National Alliance on Mental Illness

Vincent Lo Re III, MD, MSCE, Chair
Drug Risk Management Committee

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

Re: FDA-2024-N-3617-0001

Dear Drs. Lo Re and Narendran:

Thank you for the opportunity to submit comments for consideration during the "Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee" where the Committees will discuss reevaluation of the Clozapine Risk Evaluation and Mitigation Strategy (REMS). NAMI, the National Alliance on Mental Illness, is the nation's largest grassroots mental health organization and is dedicated to building better lives for people affected by mental illness. As NAMI's Chief Medical Officer, I have heard countless stories from families and individuals who have been positively impacted by clozapine and negatively impacted by the requirements of REMS.

As discussed in the comments below, we are concerned that the current REMS process presents barriers to treating people with schizophrenia. We strongly encourage FDA to remove barriers to care, by allowing patients to have the choice to opt out of the REMS after the initial highest risk period and to allow for emergency prescriptions when the administrative barriers are not met. We believe these options would more appropriately allow patients, families and providers to weigh the burdens of REMS and blood draws with the risks inherent to clozapine.

Specifically, we believe that people who live with schizophrenia should have the right to opt out of the REMS requirement after the highest risk period (e.g. 6 months or one year as informed by the 3 studies FDA is conducting and the literature). Such an option would allow patients to work with their doctor to understand and address the rare risk of infection that might result if they opt out. We also believe that adding a provision for emergency prescription when administrative hurdles are not met in a timely manner represents another essential way to let people make informed decisions with their doctors.

**Background on Schizophrenia**

Helping people with schizophrenia has been a core part of NAMI's work since our founding in 1979. Schizophrenia is a serious mental illness that interferes with a person's ability to think clearly, manage emotions, make decisions and relate to others. It is a complex, long-term medical illness. Approximately 3.7 million adults aged 18 to 65 (1.8 percent) had a lifetime history of schizophrenia spectrum disorders[i]. Despite its relatively low prevalence, schizophrenia is associated with significant health, social, and economic concerns. Schizophrenia is one of the top 15 leading causes of disability worldwide[ii], and individuals with schizophrenia have an increased risk of premature mortality.

Even after a century of its clinical description, schizophrenia continues to puzzle researchers with its variety of presentations and complex etiology involving the role of genetics and its interaction with environmental factors[iii]. Currently, there is no cure for schizophrenia, but treatments focus on helping people manage their symptoms, improve day-to-day functioning, and achieve personal life goals, such as completing education, pursuing a career, and having fulfilling relationships[iv]. One form of treatment is antipsychotic medications, which can help make psychotic symptoms less intense and less frequent. For people with treatment-resistant schizophrenia, clozapine is the gold standard antipsychotic medication.

**Clozapine Can be Life Changing**

Clozapine is the only FDA approved medication for treatment-resistant schizophrenia (TRS), which occurs when persistent or moderate delusions or hallucinations remain after failing two trials of antipsychotic medicines. Clozapine is considered superior to other antipsychotics[v] for TRS and offers many benefits including[vi]:

- Fewer symptoms of anxiety, delusions, and hallucinations
- Improved sleep
- Lower rates of hospitalization, and shorter hospital stays
- Reduced side effects, such as tremors or shaking
- Lower incidence of suicide and suicidal feelings
- Improvement in quality of life and social functioning
- Reduced caregiver stress and worry

These benefits have been lifechanging for many people with schizophrenia. Here are a few stories from NAMI members and people who have been impacted:

> *"Doctors prescribed clozapine; the change was simply a MIRACLE!"*
>
> *"He's been on clozapine for 20 weeks. He has no psychotic symptoms for the first time in 5 ½ years. He is not suicidal. He doesn't have akathisia. His EPS symptoms have disappeared. He attends college away from home and will graduate in December with a finance degree."*

*"Since being back on clozapine, there has been no need to call 911 or for hospitalizations. [Name] is back to his empathetic, intelligent, and caring self. I have no fear for the safety of myself, or anyone else he may encounter. I do not know where we would be without clozapine."*

*"My daughter is very clear that clozapine has turned her life around. She no longer feels socially isolated, and she is on the path to achieving her long-term goal of teaching art to children. Her movement disorder isn't fully resolved, but she no longer has the tremors and muscle stiffness that she was dealing with in her college years. It frightens me to think how close we came to not discovering clozapine."*

I have also seen the benefits of clozapine firsthand through my work as director of the clozapine clinic when I was the Medical Director of the Massachusetts Mental Health Center. Many people have shared with me personally what clozapine has done to improve their lives, both over a long career in Massachusetts and in my role at NAMI. It is clearly underutilized as a treatment modality.

**Risks to Clozapine**

Like any medication, there are multiple risks associated with clozapine. One of many serious possible side effects of clozapine is severe neutropenia, which can be life threatening and occurs when there are too few neutrophils, a type of white blood cells[vii]. A recent meta-analysis found the incidence of clozapine-induced severe neutropenia was 0.9%, with 1/7700 people exposed to clozapine dying from severe neutropenia[viii].

To help manage the risk of neutropenia, clozapine has a Risk Evaluation and Mitigation Strategy (REMS) mandated by the FDA. A REMS is a strategy to manage known or potential risks associated with clozapine to ensure that the benefits of the drug outweigh the risk of severe neutropenia. Specifically, patients taking clozapine need to have their absolute neutrophil count (ANC) monitored on a regular basis. The blood testing requirements are as follows[ix]:

- Weekly blood tests for the first 6 months
- Every 2 weeks for the next 6 months if the ANC stays normal.
- Monthly after the first year if the ANC stays normal.

**REMS As Constructed Presents Barriers to People Getting Treatment**

The ongoing burden of regular blood draws and complexity of REMS is a real barrier to getting this often life-saving treatment for some people. NAMI has heard from countless individuals and families regarding how REMS has impacted their lives. Here are a few stories:

*"I have concerns about the FDA requirements for clozapine for patients who've been on the medication for 25 years with no ANC drops or any other reactions. Having to still get a blood draw every 4 weeks and only allowed a 28-day supply is inconvenient and very frustrating to anyone who's had to deal with these ridiculous requirements for many years."*

*"Every month, for the rest of her life, my daughter is required to get a monthly blood draw for REMS. This may sound simple; however, it is not. Almost every month, there is a glitch, lack of communication or sheer incompetence in the system. The pharmacy does not receive the fax, so my daughter has to physically go to the lab, get a printout of the blood work and take it to the pharmacy. For the rest of her life, she is required to take a blood test for a medication with which she has not had one negative issue. If our whole family was not on top of the doctor, pharmacy and lab, there is no way my daughter could manage her medications."*

*"The weekly blood draws and hoops we have to jump through is bad enough. To live with the constant fear of losing the one medication that has given her a life back is terrifying--and so unfair."*

*"Going for weekly bloodwork when my son is so sick is also a challenge. Someone in psychosis, and who isn't well, typically does not want to leave the house, let alone go for a test which involves being poked weekly, and having to wait in a busy waiting room with so many other patients."*

***Based on the hundreds of comments and feedback we have received; NAMI has two fundamental themes we want to offer on clozapine and REMS. Both involve allowing people to make their own decisions in consultation with their doctor in two circumstances.***

1) **FDA Should Modify REMS to Allow an Opt-out Option (e.g. After 6 Months) to Promote Shared Decision Making.**

There is substantial evidence that the risks of neutropenia decrease over time, which presents an opportunity to reevaluate REMS and support shared decision making. The meta-analysis mentioned above also concluded that severe neutropenia associated with clozapine is a rare event and occurs early with a substantial decline in risk after one year of exposure[x]. Another study with a nationwide cohort in Finland concluded that the risk of clozapine-induced agranulocytosis decreased steeply over time, particularly after 6 months[xi]. While there might be debate on the exact time frame, the evidence shows that there is a very low risk period for people who stay on this medicine for years and decades, which is very common.

In addition to the risk decreasing over time, we think it is important to think about the risk in context of the other benefits of clozapine. One study specifically concludes that the risks of clozapine are small in contrast to other benefits:

> "The risk of clozapine-induced agranulocytosis decreases steeply over time but might be persistently greater than that of non-clozapine antipsychotics. This long-term risk excess seems small in absolute terms compared with the known magnitude of the advantages of clozapine in relevant outcomes, including life expectancy."[xii]

Therefore, given the evidence suggesting that risk decreases over time, NAMI supports amending REMS to allow for patient choice to opt out of the REMS after the initial highest risk period. This is an option that would enable people to more squarely weigh the burdens of REMS and blood draws with the risks inherent to clozapine. This would place REMS and risk as something to weigh in an informed way as with other risks of clozapine as well as medical procedures that also carry significant risks and benefits.

Anyone, including those with schizophrenia, who interacts with the health care system has to make difficult decisions based on the potential benefits, harms and risks of any medical treatment or interventions. People who live with schizophrenia make medical decisions every day in conversation with their caregivers and doctors. Common risks currently taken by people with schizophrenia include the risk of diabetes on many antipsychotics including clozapine, the risks of dependence for taking benzodiazepines over a long period, and the risk of kidney disease while on lithium. There is already a list of severe medical risks that patients take when adhering to a clozapine regimen spelled out on the label. People with schizophrenia make these difficult decisions every day and should be prepared to identify symptoms of, for example, gastric hypomotility, seizures, and myocarditis by their doctors and team. Informing a patient who opts out of REMS would add another risk awareness—that of infection—in a clozapine service.

After I reviewed the risk and benefits of a treatment option with one of my patients with schizophrenia, he told me that the ability to make informed decisions, considering the risks and the benefits that came with them, conferred dignity on him. This comment influenced my thinking, and I believe he is onto something often overlooked in our care of people with schizophrenia—that there is a dearth of shared decision making and that patient choice is itself valuable to promote recovery. In writing NAMI's first book *You Are Not Alone*, I interviewed many people whose lives had been changed by clozapine. They used their name and location in the book to change how we think about people with schizophrenia and other mental health conditions. They are in active recovery and want choices in their lives and treatment. They want the dignity to make their own decisions.

Unfortunately, the current indefinite mandate requiring blood draws for the rest of a patient's life does not confer dignity on patients. We believe it is a missed opportunity to allow people the dignity of choosing whether to accept a very low risk and continue lifesaving treatment. An opt-out option also would allow for more conservative people who want monitoring for this rare side effect to continue in the monitoring of the REMS system should they choose to do so. Most people with schizophrenia have the capacity to make decisions for themselves and this should be one of them, after the initial higher risk period.

2) **Should Allow Physicians to Offer an Emergency Supply of Clozapine when Current REMS Administrative Hurdles are not Cleared.**

The current REMS is a complex multi-step process that invites the risk of re-hospitalization and other bad outcomes due to missing doses of what is for many a lifesaving treatment. In a

situation where not all of the required REMS steps can be completed, NAMI urges the FDA to allow shared decision making, and allow an emergency supply of clozapine to be given. The patient can decide which risk they prefer to take—an unknown neutrophil count or a risk of loss of access to clozapine. This can be informed by prior risks and neutrophil counts and also by how severe symptoms were in the past before clozapine was introduced. This is a variation on challenging discussions patients have with their doctors every day. The art of medicine and psychiatry is weighing unknowns, identifying patterns and sharing information to help people make the best decisions for their own health and wellbeing. Relaxing the restrictions on emergency dosing would be an important step in the direction of allowing these critical decisions to live with doctors and their patients, which is where they belong. Loss of access to clozapine, even for a few days, is fraught with anxiety and the potential for return of often severe symptoms. We have heard many people ask for this exception and want to be sure you are aware of this experience when the multistep process is delayed.

Thank you for the opportunity to provide comments on this important issue. If you have any questions or would like to discuss this issue, please do not hesitate to contact me or Hannah Wesolowski, NAMI's Chief Advocacy Officer at hwesolowski@nami.org.

Sincerely,

Ken Duckworth MD
Chief Medical Officer, National Alliance on Mental Illness
Assistant Professor of Psychiatry, Harvard Medical School

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[i] https://www.rti.org/publication/mental-and-substance-use-disorders-prevalence-study?utm_source=press_release&utm_medium=website&utm_campaign=SSES_HHS_SAMHSAMDPSFindings

[ii] https://pubmed.ncbi.nlm.nih.gov/28919117/

[iii] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9468267/

[iv] https://www.nimh.nih.gov/health/topics/schizophrenia

[v] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8301879/

[vi] https://www.nami.org/wp-content/uploads/2024/03/FINAL11-30_Clozapine-REMS-Program-Updates_Indiv-Families.pdf

[vii] https://education.smiadviser.org/Listing/New-Clozapine-REMS-Staying-Informed-for-the-November-15-Changes-4414

[viii] https://pubmed.ncbi.nlm.nih.gov/29786829/

[ix] https://www.newclozapinerems.com/Public/home/Patient#:~:text=You%20will%20need%20to%20get,if%20your%20ANC%20stays%20normal

[x] https://pubmed.ncbi.nlm.nih.gov/29786829/

[xi] https://pubmed.ncbi.nlm.nih.gov/38697177/

[xii] https://pubmed.ncbi.nlm.nih.gov/38697177/