August 23, 2024

Dr. Vincent Lo Re III, MD, MSCE
Chair
Drug Risk Management Advisory Committee
Center for Drug Evaluation & Research
U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD. 20993

Dr. Rajesh Narendran, MD
Chair
Psychopharmacologic Drugs Advisory Committee
Center for Drug Evaluation & Research
U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD. 20993

Dear Dr. Lo Re and Dr. Narendran:

RE: **ISSUES TO CONSIDER FOR UPCOMING JOINT ADVISORY COMMITTEE MEETING**

The undersigned organizations collectively represent healthcare professionals, patients, families and governmental officials who are impacted by the Clozapine REMS on a daily basis. As your committees prepare for their joint fall 2024 meeting, we wish to emphasize that there is no data source or statistical measure that accounts for the dramatic and considerable costs to patients, families and the healthcare system of not using clozapine, interruptions in treatment with clozapine and discontinuation of clozapine treatment due to the complexity of the REMS program for clozapine.

While we have conducted small surveys of families and providers, they do not reflect the reality of a REMS that places burdens on prescribers, pharmacists, nurses, caregivers, families and most importantly patients. We believe that the anecdotal reports we receive and situations we face represent only a very small fraction of the difficulties we all encounter daily and the harm caused by this far-reaching REMS.

The regulatory adverse events caused by the REMS arise from difficulty finding prescribers willing to participate in a such a complex system, delays in obtaining and filling prescriptions due to pharmacies deciding not to participate in the complex REMS or corporate entities confused about the REMS, the inability or refusal of patients to engage in the required monitoring, communication failures among healthcare professionals and failures in the REMS program itself. These adverse events not accounted for by traditional reporting systems include continued psychosis in those never treated with clozapine, relapses in those whose treatment is interrupted and all of the adverse sequelae of untreated or incompletely treated serious mental illness including violence, self-injury, inadvertent overdose on resumption of interrupted treatment, hospitalization and death. We believe the harm done to individuals and families and the costs to families and society pale in comparison to the number of cases of severe neutropenia prevented by the REMS.

The undersigned organizations care deeply about those treated with and those who could potentially be treated with clozapine. We want to ensure that clozapine is used in the safest

manner possible and is accessible to all those who could benefit from it. However, safety is not just performing hematologic monitoring. A REMS that is narrowly focused with Elements to Assure Safe Use that deal with only a single issue does not protect our family members and patients from adverse events that may be more frequent and significant than severe neutropenia. These include bowel hypomotility, myocarditis, cardiomyopathy, altered pharmacokinetics in the face of infection and heightened risk of pneumonia. Furthermore, an overly restrictive and complex REMS results in confusion and discourages use of this essential medication which is the subject of the REMS.

The undersigned organizations ask that your committees consider making the following recommendations during your upcoming joint meeting:

- Reduce the complexity and restrictive nature of the REMS ETASU by converting the REMS into one that focuses on the education of healthcare professionals and patients regarding the broader safety concerns associated with clozapine.
- Remove requirements to report that monitoring was performed and any monitoring results to a central REMS website.
- Permanently remove any restrictions on pharmacies that impact the procurement of clozapine.
- Permanently remove any requirements that pharmacies must receive a dispensing authorization, ANC results or anything other than a lawful prescription before clozapine can be dispensed.

Though it may be beyond the immediate agenda of the upcoming joint meeting, the issue of the frequency and duration of absolute neutrophil count monitoring for clozapine is of concern to the stakeholders. We ask that the Psychopharmacologic Drugs Advisory Committee, manufacturers and FDA staff reexamine this important issue that impacts initiation and continuation of clozapine treatment as soon as possible.

We thank your committee members for their service to the public. Those individuals who deal with serious mental illnesses are among the most disadvantaged and discriminated against members of that public. Asking them, their families, caregivers and providers to also deal with the additional burdens of a complex system does not serve them or the public. We hope that your committees will support conversion of the clozapine REMS into a program that will better address their safety and reduce the obstacles that they face.

Sincerely,

American Association of Colleges of Pharmacy
American Pharmacists Association
American Psychiatric Association
American Society of Health-System Pharmacists
Dr. Ann Mandel
National Association of State Mental Health Program Directors

National Council for Mental Wellbeing
Robert Laitman
Schizophrenia & Psychosis Action Alliance
Team Daniel Running for Recovery
The Angry Moms
Treatment Advocacy Center