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To the respective chairs and members of the Drug Safety and Risk Management Advisory Committee and Psychopharmacologic Drugs Advisory Committee:

On behalf of the 2+ million people in the United States who live with schizophrenia; the clinicians who work with their patients to try to manage this severe, debilitating disease; and the many pharmacists across the country who provide the medicines their patients depend on to function; we are writing to ensure you have the full picture of just how much damage the clozapine REMS has caused to some of the most vulnerable people in this country.

We are heartened that FDA is addressing the dangerous barriers caused by the REMS that are blocking access to what can be lifesaving care for people with schizophrenia. Since its creation, the excessively onerous and complex clozapine REMS has blocked access to treatment and disrupted care for people with this severe disease. For people with schizophrenia, even one missed dose of their clozapine can send them plummeting into psychosis. This simply must end.

We look forward to the Nov. 19 Joint Advisory Committee meeting on the re-evaluation 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.

Clozapine is the only FDA-approved atypical antipsychotic medication for treatment-resistant schizophrenia. Its advantages include lowering the risk of suicide, reduced risk of a Parkinson's disease-like movement disorder called tardive dyskinesia, and fewer relapses. The nature of its indication speaks volumes: for some, this medicine is the only one that works to manage their schizophrenia.

Our comments below are based on published data as well as reports provided to us by our constituents. We thank the committee members for your review and consideration of this information as you determine how to address this grave situation. As the organizations that

represent the people most affected by the REMS, we stand ready to partner with you to fix what is so tragically broken.

I. The clozapine REMS is dangerous to people with schizophrenia and exacerbates healthcare inequities.

- Schizophrenia is a life-altering and potentially life-threatening disorder. Clozapine reduces the risk of suicide and premature death in people with schizophrenia. Disruption in access to clozapine can result in violence, self-injury, inadvertent overdose, hospitalization and death.

- The REMS puts a substantial and unnecessary burden on patients, families and caregivers. This burden exacerbates healthcare disparities for minorities, people living in rural areas and anyone who already faces barriers in accessing healthcare. Some of the obstacles that cause this burden – and these disparities – include:
  - Difficulty finding prescribers who are willing to participate in the complex REMS.
  - Difficulties finding pharmacies that are certified or willing to participate.
  - Requirements that fly in the face of the nature of the disease. For example, people with severe schizophrenia symptoms may refuse to leave their bedrooms; leaving home frequently for blood draws can be an insurmountable hurdle.
  - Delays in receiving their critically important medicine due to an error with even a single step in the complex process – including something as simple and common as a REMS computer glitch.
  - The inability of systems such as jails and prisons – where people with schizophrenia often are warehoused following psychosis-induced problems – to comply with the REMS due to lack of resources.

- The REMS limits the quantity of clozapine that can be dispensed, yet there is no supporting rationale. The medicine is rationed into 7-, 14- or 30 day increments, yet the Patient Status Form is only required every 37 days. Eliminating these meaningless restrictions would result in significantly fewer treatment interruptions, reducing the harm to patients and the burden on families and caregivers.

- There is a disturbing lack of equity in determining which drugs require a REMS and for which potential adverse events a REMS is required. For example, *numerous* agents cause agranulocytosis at a higher rate than clozapine, yet they do not require submission of laboratory data, pharmacy dispensing restrictions or a REMS.

- The REMS exacerbates treatment inequities among minorities and those who live in rural areas. Among people of African or Middle Eastern descent, this is due in part to

prescriber fear (fanned by the REMS) of the lower starting neutrophil counts in this population. But even African Americans whose neutrophil levels are similar to Caucasians have less access to clozapine. For example:

- They may have less access to behavioral health specialists who are most likely to prescribe and monitor clozapine.
- They may have transportation challenges to obtain the required laboratory monitoring.
- They are more likely to live in pharmacy deserts.

The stringent monitoring provisions of the REMS and the lack of flexibility regarding dispensing quantities of clozapine intensify these inequities.

- Cognitive impairment is a frequent component of schizophrenia that can interfere with a person's ability to manage complex tasks. Adhering to the restrictions of the complicated clozapine REMS can be impossible for someone with cognitive impairment – blocking access to a treatment that could be the only one that works for them.

<u>II. The harms caused by the REMS greatly outweigh its minimal benefits.</u>

- There is little evidence that the dispensing restriction, purchasing restrictions and REMS reporting requirements reduce morbidity or mortality. For example:
  - The delay in the required reporting of ANCs may be too great to assure that a lifesaving intervention can be implemented in a case of severe neutropenia. This renders the REMS ineffective.
  - Problems in the prescribing/dispensing system may interrupt treatment, which can severely exacerbate a patient's illness, including triggering damaging psychosis. This, in turn, can put the patient back at square one: requiring the re-start of clozapine. Re-starting clozapine without appropriate re-titration may result in a black box adverse event.

- Numerous studies indicate that there is less risk of agranulocytosis from clozapine than was thought when the drug was approved. Data further indicate that an elevated risk may be time-limited, removing the need for indefinite monitoring.

Furthermore, psychiatrists are sufficiently capable and confident to appropriately monitor a patient's hematologic status – and intervene when appropriate – without central reporting.

<u>III. The clozapine REMS discourages providers from prescribing and dispensing a treatment that in some cases, is the only one that works for people with schizophrenia.</u>

- The REMS increases prescriber workload by requiring use of a system that is not coordinated with mainstream electronic health record (EHR) systems.
    - Completion of the Patient Status Form is required on a timeline that does not align with the receipt of laboratory reports or patient visits. As a result, prescribers receive additional emails from the REMS vendor and must often address/fix pharmacy issues on top of these additional administrative tasks.

- Participating in the REMS puts excessive and unnecessary burdens on pharmacists.
    - They must take extra steps to receive the REMS Dispensing Authorization.
    - Some pharmacies do not have open internet access that allows communication with the REMS vendor program.
    - Corporate policies designed to assure compliance with PBMs and legal guidelines may result in requests for additional information from prescribers.
    - The completion of training and registration just to purchase clozapine is time consuming.
    - Pharmacists must continuously educate temporary staff and other shift workers on the complex management of clozapine prescriptions.

- The extreme complexity of the clozapine REMS sometimes precludes compliance with it, as it contains too many potential points of failure. These include system registration, prescribing, reporting, laboratory monitoring, transitions among prescribers or healthcare settings, dispensing and communication with the REMS vendor. These potential points of failure are exacerbated by the REMS "enforcement discretion" status and resulting confusion.
    - Patients and their families tell us that the majority of pharmacies' refusals to dispense clozapine are caused by complexities in the REMS – not because of neutropenia.

- The severe barriers to care the REMS has created have damaged prescriber opinion of the medicine, making many unwilling to prescribe it to those for whom it may be the only effective option.

By law (21 USC 355-1), the elements of a REMS:

- Shall be "commensurate with the specific risk…"
- "Not be unduly burdensome on patient access to the drug, considering in particular:
    - Patients with serious or life-threatening diseases or conditions.
    - Patients who have difficulty accessing health care…
    - Patients with functional limitations…"

The clozapine REMS fails each of those conditions, and the time has come to stop the harms it has caused for people with schizophrenia. The FDA does not approve medicines that lack proof of safety and efficacy, and it should not allow the continuation of REMS interventions that are both ineffective and unsafe.

Sincerely,

American Association for Community Psychiatry
American Association of Psychiatric Pharmacists
American Pharmacists Association
American Psychiatric Association
American Psychiatric Nurses Association
Black Psychiatrists of America, Inc.
CURESZ Foundation
HEALING MINDS NOLA
National Association of State Mental Health Program Directors
National Shattering Silence Coalition
Schizophrenia & Psychosis Action Alliance
Team Daniel Running for Recovery from Mental Illness
The Angry Moms
The National Council for Mental Wellbeing
Treatment Advocacy Center