**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 Peripheral and Central Nervous System Drugs Advisory Committee
# April 14, 2023

Location: Please note that due to the impact of the COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online videoconference platform.

Topic: The committees discussed supplemental new drug application (sNDA) 205422 s009, efficacy supplement for REXULTI (brexpiprazole) tablets, submitted by Otsuka Pharmaceutical Company, Ltd., and Lundbeck, Inc., for the proposed treatment of agitation associated with Alzheimer's dementia.

These summary minutes for the April 14, 2023 joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration were approved on May 16, 2023.

I certify that I attended the April 14, 2023 joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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| **/s/** | **/s/** |
| Joyce Frimpong, PharmD | Rajesh Narendran, MD |
| Designated Federal Officer, PDAC | Chairperson, PDAC |

**Final Summary Minutes of the Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Peripheral and Central Nervous System Drugs Advisory Committee April 14, 2023**

The Psychopharmacologic Drugs Advisory Committee (PDAC) and the Peripheral and Central Nervous System Drugs Advisory Committee (PCNS) of the Food and Drug Administration, Center for Drug Evaluation and Research met on April 14, 2023. The meeting presentations were heard, viewed, captioned, and recorded through an online videoconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Otsuka Pharmaceutical Company Ltd. The meeting was called to order by Rajesh Narendran, MD (Chairperson). The conflict of interest statement was read into the record by Joyce Frimpong, PharmD (Designated Federal Officer). There were approximately 685 people online. There were 14 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 supplemental new drug application (sNDA) 205422 s009, efficacy supplement for REXULTI (brexpiprazole) tablets, submitted by Otsuka Pharmaceutical Company, Ltd., and Lundbeck, Inc., for the proposed treatment of agitation associated with Alzheimer's dementia.

**Attendance:**
**Psychopharmacologic Drugs Advisory Committee Members Present (Voting):** Jess G. Fiedorowicz, MD, PhD; Satish Iyengar, PhD; Rajesh Narendran, MD (*Chairperson*); Patrick S. Thomas, Jr., MD, PhD; Kim O. Witczak (*Consumer Representative*)

**Psychopharmacologic Drugs Advisory Members Not Present (Voting):** Walter S. Dunn, MD, PhD; Jessica J. Jeffrey, MD, MPH, MBA; William R. Keller, MD, MBA; Sonia L. Krishna, MD, FAPA, DFAACAP

**Psychopharmacologic Drugs Advisory Committee Member Present (Non-Voting):** Robert W. Baker, MD (*Industry Representative*)

**Peripheral and Central Nervous System Drugs Advisory Committee Members Present (Voting):** Merit E. Cudkowicz, MD, MSC; Liana G. Apostolova, MD, MSc, FAAN

**Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present (Voting):** Thomas J. Montine, MD, PhD (*Chairperson*); Robert C. Alexander, MD; Richard J. Kryscio, PhD; Michelle M. Mielke, PhD

**Peripheral and Central Nervous System Drugs Advisory Committee Members Not Present (Non-Voting):** Michael Gold, MS, MD (*Industry Representative*)

**Temporary Members (Voting):** Colette Johnston (*Patient Representative*); Sabrina Paganoni, MD, PhD; David Weisman, MD

**FDA Participants (Non-Voting):** Teresa Buracchio, MD**;** Tiffany R. Farchione, MD; Bernard Fischer, MD; Marc Stone, MD; Jean Kim, MD; Shamir N. Kalaria, PharmD, PhD; Peiling Yang, PhD; Yang (Kelly) Yang, PhD

**Designated Federal Officer (Non-Voting):** Joyce Frimpong, PharmD

**Open Public Hearing Speakers:** Ian Kremer (Leaders Engaged on Alzheimer's Disease (LEAD Coalition)); Ashok Patel, MD; Nina Zeldes, PhD (Health Research Group); Debra Tann, EdD; Gary Small, MD; Martha Villanigro-Santiago, JD (Aging and Moving Forward LLC); Susan Peschin (Alliance for Aging Research); Diana Zuckerman, PhD (National Center for Health Research); Russ Paulsen (Us Against Alzheimer's); Jacob Mintzer, MD, MBA, Jim Taylor (Voices of Alzheimer's); Martin Schreiber; James Lewis (American Society of Consultant Pharmacists); Meryl Comer

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***The agenda was as follows:***

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| Call to Order | **Rajesh Narendran, MD**<br>Chairperson, PDAC |
| Introduction of Committee and Conflict of Interest Statement | **Joyce Frimpong, PharmD**<br>Designated Federal Officer, PDAC |
| FDA Opening Remarks | **Tiffany R. Farchione, MD**<br>Director<br>Division of Psychiatry (DP)<br>Office of Neuroscience (ON)<br>Office of New Drugs (OND), CDER, FDA |
| **APPLICANT PRESENTATIONS** | **Otsuka Pharmaceutical Company, Ltd.** |
| Introduction | **Mary Hobart, PhD**<br>Vice President<br>Global Regulatory Affairs<br>Otsuka Pharmaceutical Company, Ltd |
| Unmet Need in Agitation Associated with Alzheimer's Dementia | **Zahinoor Ismail, MD, FRCPC**<br>Professor<br>Hotchkiss Brain Institute &<br>O'Brien Institute for Public Health<br>University of Calgary |
| Efficacy | **Robert McQuade, PhD** |

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| | Executive Vice President and<br>Chief Strategy Officer<br>Otsuka Pharmaceutical Company, Ltd. |
| Safety | **John Kraus, MD, PhD**<br>Executive Vice President and<br>Chief Medical Officer<br>Otsuka Pharmaceutical Company, Ltd. |
| Clinical Perspective | **Alireza Atri, MD, PhD**<br>Director<br>Banner Sun Health Research Institute |
| Benefit/Risk Summary | **Mary Hobart, PhD** |
| Clarifying Questions to Applicant | |
| **BREAK** | |
| **FDA PRESENTATIONS** | **Shamir N. Kalaria, PharmD, PhD**<br>Clinical Reviewer<br>DP, ON, OND, CDER, FDA |
| Efficacy | |
| Safety | |
| Clarifying Questions to FDA | |
| **LUNCH** | |
| **OPEN PUBLIC HEARING** | |
| Questions to the Committee/Committee Discussion | |
| **ADJOURNMENT** | |

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***Questions to the Committee:***

1. **DISCUSSION:** Discuss the overall benefit/risk assessment of brexpiprazole for the treatment of agitation associated with Alzheimer's dementia. In your discussion, take into consideration the following:

- The increased risk of death among elderly patients with dementia receiving antipsychotic treatment
- The risks of medications that are often used off-label for the treatment of agitation in dementia (e.g., antiepileptics, benzodiazepines) without established evidence of efficacy.

***Committee Discussion***: *Many members of the committee agreed that brexpiprazole had an effect on agitation and fulfilled a serious unmet medical need; the efficacy was not in question. Several committee members also highlighted that brexpiprazole exhibited a positive dose-response relationship that further adds to the evidence of efficacy. Several other committee members acknowledged that the small duration of the trial (12 weeks) and the small effect size are a deterrent to the benefit and that should be further characterized. Committee members also highlighted the high placebo response rate in the AAD population and agreed that it was consistent with high placebo response observed in trials evaluating other psychiatric conditions. Regarding risks, several committee members noted that extrapolating data from a 12-week trial was difficult, and that the clinical community would not know how this would translate in the real world, where patients will be administered this medication more broadly. A majority of the committee members also agreed that continuing with the Boxed Warning would provide the opportunity to educate patients and families about the risks and the benefits. Committee members also noted the wide confidence intervals for the estimate mortality risk and recognized that there was great uncertainty. Several committee members recommended more data collection on brexpiprazole's long-term safety and what it will translate to the real world. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** Discuss whether there is a population of patients with Alzheimer's dementia for whom the benefit/risk of brexpiprazole appears acceptable. Is there a population for whom the benefit/risk does not appear to be favorable?

***Committee Discussion***:
*Many of the committee members agreed that brexpiprazole could be a reasonable option for patients with moderate to severe agitation. Several members noted that patients with mild agitation would likely benefit with nonpharmacological treatment alone. Regarding a population where brexpiprazole would not be favorable, committee members agreed that there is not a clear discernible subgroup (possible due to insufficient data) that would not benefit from brexpiprazole, but if any it would be patients with very severe agitation and those with acute agitation. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Has the Applicant provided sufficient data to allow identification of a population in whom the benefits of treating agitation associated with Alzheimer's dementia with brexpiprazole outweigh its risks?

    - If you do not believe the Applicant has provided sufficient data, what additional data is needed to support the use of brexpiprazole for the treatment of agitation associated with Alzheimer's dementia?

    **Vote Result: Yes: 9 No: 1 Abstain: 0**

    ***Committee Discussion***: *The majority of the panel agreed that the Applicant provided sufficient data to allow identification of a population in whom the benefits of treating agitation associated with Alzheimer's dementia with brexpiprazole outweigh its risks. The one panel member who did not agree had concerns and stated more data is needed to demonstrate that brexpiprazole is effective and safe. However, the panel member did not specify what additional data would be needed to support the use of brexpiprazole for AAD. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 3:25 p.m.