**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Final Summary Minutes of the Drug Safety and Risk Management Advisory Committee and Psychopharmacologic Drugs Advisory Committee Meeting**

**Location:** FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform.

**Topic:** The Committees discussed the reevaluation of the Clozapine Risk Evaluation and Mitigation Strategy (REMS) and possible changes to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of clozapine.

These summary minutes for the November 19, 2024 joint meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Psychopharmacologic Drugs Advisory Committee (PDAC) of the Food and Drug Administration were approved on Dec 12 2024.

I certify that I attended the November 19, 2024 joint meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Psychopharmacologic Drugs Advisory Committee (PDAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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| **/s/** | **/s/** |
| Jessica Seo, PharmD, MPH | James Floyd, MD, MS |
| Acting Designated Federal Officer, DSaRM | Acting Chairperson, DSaRM |

**Summary Minutes of the Drug Safety and Risk Management Advisory Committee and Psychopharmacologic Drugs Advisory Committee Meeting**
**November 19, 2024**

The Drug Safety and Risk Management Advisory Committee (DSaRM) and the Psychopharmacologic Drugs Advisory Committee (PDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 19, 2024, at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and the Clozapine Product Manufacturers Group (CPMG). The meeting was called to order by James Floyd, MD, MS (Acting Chairperson). The conflict of interest statement was read into the record by Jessica Seo, PharmD, MPH (Acting Designated Federal Officer). There were approximately 150 people in attendance in-person and approximately 479 people online. There was a total of 29 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 reevaluation of the Clozapine Risk Evaluation and Mitigation Strategy (REMS) and possible changes to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of clozapine.

**Attendance:**

**Drug Safety and Risk Management Advisory Committee Members Present (Voting)**: Maryann Amirshahi PharmD, MD, MPH, PhD, BCPS, FACMT, FACEP, FASAM, FCP; Michael C. Dejos, PharmD, MBA, BCPS, CHOP, CPPS; Sascha Dublin, MD, PhD; James Floyd, MD, MS (*Acting Chairperson*); John B. Hertig, PharmD, MS, CPPS, FASHP (*via video conferencing platform*); Elizabeth Rebo, PharmD, MBA, CPPS

**Drug Safety and Risk Management Advisory Committee Members Not Present (Voting)**: Krista F. Huybrechts, MS, PhD; Vincent Lo Re III, MD, MSCE (*Chairperson*); Mara McAdams DeMarco, MS, PhD;

**Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting)**: Ignacio Rodriguez, MD (*Industry Representative*)

**Acting Industry Representative to the Drug Safety and Risk Management Advisory Committee (Non-Voting)**: Jens-Ulrich Stegmann, RN, MD (*Acting Industry Representative*)

**Psychopharmacologic Drugs Advisory Committee Members Present (Voting)**: Walter S. Dunn, MD, PhD; Jess G. Fiedorowicz, MD, PhD (*via video conferencing platform*); Rajesh Narendran, MD

**Psychopharmacologic Drugs Advisory Committee Members Not Present (Voting):** Patrick S. Thomas, Jr., MD, PhD

**Psychopharmacologic Drugs Advisory Committee (Non-Voting)**: Carla M. Canuso, MD (*Industry Representative*)

**Temporary Members (Voting)**: Jacob S. Ballon, MD, MPH; Michael Brisbin (*Patient Representative*); Megan J. Ehret, PharmD, MS, BCPP; Jeremy G. Perkins, MD, FACP, COL, US Army (ret); Brian W. Salvas, PharmD, RPh; Gopal Vyas, DO

**FDA Participants (Non-Voting):** Gerald Dal Pan, MD, MHS; Irene Z. Chan, PharmD; Teresa Buracchio, MD; Cynthia LaCivita, PharmD; Tiffany R. Farchione, MD; Bernard Fischer, MD; Marc Stone, MD; Carolyn Tieu, PharmD, MPH

**Acting Designated Federal Officer (Non-Voting)**: Jessica Seo, PharmD, MPH

**Open Public Hearing Speakers Present:** Kerry H. Wallace; Brian Barnett, MD; Diana Zuckerman, PhD (National Center for Health Research); Robert Laitman; William Lawson, MD, PhD, DLFAPA; Christina de Fontnouvelle, MD, Matthew Zelig, MD, and Amir Jabr, MD; Rachel Ann Streiff (The Angry Moms); Elizabeth (Lisa) Castellanos (Arizona Mad Moms); Neesa Sunar, LMSW; Christen JW White; Patricia Taggart; Frances Musgrove; Margaret M. Chou, MD (The Clozapine Community Facebook Support Group); Analisa Chase; Max E. Block; Deanna L. Kelly, PharmD, BCPP (Maryland Psychiatric Research Center); Javan Pastoriza; Phyllis Tarbell; Janina Rotaru (Copa Health); Jane Jepson; Basava Jonnala (Athelas and Golden Gate Pharmacy Services); Lynda Michaud Cutrell; Kathryn Erickson-Ridout, MD, PhD (American Psychiatric Association); Angela Brisbin; Raymond C. Love, PharmD, BCPP, FASHP (American Society of Health System Pharmacists; Association of Psychiatric Pharmacists); Crystal Fox, RN, BSN; Apurva Bhatt, MD (American Academy of Child and Adolescent Psychiatry); Ken Duckworth, MD (National Alliance on Mental Illness); Regina Graham, MD

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

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| 8:30 a.m. | Call to Order and Introduction of Committee | **James Floyd, MD, MS**<br>Acting Chairperson, DSaRM |
| 8:35 a.m. | Conflict of Interest Statement | **Jessica Seo, PharmD**<br>Acting Designated Federal Officer, DSaRM |

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| 8:40 a.m. | FDA Opening Remarks | **Tiffany R. Farchione, MD**<br>Director<br>Division of Psychiatry (DP)<br>Office of Neurosciences (ON)<br>Office of New Drugs (OND)<br>CDER, FDA |
| 8:50 a.m. | Clozapine Background & Regulatory History | **Leah Hart, PharmD**<br>Risk Management Analyst<br>Division of Risk Management (DRM)<br>Office of Medication Error Prevention and Risk Management (OMEPRM)<br>Office of Surveillance and Epidemiology (OSE)<br>CDER, FDA |
| 9:10 a.m. | **INDUSTRY PRESENTATIONS** | **Clozapine Product Manufacturers Group (CPMG)** |
| | Overview of Clozapine | **Jason A. Gross, PharmD**<br>Vice President, Scientific Affairs<br>HLS Therapeutics |
| | Clinical Context of Clozapine | **John M. Kane, MD**<br>Professor, Department of Psychiatry and Molecular Medicine<br>The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell<br>Institute of Behavioral Science, Feinstein Institutes for Medical Research |
| | Clinical Implications | **Robert O. Cotes, MD**<br>Professor, Department of Psychiatry and Behavioral Sciences<br>Emory University School of Medicine |
| | REMS Operation and Assessments | **James Shamp**<br>Vice President, Data Intelligence and Program Analytics<br>United BioSource (UBC) |
| | AE Reporting, Stakeholder Feedback, and Opportunities for Improvements | **Jason A. Gross, PharmD** |
| 10:25 a.m. | Clarifying Questions | |
| 10:55 a.m. | **BREAK** | |

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| 11:10 a.m. | **FDA PRESENTATIONS** | |
| | Summary of Studies Conducted for FDA's Re-Evaluation of the Clozapine REMS | **Cynthia LaCivita, PharmD**<br>Director<br>DRM, OMEPRM, OSE, CDER, FDA |
| | FDA's Updated Assessment of Severe Neutropenia and Gaps in Healthcare | **Carolyn Tieu, PharmD, MPH**<br>Team Leader<br>DRM, OMEPRM, OSE, CDER, FDA |
| 12:05 p.m. | Clarifying Questions | |
| 12:35 p.m. | **LUNCH** | |
| 1:35 p.m. | **OPEN PUBLIC HEARING** | |
| 3:05 p.m. | **BREAK** | |
| 3:20 p.m. | Questions to the Committee/Committee Discussion | |
| 5:00 p.m. | **ADJOURNMENT** | |

***Questions to the Committee:***

1. **DISCUSSION:** How reassured or concerned are you that current and potential clozapine healthcare providers have sufficient knowledge and access to resources about the risk of neutropenia and need for absolute neutrophil count (ANC) monitoring?

   ***Committee Discussion****: Panel members were largely in agreement that the data presented indicate current clozapine prescribers, particularly psychiatrists, are well-informed about neutropenia risks. However, several participants noted an excessive focus on neutropenia through the REMS that potentially results in prescribers losing sight of other critical issues related to clozapine use (e.g., metabolic syndrome, constipation, myocarditis). Some panel members also expressed less certainty regarding adequacy of knowledge about neutropenia risk for other clozapine prescribers, such as psychiatric nurse practitioners or physician assistants, as the studies presented did not look at these types of providers. Many panel members acknowledged the REMS requirements create logistical barriers, which discouraged prescribing by community-based providers and expressed concern about a lack of familiarity with clozapine among rural or non-psychiatrist providers.*

   *Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** How reassured or concerned are you that current and potential clozapine healthcare providers will perform ANC monitoring without the requirements of the Risk Evaluation and Mitigation Strategy (REMS)?

***Committee Discussion:*** *Most panel members expressed confidence that prescribers will monitor ANC per labeling requirements without REMS enforcement. Several panel members cited examples of prescribers conducting monitoring with other drugs associated with severe safety concerns that do not have REMS requirements (e.g., Depakote, cancer drugs). One member noted that clozapine has now been prescribed for decades and monitoring has become a part of standard practice.*

*Others expressed that ANC monitoring may not be performed in all patients without the REMS requirements, but were not concerned as this was seen as removing a potential barrier to accessing clozapine, and prescribers are capable of making the benefit-risk assessment for a lapse in monitoring to ensure treatment-resistant schizophrenia does not go untreated. One of these panel members suggested integrating support systems into electronic medical records (EMRs) to assist providers with monitoring compliance in the absence of a REMS.*

*Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** Are the requirements for the prescriber to document ANC results and the pharmacy to verify the ANC results through the REMS necessary to ensure safe use? Please provide your rationale for your vote.

**Vote Result:** Yes: 1 No: 14 Abstain: 0

***Committee Discussion****: The Committee members were in near unanimous agreement that the REMS requirements for documentation of ANC results by providers and pharmacies to verify those results were not necessary to ensure safe use of clozapine. Those who voted "No" were in agreement the REMS requirements create undue barriers to clozapine access without providing significant additional safety benefits and pointed to other medications with comparable risks that do not require such extensive REMS documentation. One panel member clarified appropriate ANC monitoring by prescribers is important; however, verification of results by the pharmacy is not needed and creates an unnecessary barrier. Panel members noted that providers should be trusted to follow the package insert guidelines, and be allowed to collaborate with their patient to create a patient-centered care plan without the requirements of the REMS. There was general agreement that the life-saving benefits of clozapine for treatment-resistant schizophrenia outweigh the risks of neutropenia.*

*The panel member who voted "Yes" suggested that there can be a role for REMS requirements during the first 18 weeks of therapy when neutropenia risks are highest, provided the system is streamlined and pharmacies can avoid the ANC documentation requirement if an absolute barrier to care exists.*

*Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Is the requirement to educate healthcare providers through the REMS about the risk of severe neutropenia and the need for ANC monitoring necessary to ensure safe use? Please provide your rationale for your vote.

   **Vote Result:** Yes: 1 No: 14 Abstain: 0

   ***Committee Discussion****: The Committee members were in near unanimous agreement that the REMS requirements for education of healthcare providers about the risk of severe neutropenia and need for ANC monitoring were not necessary to ensure safe use of clozapine. Those who voted "No," expressed that education on clozapine risks, including neutropenia, is already part of standard medical training and widely accessible resources. The monitoring information provided in the package insert was viewed as sufficient, and the education requirements of the REMS were criticized as an additional barrier to clozapine access. It was noted that data presented during the meeting did not demonstrate knowledge learned through the REMS contributed to mitigating the risk of severe neutropenia and was suggested that removing education requirements under the REMS could reduce systemic hurdles and improve patient access to this medication.*

   *The panelist who voted "Yes," acknowledged the life-saving potential of clozapine and advocated for a REMS where only the education component is maintained to help ensure understanding of clozapine's management complexities.*

   *Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:53pm ET.