitigation strategy (REMS), do the benefits outweigh the risks of esketamine for the treatment of treatment-resistant depression?

   Vote Result*:* ***Yes: 14*** ***No: 2*** ***Abstain: 1***

Committee Discussion: *The majority of the members agreed that benefits outweigh the risks of esketamine for the treatment of treatment-resistant depression. Those who voted "Yes" stated esketamine demonstrated adequate effectiveness and the outcomes were well characterized. Most of the panel members agreed that the Risk Evaluation and Mitigation Strategy (REMS) program appeared to be appropriate to the safety profile; however, those who voted "No" were concerned about the REMS program. The one member who abstained from voting noted that the magnitude of the benefit, if any, was not clear and thus could not answer the question. Please see the transcript for details of the committee discussion.*

4. **DISCUSSION:** Discuss whether the FDA's proposed REMS would assure safe use of esketamine and what additional safeguards would be needed, if any.

   Committee Discussion: *The panel members had concerns about defining the setting. It was commented among members that esketamine, if approved, should be available in a practice setting that is providing comprehensive medical/psychiatric care and not "esketamine mills" that only prescribe esketamine without providing other options for treatment/care. One member voiced concern for patients 65 years and older. Another member voiced concern about drug-interactions and the need for registry to include other prescription sedatives, opioids and over-the counter drugs (such as cannabidiol) the patients are on as well. Most panel members agreed that specific recommendations as to frequency of blood pressure monitoring, use of standardized scales to monitor sedation, suicidality etc. should be specified in the Risk Evaluation and Mitigation Strategy (REMS). However, members also expressed caution in making the REMS too restrictive to mitigate risks because they did not want to limit access to the esketamine. Please see the transcript for details of the committee discussion.*

5. **DISCUSSION**: Are additional data needed pre- or post-approval to address outstanding issues? Discuss whether such data should be required prior to approval.

   Committee Discussion: *Some members wanted to see more data on the functional outcomes and quality of life. Some members wanted to see a study to further characterize the risk of suicide. Studies to examine its effectiveness in individuals over 65 years of age were suggested as well. Studies on informed decision making (who signs up for treatment), heterogeneity of response (sub-groups of responders that may benefit the most), long-term effectiveness and adverse effects, patients with psychosis, patients with alcohol and drug use disorders (including patients on naltrexone), patients intolerant to Electroconvulsive Therapy (ECT) and anti-psychotics were all recommended by the panel. There were also members who suggested looking at the mechanism of action and continue to further investigate the rapid anti-depressant effect in acutely suicidal patients. Please see the transcript for details of the committee discussion.*

   The meeting was adjourned at approximately 4:00 p.m.