FDA Briefing Document

Risk Evaluation and Mitigation Strategy (REMS) for Clozapine Products

Clozapine REMS

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Psychopharmacologic Drugs Advisory Committee

November 19, 2024

Division of Risk Management/Office of Medication Error Prevention and Risk Management

and

Division of Psychiatry/Office of Neuroscience

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Glossary

ABPN	American Board of Psychiatry and Neurology
AC	Advisory Committee
ACGME	Accreditation Council for Graduate Medical Education
ACP	The American College of Psychiatrists
ANC	absolute neutrophil count
APA	American Psychiatric Association
BWH	Brigham and Women's Hospital
CI	confidence interval
CPMG	Clozapine Product Manufacturers Group
DEPI	Division of Epidemiology
ETASU	elements to assure safe use
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
IR	incidence rate
IRR	incidence rate ratio
NDA	new drug application
PDAC	Psychopharmacologic Drugs Advisory Committee
PSF	patient status form
PY	patient years
RCT	randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategy
RDA	REMS Dispense Authorization
SD	standard deviation
SDD	Sentinel Distributed Database
TRS	Treatment-Resistant Schizophrenia
VA	Veterans Affairs
WBC	white blood cells

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The FDA is convening this Advisory Committee meeting to discuss the Agency's re-evaluation of the Clozapine Risk Evaluation and Mitigation Strategy (REMS). The risk of severe neutropenia, monitoring for severe neutropenia, and management of severe neutropenia under the REMS are the focus of the meeting.[1] Specifically, we are asking the Committee if the education requirements to prescribe and dispense clozapine and/or the requirements to document the absolute neutrophil count (ANC) monitoring need to continue under the REMS or whether the Clozapine REMS can be simplified, reduced in scope, or even eliminated without reducing patient safety. Information from our re-evaluation of the risk of severe neutropenia associated with clozapine must be weighed with the benefits of clozapine treatment and burden imposed by a REMS with elements to assure safe use (ETASU).[2]

The meeting will not focus on other serious risks associated with clozapine, though we acknowledge that there are other important serious risks and patient care considerations that influence a clinician's decision to prescribe and a patient's decision to take clozapine.

1.2 Context for Issues to Be Discussed at the AC

Clozapine is an atypical antipsychotic approved for treatment-resistant schizophrenia and reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder. Clozapine can cause severe neutropenia, which can lead to serious and fatal infections. For almost 40 years, since its initial approval in 1989, prescribing, dispensing, and being treated with clozapine required enrollment of prescribers, pharmacies, and patients in a restricted distribution program to mitigate the risk of severe neutropenia. The Clozapine REMS currently involves more than 35,000 active, enrolled prescribers; more than 27,000 active, enrolled pharmacies with more than 149,000 enrolled patients (REMS Assessment Report 7). This REMS is complex because of the large number of enrolled participants combined with the need for frequent monitoring of ANC (e.g., weekly for the first 6 months) and the time-sensitive nature of obtaining, reviewing, and documenting ANC test results so the pharmacy is authorized to dispense clozapine to the patient.

For the past 9 years, the REMS has not been fully implemented or functioned as intended. The initial transition in 2015 from six separate restricted distribution programs to one single REMS was fraught with implementation challenges, including technical issues with the website, data migration, and long call wait times. Additional implementation challenges occurred when the REMS transitioned in 2021 to a new REMS administrator who needed to develop and implement a new system to coordinate the

[1] Previous versions of clozapine labeling referred to the risk of agranulocytosis, which is defined as absence of granulocytes (neutrophils, basophils, and eosinophils). Neutrophils constitute the majority of granulocytes and the presence or absence of other granulocytes is not important to the existence of the risk. To improve and standardize understanding, "severe neutropenia," which signifies a neutrophil count of less than 500/µL, replaces the previous term agranulocytosis in the current labeling. Additionally, previous versions of clozapine labeling used cubic millimeters (mm^3) as the unit of measure for ANC. Current labeling uses microliters (µL). These units of measure are equivalent. This briefing document uses microliters (µL) throughout.

[2] Burden reflects the additional effort that healthcare professionals and other stakeholders expend in complying with the REMS requirements beyond what is required for good clinical care. See draft Guidance for Industry: REMS Assessment: Planning and Reporting. January 2019. Accessed on September 2, 2024, at https://www.fda.gov/media/119790/download.

enrollment of prescribers, pharmacies, and patients and the transfer of ANC information to allow clozapine to be dispensed to the patient. As a result of these implementation challenges and their potential to cause treatment interruption and barriers to patient access, FDA announced that it would exercise enforcement discretion for certain aspects of the REMS, as described more fully below. FDA, through enforcement discretion, has purposely chosen not to require that the CPMG fully implement the REMS given the potential negative impact on patient access and treatment disruption as described more fully below in Section 2.3. The seriousness of schizophrenia and the deleterious consequences of treatment interruption must be balanced with implementing safe use requirements intended to address the risk of severe neutropenia. The clozapine product manufacturers group (CPMG) suggests that over 45,000 patients per year could have their clozapine treatment withheld or delayed if all REMS safe use requirements were implemented as intended (Assessment Reports 6 and 7).

As part of our regular review of all REMS, and in light of the Agency's continued exercise of enforcement discretion with respect to implementing certain aspects of the Clozapine REMS and concern regarding patient access, FDA announced that it was conducting a re-evaluation of the Clozapine REMS to inform possible changes (including consideration of elimination) to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of clozapine.

1.3 Summary of FDA's Re-evaluation of the Clozapine REMS

The FDA used a systematic, structured approach for the re-evaluation of the Clozapine REMS.[3] The re-evaluation consisted of two assessments: the risk assessment and care gap[4] assessment. The purpose of the risk assessment is to evaluate if the risk of clozapine-induced severe neutropenia has changed since 1989. The purpose of the care gap assessment is to evaluate if the healthcare gaps that the current Clozapine REMS is designed to address persist. Together, these assessments provide the situational context for clozapine prescribing to help determine whether problems associated with the risk of severe neutropenia remain that require a REMS program to ensure the benefits of clozapine outweigh its risks.

Briefly, the current Clozapine REMS includes enrollment of prescribers, pharmacies, and patients. Prescribers and pharmacy staff must complete training to become certified to prescribe and dispense clozapine. Prior to starting treatment, prescribers agree to obtain a baseline ANC for the patient and monitor a patient's ANC during clozapine treatment according to the patient's risk category (general population versus patients with benign ethnic neutropenia), ANC test results, and duration of clozapine treatment. During the first 6 months, patients must have weekly blood draws, every 2 weeks for months 6 to 12, and every month after 1 year of treatment. Prescribers document the patient's ANC test results using the REMS Patient Status Form, which requires prescribers (or staff they designate to assist with the REMS) to access the web-based REMS system or fax the completed form to the REMS administrator. Completion of the form with acceptable ANC results or the prescriber's authorization to continue treatment despite a moderate/severe neutropenia authorizes the patient to be dispensed more

[3] Food and Drug Administration. REMS Logic Model: A framework to link program design with assessment. Guidance for industry (draft). May 2024. Accessed October 1, 2024. Available at https://www.fda.gov/media/178291/download.

[4] A care gap is the discrepancy between best practices and the care that is provided or anticipated to be provided in clinical practice. For REMS, the discrepancy between the necessary care a patient needs for the benefits of the drug to outweigh its risks and the care that is actually (or anticipated to be) provided. Food and Drug Administration. REMS Logic Model: A Framework to Link Program Design With Assessment Guidance for Industry (draft). May 2024. Accessed on Oct 1, 2024. Available at: https://www.fda.gov/media/178291/download.

clozapine. The pharmacy receives authorization to dispense clozapine by calling the REMS or checking the Clozapine REMS web-based system.

Updated Assessment of Severe Neutropenia

The data indicate that clozapine can cause severe neutropenia, though estimates of its frequency vary. Perhaps because of this variability and the overall relatively low likelihood of developing severe neutropenia, there are conflicting perceptions among the public about the risk of neutropenia with clozapine.[5,6] Some perceive the risk as low and believe that it aligns with the risk of severe neutropenia observed with other drugs that are approved without a REMS, that the risk is greatest in the first several months of treatment, and that the risk is unlikely to result in fatal outcomes. The purpose of conducting an updated risk assessment was to assess the cumulative incidence of severe neutropenia over time with clozapine use as well as any related clinical outcomes, such as death and infection, that result from severe neutropenia. FDA conducted several activities to assess the risk, including 1) a review of the biomedical literature, 2) a review of adverse event reports in the FDA Adverse Event Reporting System (FAERS), 3) studies analyzing data from FDA's Sentinel System,[7] 4) a pharmacoepidemiological study in collaboration with researchers from Brigham and Women's Hospital (BWH), and 5) a pharmacoepidemiological study conducted in collaboration with the Department of Veterans Affairs (VA). Collectively, these studies provide approximately 20 years of data and capture different settings of patient care (outpatient, inpatient) and different types of healthcare system considerations (integrated healthcare system, private and public insurance).

Our updated assessment of the risk led FDA to conclude that the risk of severe neutropenia remains the same – it is greatest with clozapine in the first 6 months of treatment and, beyond that timepoint, it never reaches zero across the studies conducted. This is consistent with the currently approved clozapine label, which states that the risk is greatest in the first 18 weeks of clozapine initiation.

We also found that the cumulative incidence of severe neutropenia, with some degree of monitoring, is 0.4% at 1 year in the VA study and 0.8% at 1 year from our literature review (Alvir et al. 1993), compared to 1.3% at 1 year, as reported in the 1989 clozapine label. However, these lower rates may not be generalizable to all patients in the United States, thus our risk assessment remains unchanged. Additionally, our assessment confirms that frequent ANC monitoring remains necessary to identify neutropenia early so that healthcare providers can intervene and may prevent progression to more severe cases. Very few deaths related to clozapine-induced neutropenia were found in the retrospective observational studies we conducted.

Updated Healthcare Gap Assessment

As currently designed, the Clozapine REMS addresses two care gaps: (1) knowledge of the risk of severe neutropenia and the need for ANC monitoring in the prescribing population and (2) ensuring that ANC monitoring of patients occurs. Clozapine has been approved for almost 40 years and the landscape of healthcare delivery has changed significantly since clozapine was first approved in 1989. The purpose of

[5] The Angry Moms. https://www.theangrymoms.com/.
[6] National Alliance on Mental Illness. https://www.nami.org/NAMI/media/NAMI-Media/PDFs/FINAL11-30_Clozapine-REMS-Program-Updates_Indiv-Families.pdf.
[7] The Sentinel System is CDER's active medical product safety surveillance system. Through the Sentinel System, CDER conducts analyses in electronic healthcare data, including administrative claims and electronic health records, using routine analytic tools and custom programming.

FDA conducting an updated care gap assessment is to determine whether gaps in knowledge and behavior in the prescribing population persist.

- For the first care gap, we *sought to understand if practitioners understand the risk of clozapine-related neutropenia and the appropriate actions that need to occur if neutropenia is detected*. The updated assessment evaluated prescriber knowledge survey data; examined available non-REMS training, guidelines, and resources; and assessed the extent to which education on the risk of severe neutropenia and the need for ANC monitoring with clozapine is incorporated in the healthcare delivery system today.

  REMS Assessment knowledge survey data have shown sustained knowledge about the risk of neutropenia associated with clozapine and the need for monitoring among healthcare providers who are participating in the REMS. Data from the VA and Sentinel studies among prescribers, who may or may not participate in the REMS due to enforcement discretion, suggest that prescribers' understanding of the risk of severe neutropenia and how to manage it is supported by the actions that they are taking in patients who develop neutropenia. Information collected through the two different surveys (see section 3.2 and section 4.3.3) also indicates that prescribers seek information about clozapine and monitoring neutropenia from resources outside of the REMS (e.g., common clinical decision support tools such as UpToDate, Micromedex, ePocrates). Recommendations for managing patients on clozapine are available in varying levels of detail across eight of nine treatment guidelines for schizophrenia and books we reviewed. We also reached out to three professional organizations to ascertain the extent to which information about clozapine and its risk of neutropenia is incorporated into psychiatry training (see section 6.1.2).[8] In summary, our evaluation suggests that there is broader knowledge of the risk of severe neutropenia and need for ANC monitoring with clozapine today as compared to the initial approval in 1989, and the knowledge gap has narrowed due to the availability of resources beyond the educational materials in the Clozapine REMS. Unlike in 1989, today, experience with managing neutropenia associated antipsychotic medications, including clozapine, is incorporated into medical training.

- For the second care gap, we *sought to understand the extent to which ANC monitoring is performed.* An analysis of prescribers' adherence to ANC monitoring as described in the prescribing information was done by evaluating REMS assessment reports, conducting a literature review, and evaluating the findings from FAERS, BWH studies, Sentinel studies, and a study conducted with the VA. We evaluated a variety of sources, gathering information on prescribers participating in and outside of the REMS, to provide a robust picture of the extent to which ANC monitoring is routinely performed.

  Among the stakeholders participating in the REMS, data from REMS assessment reports suggest high adherence with the ANC monitoring described in the prescribing information across all recommended ANC monitoring schedules. Although data from the literature review and FAERS reports, where information for ANC monitoring is available, suggest that most providers are following ANC monitoring consistent with the prescribing information, many of these cases involved clozapine management in complex scenarios (e.g., concurrent cancer treatment).

  In contrast, the findings were different in the BWH and Sentinel studies, which use claims data, and may include stakeholders who are not participating in the REMS due to the enforcement discretion. These studies showed that new clozapine users have a median of 2.1 (in BWH) and 3.1 (in Sentinel) ANC tests per month for the first 6 months of treatment despite the prescribing information recommending weekly monitoring, which is 4 tests in a month. The second analysis in Sentinel

[8] Accreditation Council for Graduate Medical Education (ACGME), The American College of Psychiatrists (ACP), American Board of Psychiatry and Neurology (ABPN).

looking at time periods between ANC tests showed that 10% or less of clozapine episodes had perfect adherence to the monitoring frequency and when loosening the definition of adherence, adherence only increased to 41%. Furthermore, approximately, 63% of clozapine users had a baseline ANC in the 30 days prior to initiating clozapine.

In summary, these data demonstrate that ANC monitoring is performed but likely less frequently than what the prescribing information recommends during the first six months of clozapine treatment.

There are several factors to consider when re-evaluating whether the clozapine REMS is necessary to ensure the benefits of clozapine outweigh the risk of severe neutropenia. First, the REMS has been operating under enforcement discretion since shortly after the REMS approval, under which the Agency does not object to dispensing to patients without verifying safe use requirements in the REMS. It is unclear the extent to which the REMS itself is contributing to ensuring ANC monitoring is performed and reducing the risk of severe neutropenia. Despite patients undergoing ANC monitoring less frequently than recommend in labeling, especially in the first six months of treatment, very few cases of death and hospitalizations were seen in the observational studies we have conducted. Second, clozapine has been approved for almost 40 years and monitoring recommendations have been in place throughout that time. The knowledge gap has narrowed while the availability of resources and practice guidelines has grown. Third, there are burden and access issues for patients with schizophrenia resulting in significant health disparities to clozapine use (Tiihonen et al. 2009; Cahoon et al. 2013; Farooq et al. 2019; Vermeulen et al. 2019). Fully implementing the REMS may result in more burden than what we are seeing today. The burden of the REMS must be weighed against the benefits of clozapine, which is currently the only treatment approved for treatment-resistant schizophrenia and reducing suicidality in patients with schizophrenia (Keepers et al. 2020). Lastly, there are other healthcare gaps that contribute to burden and impact patient access to clozapine that will continue to exist regardless of whether the REMS is changed or eliminated to reduce burden. For example, healthcare provider's comfort and familiarity around prescribing clozapine as it is associated with other serious adverse effects, patient difficulty in accessing psychiatric care, fragmentation of services that should be coordinated (e.g., transition from inpatient to outpatient, insurance coverage), or rising costs of healthcare services will impact patient access to clozapine. Furthermore, changing or eliminating the REMS does not remove the need for prescribers to monitor ANCs.

1.4 Draft Points for Consideration

As you review the AC briefing materials, we ask that you consider the following points in advance of the meeting:

- 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 ANC monitoring?
- How reassured or concerned are you that current and potential clozapine healthcare providers will perform ANC monitoring without the requirements of the REMS?
- 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?
- Is the requirement to educate healthcare providers on the risk of severe neutropenia and the need for ANC monitoring through the REMS necessary to ensure safe use?

2 Background

2.1 Background of the Condition/Standard of Clinical Care

Clozapine, marketed as Clozaril (New Drug Application [NDA] 019758), Fazaclo ODT (NDA 021590), Versacloz (NDA 203479), and generics, is an antipsychotic medicine indicated for schizophrenia in patients whose symptoms are not controlled with standard (non-clozapine) antipsychotic drugs (i.e., treatment-resistant schizophrenia). It is the only drug approved for this indication. Clozapine is also the only drug indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.

2.1.1 Treatment-Resistant Schizophrenia

Schizophrenia is a serious psychiatric disorder that can impact all aspects of the affected individual's life. Although the international prevalence of schizophrenia among non-institutionalized persons is 0.33% to 0.75%, because of the social, educational, occupational functioning, physical health, self-care, and quality of life issues associated with the disorder, schizophrenia is the twelfth leading cause of years lost to disability worldwide (Charlson et al. 2018). The clinical presentation of schizophrenia includes positive symptoms (e.g., delusions, hallucinations), negative symptoms (e.g., blunted affect, avolition), and cognitive impairment, and may require short-term or long-term hospitalization. Many individuals with schizophrenia require chronic treatment to control and prevent recurrence of positive symptoms.

Antipsychotic pharmacotherapy is the mainstay of treatment for the positive symptoms of schizophrenia, although nonpharmacological interventions may be useful for certain symptoms. Antipsychotic medications have consistently demonstrated efficacy in reducing positive symptoms, but it is generally recognized by clinicians that they do not significantly improve negative and cognitive symptoms. The majority of patients with first-episode psychosis will respond to their first antipsychotic treatment trial. Unfortunately, a significant subset of individuals with schizophrenia will continue to experience psychosis despite adequate trials of antipsychotic treatment. For those patients, subsequent treatment with a different non-clozapine antipsychotic is less likely to result in significant symptom improvement, and data suggest that response rates for a third non-clozapine antipsychotic treatment trial are even lower (Kane et al. 2019).

Approximately one-third of persons with schizophrenia are estimated to meet criteria for treatment-resistance, with a recent systematic review and meta-analysis of 50 studies including subjects with schizophrenia showing a mean prevalence of treatment-resistance of 36.7% (Diniz et al. 2023). A recent modeling approach estimated the prevalence of treatment-resistant schizophrenia in the United States at approximately 22% (Mørup et al. 2020).

Treatment-resistant symptoms have a large impact on individuals with schizophrenia, their families and caregivers, their treatment teams, and society. Individuals with treatment-resistant schizophrenia generally exhibit more severe positive and negative symptoms, worse neurocognitive functioning, lower quality of life and community functioning, and higher health care costs compared to those who respond to antipsychotic medications (Kane et al. 2019). Treatment-resistant symptoms require a substantial amount of time and resources for patient-care activities, which may impact the healthcare delivery system. As disease progresses over time, the negative effects on families and caregivers also grow, including decreases in family cohesion and flexibility (Koutra et al. 2014).

Clozapine is the only antipsychotic medication approved for treatment-resistant schizophrenia. Despite adverse reactions limiting its use in the general population of persons with schizophrenia in the United States, the American Psychiatric Association's (APA) practice guideline for the treatment of patients with schizophrenia states that clozapine is considered the treatment of choice for those experiencing treatment-resistant schizophrenia symptoms. This is consistent with other U.S. and international treatment guidelines that recommend clozapine for persons with treatment-resistant schizophrenia (American Psychiatric Association).

Clozapine's efficacy in treatment-resistant schizophrenia compared to other antipsychotic medications has been evaluated in published studies, meta-analyses, and systematic reviews of schizophrenia clinical trials (Kane et al. 1988; Chakos et al. 2001; Essali et al. 2009; Samara et al. 2016; Siskind et al. 2016; Dong et al. 2024). In the clinical study that supported marketing approval in the United States, clozapine demonstrated significantly greater efficacy compared to a comparator antipsychotic in treating the symptoms of treatment-resistant schizophrenia (Kane et al. 1988). The multicenter, randomized, double-blind, active-controlled study included subjects with schizophrenia who had trials of at least three different antipsychotics and inadequate response to a 6-week trial of a non-clozapine, non-comparator antipsychotic in a single-blind, lead-in phase. At the end of the 6-week, double-blind treatment period, 30% of the subjects in the clozapine group, compared to 4% of the subjects in the comparator group, met criteria for treatment response (at least 20% decrease in the Brief Psychiatric Rating Scale score and either a Clinical Global Impressions-Severity score meeting criteria for mildly ill or a Brief Psychiatric Rating Scale score of ≤35 (Clozaril U.S. Prescribing Information, revised May 2023).

Despite being the only approved drug for treatment-resistant schizophrenia and practice guideline recommendations, drug utilization data analyses indicate just under 148,000 patients were dispensed a clozapine outpatient prescription in the United States in 2023 (Division of Epidemiology (DEPI) consult response. Ramzan, et al., August 19, 2024). For comparison, the universe of patients who meet the criteria for treatment-resistant schizophrenia is approximately 814,000 to 1.2 million people in the United States (using the estimate that 3.7 million (1.8%) of adults in the United States have a lifetime history of schizophrenia and approximately 22% to one-third will meet criteria for treatment resistant schizophrenia (Diniz et al. 2023). Under-utilization of clozapine has been documented through U.S. VA and U.S. Medicaid claims. From 2000 to 2021, 5% of the 134,000 veterans diagnosed with schizophrenia or schizoaffective disorder were treated with clozapine, including 9% of 3,407 veterans with a history of attempted suicide (Emerson 2023). Similarly, almost 80,000 treatment episodes of adult Medicaid beneficiaries met criteria for treatment-resistant schizophrenia, but clozapine was started in only 5.5% of these patients (Stroup et al. 2014). Although clozapine will not be appropriate for every patient with treatment-resistant schizophrenia, these data indicate that clozapine use is low in the indicated patient population.

2.1.2 Reducing Suicidal Behavior in Patients with Schizophrenia or Schizoaffective Disorder

Rates of suicidal ideation and behavior, including suicide attempts and deaths by suicide, are higher in people with schizophrenia and schizoaffective disorder compared to the general population. Between 10% to 50% of people with schizophrenia attempt suicide during their lifetimes (Meltzer 2001; Lu et al. 2019), and approximately 5% die by suicide (Hor and Taylor 2010). A meta-analysis of all specific-cause mortality in people with schizophrenia showed that suicide was the greatest risk factor for mortality in individuals with schizophrenia (Correll et al. 2022).

The APA treatment guidelines for schizophrenia recommend that patients be treated with clozapine if the risk for suicide attempts or suicide remains substantial despite management with other treatments (American Psychiatric Association, 2020). Treatment with clozapine can be effective in reducing rates of suicide and suicide attempts in people with schizophrenia, even in those who have not met formal criteria for treatment resistance.

Clozapine's efficacy in reducing suicidal ideation and behavior was demonstrated in a multicenter, international trial comparing the risk for suicidal behavior in 956 people with schizophrenia or schizoaffective disorder at high suicide risk who were randomized to clozapine or olanzapine (Meltzer et al. 2003). In this trial, which supported marketing approval for the indication of suicidality in the United States, subjects treated with clozapine had a statistically significant longer delay in time to recurrent suicidal behavior in comparison with olanzapine. As described Section 14.2 in the U.S. Prescribing Information, the probability of experiencing either (1) a significant suicide attempt (including a completed suicide) or (2) hospitalization because of imminent suicide risk, including increased level of surveillance for suicidality for hospitalized subjects was lower in the clozapine group compared to the comparator group at Week 104 (24% compared to 32%, 95% Confidence Interval (CI), 2%, 14%) (Clozaril U.S. Prescribing Information, revised May 2023). A recent systematic review of studies investigating the efficacy of clozapine in reducing suicidality[9] concluded that most data suggest a superior effect for clozapine compared to other antipsychotics or no antipsychotic treatment (Masdrakis and Baldwin 2023).

2.2 Serious Non-Neutropenia Risks Associated with Clozapine

Although severe neutropenia may be the most well-known risk with clozapine, clozapine is associated with numerous non-neutropenia related risks. These risks are not the focus of the Clozapine REMS but weigh heavily on the burden of patient management and may impact a prescriber's decision to treat a patient with clozapine. Adverse reactions range from bothersome enough to cause poor adherence (e.g., salivary hypersecretion) to dangerous and life-threatening. Uniquely among second generation antipsychotics, clozapine carries boxed warnings for orthostatic hypotension, bradycardia, syncope, cardiac arrest, seizures, myocarditis, cardiomyopathy, and pericarditis. Additional serious adverse reactions that are also unique or particularly frequent or severe with clozapine include complications from gastrointestinal hypomotility including intestinal obstruction, infarction and toxic megacolon; anticholinergic toxicity; interference with cognitive and motor performance; recurrence of psychosis and cholinergic rebound after abrupt discontinuation of clozapine; QT prolongation; the highest rates of weight gain and hyperglycemia among second generation antipsychotics; and hepatotoxicity.

Clozapine management is further complicated by significant inter- and intra-patient pharmacokinetic variability. Factors thought to significantly affect clozapine metabolism include estrogens and other hormones, concurrent medications, smoking habits, presence of acute or chronic inflammatory conditions, age, ethnicity, or other pharmacogenetic factors. Clozapine is a substrate for many cytochrome P450 isozymes, in particular CYP1A2 and CYP3A4. There is also potential for other drugs, smoking, and caffeine to affect clozapine plasma levels, which can result in adverse reactions or decrease in effectiveness. The risk of orthostatic hypotension, bradycardia and cardiac arrest increases with the rate of dose escalation. Clozapine dosing must begin with low dosages and increases must be

[9] The agency prefers the term suicidal ideation and behavior because it is more precise. However, we retain "suicidality" based on the article.

carefully calibrated. For patients who have had an interruption in treatment, dosage must be reduced when resumed to minimize the risk of hypotension, bradycardia, and syncope.

2.3 Severe Neutropenia and Associated Risk Management for Clozapine

Despite the identified benefit of clozapine in the treatment for treatment-resistant schizophrenia and reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder, clozapine carries significant risks including the potential to cause severe neutropenia. Risk of severe neutropenia,[10] previously referred to as agranulocytosis, is the focus of the Clozapine REMS Program. At the time of the U.S. approval in 1989, the prescribing information included a boxed warning that stated,

> Agranulocytosis, defined as a granulocyte count of less than 500/mm^{3*}, has been estimated to occur in association with [clozapine] use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 US cases out of 1743 patients exposed to [clozapine] during its clinical testing prior to domestic marketing. Of the 112 cases of agranulocytosis reported worldwide in association with [clozapine] use as of December 31, 1986, 35% were fatal...It is unknown at present what the case fatality rate will be for [clozapine]-induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts.
>
> Because of the substantial risk of agranulocytosis in association with [clozapine] use, which may persist over an extended period of time, patients must have a blood sample drawn for a WBC count before initiation of treatment with [clozapine], and must have subsequent WBC counts done at least weekly for the duration of therapy, as well as for 4 weeks there-after. The distribution of [clozapine] is contingent upon performance of the required blood tests.
>
> Treatment should not be initiated if the WBC count is less than 3500/mm^{3}. If the total WBC count falls below 3000/mm^3 or the granulocyte count below 1500/mm^3, [clozapine] therapy should be interrupted and patients should be carefully monitored…. In this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500/mm^3.Patients whose total WBC counts fall below 2000/mm^3, or granulocyte counts below 1000/mm^3 during [clozapine] therapy should not be re-challenged with [clozapine].
>
> * mm^3 is equivalent to µL (international unit)

Along with this boxed warning in the prescribing information, the 1989 approval included a restricted distribution system that required weekly monitoring of white blood cells (WBC) along with prescription day supply limits to support WBC monitoring, and enrollment of prescribers, pharmacists, and patients in a registry called the Clozaril National Registry (CNR). Patients who experienced severe neutropenia were not permitted to restart clozapine. Since 1989, the prescribing information and risk mitigation requirements have evolved as more was learned about clozapine-induced neutropenia.

Beginning in the 1990s, Novartis, the manufacturer of Clozaril, submitted epidemiological analyses in 1994, 1995, and 1997 to further characterize the risk of severe neutropenia. The 1997 analysis provided by Novartis encompassed 96,821 patients treated with Clozaril in the United States with up to 5.5 years

[10] Previous versions of clozapine labeling referred to the risk of agranulocytosis, which is defined as absence of granulocytes (neutrophils, basophils, and eosinophils). Neutrophils constitute the majority of granulocytes and the presence or absence of other granulocytes is not important to the existence of the risk. To improve and standardize understanding, "severe neutropenia," which signifies a neutrophil count of less than 500/µL, replaces the previous term, agranulocytosis, in the current labeling. Additionally, previous versions of clozapine labeling used cubic millimeters (mm^3) as the unit of measure for ANC. Current labeling uses microliters (µL). These units of measure are equivalent. This briefing document uses microliters (µL) throughout.

of follow-up. Based on the accumulated data from these analyses, Novartis submitted a labeling supplement to support reduced WBC monitoring on September 3, 1997. The labeling supplement provided the background rate of severe neutropenia in the general population of 3 to 7 cases/million person-years. Based on Novartis' data in United States Clozaril-treated patients, the severe neutropenia rate in the 6 months after treatment initiation was 8.6 cases/1,000 person-years, with a peak between months 2 to 3 at 29.1 cases/1,000 person-years. The rate falls rapidly in the 6-month to 2-year period to 0.7 cases/1,000 person-years. Rates continue to fall to 0.4/1,000 person-years (after 2 to 3.5 years) and to 0.2 cases/1,000 person-years (after 3.5 to 5.5 years). The rate of severe neutropenia after 3.5 to 5.5 years was approximately 100-fold higher than the background rate in the general population. These data, included in Novartis' 1997 supplement, were discussed at the July 14, 1997, Psychopharmacologic Drugs Advisory Committee (PDAC). Novartis presented a model for projecting the number of cases of severe neutropenia under various conditions. This model projected that, if all monitoring was discontinued after 6 months of weekly testing, the severe neutropenia rate would be 3.6 cases/1,000 person-years. Novartis noted that this rate was within the range of rates reported with two marketed drugs associated with severe neutropenia (ANC <500/µL) but without mandatory WBC monitoring: ticlopidine (≥8 cases/1,000 person-years) and sulfasalazine (3 cases/1,000 person-years). Per Novartis, even if one assumed that all Clozaril-treated patients who experienced moderate leukopenia (2000 to 3000 neutrophils/µL) or severe leukopenia (500 to 2000 neutrophils/µL) progressed to severe neutropenia (<500 neutrophils/µL), the severe neutropenia rate would be 5.2 cases/1,000 person-years. In 1998, based on FDA's evaluation of the data in Novartis' labeling supplement, which took into consideration the proceedings of the 1997 PDAC and the committee's recommendation, the prescribing information and restricted distribution program requirements were updated to change the required WBC monitoring from weekly to biweekly after 6 months of continuous Clozaril therapy. The committee's recommendation that WBC monitoring should be optional after the first year of treatment was not adopted.

The PDAC reconvened to discuss WBC monitoring with clozapine again in 2003. The committee voted that the frequency of WBC monitoring could be reduced for patients who maintained a normal WBC and ANC during the first year of therapy. The committee recommended mandatory WBC monitoring should continue as part of the restricted distribution program. The committee supported adding ANC monitoring in addition to WBC. As a result, in 2005, the prescribing information and restricted distribution program requirements were updated to decrease the frequency of WBC and ANC monitoring to every 4 weeks after a patient has maintained a normal WBC and ANC for the first year of treatment.

By 2008, six restricted distribution programs for clozapine were in use including the CNR. The programs were separate, requiring enrollment in each program to prescribe, dispense, and be treated with a particular manufacturer's clozapine product; however, the programs shared a national database, the National Non-Rechallenge Master File (NNRMF). Patients were entered in the database who met the "no rechallenge" criteria. All manufacturers of clozapine products were responsible for verifying patients were not listed in the NNRMF at the time of enrollment in the restricted distribution programs and for reporting any non-rechallenge patients promptly.

In 2012, FDA determined it was necessary to combine all clozapine products in a single shared REMS to reduce the burden on the health care system and increase the safe use of clozapine. In parallel, FDA also re-evaluated how best to address the risk of severe neutropenia. During this re-evaluation, FDA

determined the neutropenia monitoring recommendations and treatment algorithms in the prescribing information and restricted distribution programs were outdated and required revision. Hematology treatment guidelines and risk management options for treating severe neutropenia had evolved after years of cumulative experience with neutropenia-causing drugs, including clozapine. After considerable research of the literature and clinical practice guidelines, and detailed discussions with hematology, psychiatry, and clinical pharmacy experts within and outside of FDA, FDA revised the prescribing information to remove contraindications and restrictions that lacked scientific evidence, updated monitoring criteria, and included modified monitoring requirements for patients with benign ethnic neutropenia. In September 2015, FDA approved these changes to the prescribing information and the Clozapine Shared System REMS (here after referred to as the Clozapine REMS) that incorporated the updated requirements for monitoring. Table 1 outlines the changes to the prescribing information and the rationale for those changes.

Table 1. 2015 Changes to the Prescribing Information and Rationale

Changes to the Prescribing Information	Rationale
Monitoring for neutropenia only by ANC as opposed to total WBC:	ANC is the primary and main determinant of risk of infection. A normal WBC does not necessarily reflect a normal ANC nor is a decreased ANC necessarily associated with low/abnormal WBC.
Lowering the ANC thresholds for interrupting clozapine treatment and removing contraindications to treating patient with pre-existing conditions or using concomitant drugs known to cause neutropenia: (see Appendix 10.1)	The updated thresholds were recommended by hematology experts and consistent with clinical practice guidelines. The previous monitoring criteria were overly strict, empirical, outdated, and unnecessarily precluded some patients from initiating or continuing clozapine treatment. Further, rapid discontinuation of clozapine treatment might provoke a rapid onset psychotic episode in some patients leading to deterioration in the quality of remission and an increased clozapine dose requirement to stabilize the patient if treatment was resumed. In addition, the ability to recognize and effectively treat severe neutropenia and neutropenic fever had improved significantly over the past 30 years. Many conditions associated with neutropenia were safely managed on an outpatient basis with oral medication. Recovery in these patients was not contingent upon withdrawing clozapine.
Creating separate ANC thresholds for patients with benign ethnic neutropenia: (see Appendix 10.1)	Applying ANC thresholds appropriate for the general population precluded many African Americans and other individuals genetically predisposed to BEN from initiating or continuing clozapine treatment because their lower ANCs fell outside clozapine treatment recommendations. BEN is the most common form of neutropenia worldwide. It primarily affects non-Caucasian ethnic groups with darker skins; 20-50% of persons of African descent, some Middle Easterners (Arab Jordanians, Black Bedouin, Falashah and Yemenite Jews), and West Indians. It is more common in men. It appears to confer no clinical disadvantage and is considered a variation of normal.
Eliminating the NNRMF and allowing patients to restart clozapine after experiencing severe neutropenia.	The revised labeling allowed clinicians to weigh the benefits of continuing treatment against risks of severe neutropenia for individual patients.

Source: Adapted from the medical officer's "rationale for neutropenia revisions to clozapine labeling." Signed August 15, 2014, by Duncan LE, Mathis MV.
Abbreviations: ANC, absolute neutrophil count; Ben, benign ethnic neutropenia; NNRMF, National Non-Rechallenge Master File, WBC, white blood cell

With the approval of the Clozapine REMS in September 2015, the CPMG was given 90 days to fully implement the REMS. Prescribers and pharmacy staff were required to enroll and complete training to become certified to prescribe and dispense clozapine. Prior to starting treatment, prescribers agreed to enroll the patient and obtain a baseline ANC for the patient and monitor a patient's ANC during clozapine treatment according to the patient's risk category (general population versus patients with benign ethnic neutropenia), ANC test results, and duration of clozapine treatment. During the first 6 months, patients were required to have weekly blood draws, every 2 weeks for months 6 to 12, and every month after 1 year of treatment. Prescribers needed to document the patient's ANC test results using the web-based REMS system or fax a completed monitoring form to the REMS administrator. Completion of the monitoring form with acceptable ANC results or the prescriber's authorization to continue treatment despite a moderate/severe neutropenia authorized the patient to be dispensed

clozapine. Through an electronic communication with the REMS or contacting the call center, a dispense authorization was obtained by the pharmacy prior to dispensing clozapine. The authorization was successful if both the prescriber and pharmacy were certified, the patient was enrolled and had an ANC that was current and acceptable, or the prescriber had authorized continuing treatment if the ANC was abnormal.

In the first 90 days after approval of the shared system REMS, it proved challenging for the CPMG to transition from six separate restricted distribution programs that included 50,000 registered prescribers, 28,000 registered pharmacies and 90,000 pre-existing patient records to one REMS. There were significant implementation challenges, which included technical problems with data migration and programming of the shared system website. These implementation issues resulted in long wait times for participants when calling for assistance and disrupted access to treatment for many patients as well as pharmacies' access to clozapine for dispensing.

Because of these challenges and to prevent further interruptions in treatment, in November 2015 the Agency announced that the prescriber and pharmacy REMS certification deadlines were extended. On January 14, 2016, the FDA allowed CPMG additional time to fully implement the approved REMS provided they continue working with the FDA and others to move toward full implementation. Due to the substantial nature of the problems identified with the operationalization of the REMS, CPMG would need to make significant revisions to the entire REMS system. It became apparent that full implementation would require a slower, more stepwise approach than FDA or CPMG originally anticipated.

In May of 2016 the CPMG released changes to the REMS system to allow pharmacies to verify patient enrollment through a dispense authorization. The dispense authorization was intended to verify all safe use requirements prior to each dispense of clozapine; however, the dispense authorization put in place in 2016 did not verify all safe use requirements, specifically if the prescriber or pharmacy were certified in the REMS. This meant that the REMS did not restrict distribution to only certified prescribers and pharmacies. Furthermore, although the original intent of the dispense authorization requirement was for the REMS system to verify that the ANC results were both current[11] and in the acceptable range before dispensing, implementation challenges persisted. In August 2016, the CPMG reported to the Agency that an estimated 52% of clozapine patients would not receive clozapine if the REMS system required the prescriber to document a current ANC in the REMS systems as part of the dispense authorization. Denying clozapine to patients who may have had a current ANC in the acceptable range (but simply not documented in the REMS system) was especially concerning to the Agency. To address this concern, the CPMG encouraged pharmacists to contact the prescriber to acquire the most recent ANC and dispense clozapine as appropriate. From 2016 to the beginning of 2019, FDA and CPMG continued to work toward implementing a more functional system while making accommodations for continued access for patients during the transition. Beginning February 28, 2019, the REMS began enforcing prescriber and pharmacy certification as part of the dispense authorization. However, the FDA remained concerned that patients would be denied access to clozapine if the requirement for prescribers to document ANC results in the REMS system as a condition of dispensing was implemented. Therefore, requiring a current ANC be documented in the REMS system as part of the dispense

[11] Clozapine REMS definition of a current laboratory was based on the patient's monitoring frequency. Weekly monitored patients had to have a lab within 7 days of the attempted dispense, biweekly monitored patients within 15 days, and monthly monitored patients within 31 days.

authorization was not implemented in 2019. Furthermore, because of the COVID-19 Public Health Emergency that occurred beginning in March 2020, patients who were prescribed clozapine continued not to be subject to the ANC monitoring requirements.[12]

In July 2021, the FDA approved changes to the REMS that took effect in November 2021 to address the continued prescriber challenges with ANC reporting frequency and a change to a new REMS administrator. These program changes included reducing the frequency that prescribers were required to report ANCs to the REMS for all patients to monthly regardless of the monitoring frequency and implementing a new process for how pharmacies verified that the safe use requirements were met before dispensing. This change to the verification process was necessary because the processes and information technology platform used by the previous REMS administrator that supported the major operations of the program (call center and system) would be different under the new administrator. In preparing for the transfer of data to the new REMS administrator's database, the CPMG identified issues with duplicate and incomplete data which resulted in all prescribers, pharmacies, and patients having to recertify or re-enroll in the REMS to establish an accurate database (see Section 2.4 for more detailed information about the current Clozapine REMS requirements). Implementation challenges with the new system resulted in disrupted access to treatment for many patients. In November 2021, FDA delayed implementation of these updates, including the requirement that pharmacies be certified in the program to receive clozapine and the requirements that pharmacies verify patient enrollment and ANC monitoring before dispensing clozapine.

In November 2022, to facilitate efficient transition from the inpatient setting to the outpatient setting, inpatient pharmacies were allowed to dispense at discharge the days' supply of clozapine that aligned with the patient's ANC monitoring frequency to ensure continuity of care for patients.

Table 2 indicates the REMS requirements in place over the years since approval of the Clozapine REMS in 2015 and the status of the enforcement.

[12] In March of 2020, the Agency released the following guidance for industry and health care professionals- Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency. FDA recognized that during the COVID-19 Public Health Emergency (PHE), completion of REMS-required laboratory testing or imaging studies may be difficult because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. For drugs such as clozapine, health care providers prescribing and/or dispensing these drugs could consider whether there were compelling reasons not to complete the REMS-required laboratory testing or imaging studies during the PHE and use their best medical judgment in weighing the benefits and risks of continuing treatment in their absence.

Table 2. Status of Enforcement of REMS Requirements From 2015 to Present

REMS Requirement	Nov 2015	May 2016	Feb 2019	Nov 2021	Oct 2024
Patient must be enrolled.	Not enforced	Enforced	Enforced	Not enforced	Not enforced
Patient has at least one ANC on file.	Not enforced	Enforced	Enforced	Not enforced	Not enforced
Patient's most recent ANC within normal range. If ANC indicates neutropenia, prescriber can choose to continue the patient on clozapine therapy.	Not enforced	Enforced	Enforced	Not enforced	Not enforced
Outpatient prescribers and prescribers initiating clozapine in inpatient setting must be certified.	Not enforced	Not enforced	Enforced	Not enforced	Not enforced
Pharmacy must be certified.	Not enforced	Not enforced	Enforced	Not enforced	Not enforced
Patient's most recent ANC is current.[%]	Not enforced	Not enforced	Not enforced	Not enforced^	Not enforced^

Source: Table generated by the FDA risk management analyst.
*Assumes lab draw date is 0
^ In 2021, the REMS changed to a less frequent/less stringent ANC documentation schedule using receipt of a Patient Status Form within the last 37 days
[%]Current is defined based on the monitoring frequency. For weekly monitoring frequency, the last ANC result reported to the Clozapine REMS Program must have been drawn* within 7 days prior to dispense authorization transaction date.
For every two-week monitoring frequency, the last ANC result reported to the Clozapine REMS Program must be drawn* within 15 days prior to the dispense authorization transaction date. For monthly monitoring frequency, the last reported ANC result reported to the Clozapine REMS must be drawn* within 31 days prior to the dispense authorization transaction date.
*Assumes lab draw date is 0
Abbreviations: ANC, absolute neutrophil count; REMS, Risk Evaluation and Mitigation Strategy

Currently, prescribers, patients, and pharmacies do not need to participate in the REMS for patients to have access to clozapine. However, based on outpatient drug utilization data (DEPI Drug Utilization Review. August 2024) and the number of unique outpatients with at least one clozapine dispense authorization (CPMG October 17, 2023, Information Request response), we estimate that approximately 65% of outpatients who are treated with clozapine are currently participating in the REMS.

2.4 Summary of Clozapine REMS Requirements if Fully Implemented

This section provides an overview of the program requirements for the currently approved Clozapine REMS. This program has never been fully implemented as described in this section.

All formulations of clozapine are subject to the Clozapine REMS, a restricted distribution program designed to identify severe neutropenia early so that prompt intervention can be taken to reduce serious outcomes, including infection and death, associated with clozapine use. The goal of the REMS is to mitigate the risk of severe neutropenia associated with the use of clozapine by:

- Educating prescribers and pharmacists about the risk of severe neutropenia and appropriate monitoring requirements.
- Informing patients about the risk of severe neutropenia and appropriate monitoring requirements.
- Ensuring prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia.
- Ensuring the prescriber documents a risk-benefit assessment when ANC falls below the acceptable range as described in the Prescribing Information.
- Establishing long-term safety and safe use of clozapine by enrolling all patients who receive clozapine in the registry.

The Clozapine REMS consists of ETASU, an implementation system, and a timetable for the submission of assessments of the REMS.

The Clozapine REMS consists of the following ETASU:

- Healthcare providers who prescribe clozapine must be certified (Prescriber Certification).
- Pharmacies that dispense clozapine must be certified (Pharmacy Certification).
- Clozapine must only be dispensed to patients with documentation of safe use conditions (documentation of patient enrollment, ANC monitoring, or prescriber authorization to continue treatment if the patient misses a lab or the most recent ANC indicates moderate or severe neutropenia for general population patients or severe neutropenia for BEN patients).
- Patients must be monitored (ANC monitoring for neutropenia).
- Patients must be enrolled in the clozapine registry.

To support operations and compliance with a restricted distribution program, CPMG contracts with wholesalers who agree to put policies and procedures in place to ensure that clozapine is distributed only to certified pharmacies, train all relevant staff on the requirements of the REMS, maintain distribution records, and comply with audits.

2.4.1 Prescriber Related Requirements

Healthcare providers who prescribe clozapine for outpatient use, or initiate clozapine for inpatient use, must be certified in the Clozapine REMS. To become certified to prescribe clozapine, the prescriber must review the prescribing information and the Guide for Healthcare Providers, complete a knowledge assessment, and complete the enrollment form. The Prescriber Enrollment Form includes a list of responsibilities that the prescriber must agree to become certified in the Clozapine REMS.

Before treatment initiation, as part of enrolling the patient, the prescriber must counsel the patient or caregiver, assess the patient's baseline ANC, and document the patient's ANC on the Patient Enrollment Form.

During treatment, prescribers must monitor the patient's ANC. The frequency of monitoring for a given patient is based on the duration of clozapine treatment and ANC results (referred to as the patient's "monitoring frequency"). The prescriber must submit a completed Patient Status Form (PSF) to the REMS monthly, regardless of the patient's monitoring frequency, for each patient continuing treatment with clozapine that includes the ANC results or to report a "treatment rationale" to authorize continuing clozapine treatment when an ANC falls below the acceptable range as described in the prescribing information. The PSF can also be used by the prescriber or their designee to verify or change the patient's monitoring frequency; interrupt, discontinue and resume treatment; and report any adverse events due to clozapine-induced neutropenia. Only the prescriber may use this form to designate a patient as either hospice[13] or BEN or authorize the continuation of therapy if one or more required ANC test results are missing.

If a patient's ANC indicates moderate or severe neutropenia for the general patient population, or severe neutropenia for BEN patients, a patient will be classified as interrupted in the REMS which could

[13] For hospice patients, the prescriber may reduce the ANC monitoring frequency to, at a minimum, once every six months, after a discussion with the patient and his/her caregiver. Designating a patient as a hospice care patient reduces the frequency of submitting a PSF to once every six months.

prevent the patient from obtaining clozapine from the pharmacy. Before clozapine can be dispensed to a patient in an interrupted status, the prescriber must provide a treatment rationale to resume treatment.

2.4.2 Patient-Related Requirements

Patients treated with clozapine must be enrolled in the Clozapine REMS. Before treatment initiation, they receive counseling about the risk and to have a baseline ANC measured. During treatment, as directed by their prescriber, they have their ANC assessed. Patients are directed to inform their prescriber if they have signs or symptoms of infection.

2.4.3 Pharmacy-Related Requirements

Inpatient and outpatient pharmacies that dispense clozapine must be certified in the Clozapine REMS. To become certified to dispense clozapine, all pharmacies must designate an authorized representative who will carry out the certification process and oversee implementation and compliance with the REMS program on behalf of the pharmacy. The authorized representative must review the Guide for Pharmacists, successfully complete a knowledge assessment, and enroll in the REMS by completing the appropriate enrollment form. Before dispensing clozapine, a certified pharmacy must obtain authorization to dispense, known as a REMS Dispense Authorization (RDA). An RDA is a unique identifying number generated from the Clozapine REMS administrator and provided directly to a requesting pharmacist from a certified pharmacy provided all safe use requirements have been met.

For the ***first dispensing*** of clozapine after patient enrollment, the receipt of the RDA means the following requirements have been met:

- The patient is enrolled
- The patient's baseline ANC is in the acceptable range

For a ***subsequent dispensing***, the receipt of the RDA means the following requirements have been met:

- The patient is enrolled
- A PSF has been completed in the last 37 days (30 days plus a 7-day grace period)
- The prescriber has authorized the continuation of treatment if one or more ANC test results are missing
- The prescriber has provided a treatment rationale if the most current ANC test result is below the acceptable range
- The patient's treatment status is not interrupted or discontinued

Outpatient pharmacies must obtain an RDA before each prescription and inpatient pharmacies must obtain an RDA only before the first dose. When a pharmacist does not receive authorization to dispense because of an overdue PSF, pharmacies can provide a current ANC obtained from the patient or their prescriber (within 30 days of the attempted fill) that is within an acceptable range for the patient, provide the prescriber's NPI number to the REMS administrator, then proceed with dispensing. This option in the REMS is referred to as a "Dispense Rationale." There is a limit of three Dispense Rationales per patient per year for outpatient pharmacies, whereas there is no limit to the number of Dispense Rationales used by inpatient pharmacies. This accommodation provides an opportunity for the pharmacist to apply clinical judgement to avoid unnecessary disruptions in patient treatment with

clozapine and provides an opportunity for the REMS to reach out to the prescriber to encourage compliance with the REMS.

There are no limitations on the amount of clozapine that can be dispensed for outpatients; however, the *Guide for Pharmacists* recommends dispensing a days' supply consistent with the patient's monitoring frequency. At the time of discharge, an inpatient pharmacy is limited to dispensing a 7-day supply.

Finally, pharmacies must also comply with audits to ensure all REMS related processes and procedures are in place and being followed.

2.4.4 Clozapine Registry

The Clozapine REMS includes a registry to establish long-term safety and safe use of clozapine by enrolling all patients who receive clozapine in the registry. Information from the PSF is used by the REMS administrator to populate the registry, including ANC data (mild/moderate/severe or the numeric value of the ANC result) and adverse event information. If the reporter indicates an adverse event occurred, the CPMG follows up with the reporter to obtain additional information.

3 Summary of Clozapine REMS Assessments [14]

The CPMG is required to submit REMS assessment reports to the Agency based on the schedule defined in the REMS document. Since 2015, the CPMG has submitted seven assessment reports. Given that the Clozapine REMS has never been fully implemented and considering problems with data integrity and insufficient data for analysis, neither the Agency nor the CPMG have been able to determine the contribution the Clozapine REMS has had on mitigating the risk of severe neutropenia. Data integrity issues resulted in duplicative patient enrollments as described in section 3.1 (Assessment Reports 1-5), and erroneous reports of neutropenia due to ANC test results being entered on the PSF with incorrect units as described in section 3.5.1 contributed to data integrity issues (Assessment Reports 6 and 7[15]).

The Clozapine REMS has not been fully implemented; thus, a compliance program to evaluate and monitor stakeholders' compliance with the REMS requirements has not been implemented. Consequently, the actual number of patients who are receiving clozapine but are not participating in the REMS cannot be determined. The assessment data we have to date may not include all prescribers, pharmacies and patients involved in clozapine treatment. Additionally, we lack data that would help FDA determine if all patients had a baseline ANC measured prior to initiating treatment with clozapine or if all patients are being monitored as stated in labeling. In assessment reports that the CPMG submitted prior to the implementation of the 2021 modification, the data were insufficient to determine if prescribers were monitoring ANC but had delayed or not provided the ANC test results to the Clozapine REMS. For all patients across all time periods whose ANC falls below the acceptable range, the data do not allow us to determine if the prescriber assessed that the benefits of continuing clozapine treatment outweighed the risks of developing severe neutropenia.

Data from the first seven REMS assessment reports are described in Sections 3.1 to 3.8 of this document. REMS Assessment Reports 1 through 5 cover the reporting periods from September 15, 2015, through November 15, 2021. The sixth REMS Assessment Report reporting period is July 29, 2021,

[14] This section includes data submitted by the CPMG in the Clozapine assessment reports as well as other supportive data including additional supplemental information from CPMG and FDA internal analyses of drug utilization data from proprietary databases.

[15] Assessment Report 7 was submitted to the FDA on August 9, 2024, and is currently under review.

through November 30, 2022; there is an overlap with the fifth Assessment Report from July 29, 2021, to November 15, 2021. This overlap allowed for data collected after approval of the July 2021 REMS modification and prior to implementation of this modification on November 15, 2021. The seventh REMS Assessment Report reporting period is December 1, 2022, through May 29, 2024.

3.1 Stakeholder Participation

With the change to a new REMS administrator in November 2021, prescribers and pharmacies needed to re-certify and patients needed to re-enroll in the REMS. Due to data integrity issues, the CPMG could not ascertain how many of these stakeholders were successfully transitioned into the new REMS database by re-certifying or re-enrolling.

Table 3 provides the total and active number of prescribers, prescriber designees, pharmacies, wholesalers-distributors, and patients during the REMS Assessment reporting Periods 6 and 7, including stakeholders who certified or enrolled in the new administrator's REMS database from July 29, 2021, through May 29, 2024. These data can include stakeholders who were participating in the REMS before November 2021 and subsequently recertified or re-enrolled and those who are new to the Clozapine REMS.

Table 3. Clozapine REMS Stakeholders

Stakeholder	Assessment Report 6 29 Jul 2021-30 Nov 2022	Assessment Report 7 01 Dec 2022-29 May 2024
Prescribers		
Total	47,655	62,465
Active[1]	30,705	35,195
Prescriber designees		
Total	15,889	23,316
Active[2]	13,656	20,338
Pharmacies		
Total	47,764	50,439
Active[3]	25,170	27,984
Wholesalers-distributors		
Total	167	152
Active[4]	56[5]	59[5]
Patients[6]		
Total	125,240	154,178
General population patients	123,803	151,980
Benign ethnic neutropenia patients	1,437	2,198
Total patients active[7]	122,500	149,203

Source: Clozapine REMS Assessment Report 7: Tables 3, 5, 11, 13, 17, 18, 20, 21, 22 and Assessment Report 6 (page 39) and 7 (page 28).

[1] Prescribers: Active - prescribed clozapine at least once.

[2] Prescriber Designees: Active - Prescriber Designees were associated with a prescriber who prescribed clozapine at least once during the reporting period.

[3] Pharmacies: Active - dispensed clozapine at least once.

[4] Wholesalers-Distributors: Active - shipped clozapine during the reporting period.

[5] Numbers of active wholesalers-distributor were reported in Assessment Reports 6 and 7 as the data cannot be verified by the Clozapine REMS and therefore has some limitations to its completeness and accuracy.

[6] Clozapine REMS Assessment Reports 6 and 7 reported that there were less than 1% of patients in a hospice during each of these reporting periods (Assessment 6, Assessment 7).

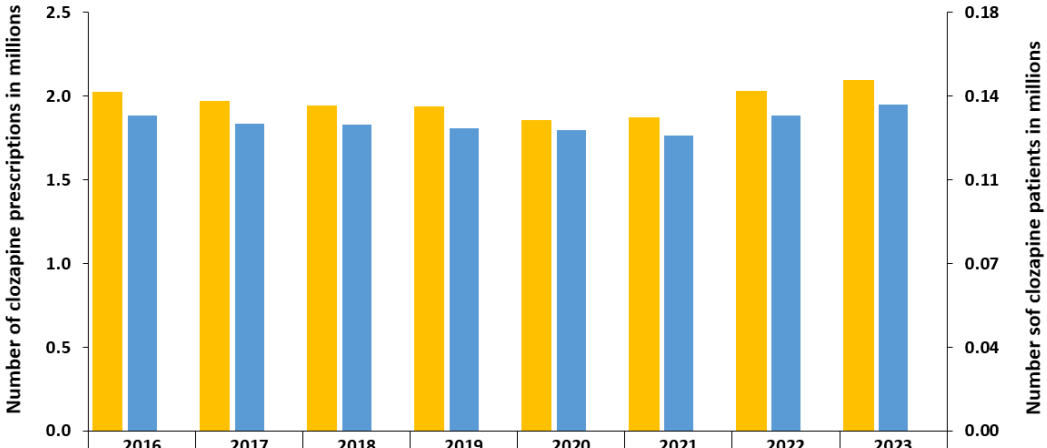
[7] Patients: Active - a patient in a status that allows a dispense (Enrolled and Active statuses)

Abbreviations: BEN, Benign ethnic neutropenia; CPMG, Clozapine Product Manufacturers Group; REMS, Risk Evaluation and Mitigation Strategy

3.1.1 Estimates of Clozapine Utilization Based on Dispensing from Outpatient Pharmacies- Internal FDA review

To better understand the number of patients who received prescriptions for clozapine and the impact of the REMS program on clozapine utilization, we examined clozapine utilization over time using the IQVIA National Prescription Audit™ database to obtain the monthly national estimates of clozapine prescriptions dispensed from U.S. outpatient pharmacies (retail, mail-order/specialty, and long-term care) from January 1992 through March 2024. We also used the Symphony Health Metys™ database to obtain the annual national estimates of clozapine prescription volumes and the number of patients who received clozapine prescriptions dispensed from U.S. outpatient pharmacies from 2016 through 2023. As shown in Figure 1, clozapine prescription volumes decreased from approximately 1.9 million prescriptions in 2016 to 1.8 million prescriptions in 2021, before increasing to 2.0 million prescriptions in 2023. Similarly, estimates of the number of patients with dispensed clozapine prescriptions decreased from approximately 142,000 patients in 2016 to 130,000 patients in 2020, before increasing to 147,000 patients in 2023.

Figure 1. National Annual Estimates of the Number of Clozapine Prescriptions and Patients Who Received Clozapine Prescriptions Dispensed from U.S. Outpatient Pharmacies (Retail, Mail-Order/Specialty, and Long-Term Care) from 2016 Through 2023



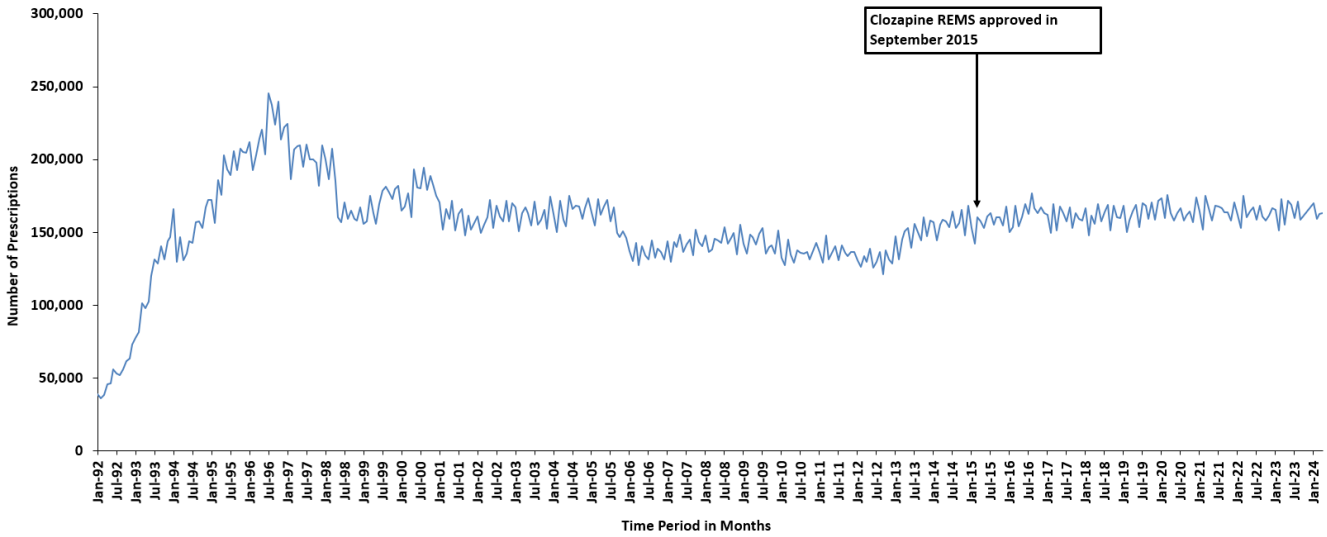
	2016	2017	2018	2019	2020	2021	2022	2023
Clozapine Prescriptions	1,883,134	1,837,739	1,828,901	1,808,877	1,799,299	1,768,088	1,886,935	1,952,315
Patients Dispensed Clozapine	141989	137939	136090	135643	130136	131248	142240	146762

Source: Symphony Health Metys™, 2016-2023. Data extracted July 2024

* Unique patient counts may not be added across time periods, as this could lead to overestimates due to the possibility of double counting patients receiving treatment over multiple periods in the study.

In addition, we also looked at the national monthly estimates of clozapine prescriptions dispensed from 1992 to 2024 (Figure 2). Collectively these data indicate that the prescribing patterns and the number of patients dispensed clozapine from outpatient pharmacies remained relatively stable between 2016 to 2023; however, these data do not provide insight into interruptions and delays in treatment that may have occurred prior to dispensing clozapine. The annual estimates from clozapine prescriptions dispensed using Symphony Health Metys from the same timeframe remained similarly stable. These data suggest that clozapine utilization was consistent prior and post the 2021 modification.

Figure 2. National Monthly Estimates of Clozapine Prescriptions Dispensed from U.S. Outpatient Pharmacies (Retail, Mail-Order/Specialty, and Long-Term Care) from January 1992 to March 2024



Source: IQVIA National Prescription Audit™, January 1992 through March 2024. Data extracted March 2024
Abbreviation: REMS, Risk Evaluation and Mitigation Strategy

Interpretation of the drug utilization data findings should be considered in the context of the known limitations of the databases used. The prescription and patient estimates are nationally projected based on a sample of prescription claims from U.S. outpatient pharmacies. These data are inclusive of all the patients who received clozapine prescriptions regardless of their participation in the clozapine REMS program. Summarization and aggregation of these projected estimates across time periods may lead to differences in prescription and patient counts due to rounding attributable to the projection methodology utilized.

3.2 CPMG conducted Prescribers and Pharmacists Knowledge Assessment Surveys About the Risk of Severe Neutropenia and Appropriate Monitoring Requirements

The results of CPMG's REMS assessment knowledge surveys conducted among certified prescribers and pharmacists working in certified pharmacies in 2017, 2019, 2020, and 2024 indicate that the survey respondents were knowledgeable about the risk of severe neutropenia and the need for ANC monitoring as outlined in the Clozapine labeling. Table 4 and Table 5 show sustained knowledge over time of the risk of severe neutropenia and the need for monitoring.

Table 4. Prescriber Knowledge Rates for Survey Knowledge Domains over Time

Assessment Report	Report 1	Report 3	Report 4	Report 7
Date received by FDA	2017	2020	2021	2024
Number of survey respondents	n=200	n=300	n=300	n=316
Survey knowledge domain	% Correct (95% CI)	% Correct (95% CI)	% Correct (95% CI)	% Correct (95% CI)
1. Understand the risk of severe neutropenia associated with clozapine	86% (not reported)	92% (not reported)	92% (89-92)	93% (91-94)
2. Understand the need for appropriate patient monitoring with clozapine	79% (not reported)	86% (not reported)	82% (80-84)	93%* (91-94)

Source: Adapted by the FDA REMS assessment analyst from tables 32, 33, and 34 from REMS Assessment Report 1, tables 57, 58, and 59 from REMS Assessment Report 3, tables 61, 62, and 63 from REMS Assessment Report 4, and tables 11, 12, and 13 from Appendix 13 of REMS Assessment Report 7.

* The questions used to measure Survey Knowledge Domain 2 changed for the 2024 survey, so results are not directly comparable to prior surveys.

Note: Surveys were not conducted every year

Abbreviations: CI, confidence interval; FDA, U.S. Food and Drug Administration; n, number of survey respondents; REMS, Risk Evaluation and Mitigation Strategy

Table 5. Pharmacist Knowledge Rates for Survey Knowledge Domains over Time

Assessment Report	Report 1	Report 3	Report 4	Report 7
Date received by FDA	2017	2020	2021	2024
Number of survey respondents	n=200	n=300	n=300	n=309
Survey knowledge domain	% Correct (95% CI)	% Correct (95% CI)	% Correct (95% CI)	% Correct (95% CI)
1. Understand the risk of severe neutropenia associated with clozapine	82% (not reported)	85% (not reported)	87% (85-89)	88% (87-90)
2. Understand the need for appropriate patient monitoring with clozapine	77% (not reported)	85% (not reported)	86% (84-88)	86%* (84-88)

Source: Adapted by the FDA REMS assessment analyst from tables 55, 56, and 57 from REMS Assessment Report 1, tables 69, 70, and 71 from REMS Assessment Report 3, tables 75, 76, and 77 from REMS Assessment Report 4, and tables 30, 31, and 32 from Appendix 13 of REMS Assessment Report 7

* The questions used to measure Survey Knowledge Domain 2 changed for the 2024 survey, so results are not directly comparable to prior surveys.

Note: Surveys were not conducted every year

Abbreviations: CI, confidence interval; FDA, U.S. Food and Drug Administration; n, number of survey respondents; REMS, Risk Evaluation and Mitigation Strategy

3.3 CPMG conducted Patient Knowledge Assessment Surveys About the Risk of Severe Neutropenia and Appropriate Monitoring Requirements

The results of the CPMG's patient surveys conducted in 2019, 2020, and 2024 indicate that patient respondents or their caregivers were knowledgeable about the need to get regular blood tests. Results for surveys conducted in 2019, 2020, and 2024 indicate that more than half of the patient respondents or their caregivers were knowledgeable of the risk of severe neutropenia (Table 6).

Table 6. Patient and Caregiver Knowledge Rates for Relevant Survey Questions Over Time

Assessment Report	Assessment Report 3	Assessment Report 4	Assessment Report 7
Date received by FDA	2020	2021	2024
Number of survey respondents	n=300	n=300	n=729
Survey question	% Correct (95% CI)	% Correct (95% CI)	% Correct (95% CI)
1. Which of the following can occur when taking clozapine? Clozapine can cause white blood cells, called neutrophils, to drop in number. This is called neutropenia.	67% (62 – 72)	72% (67 – 77)	76% (72 – 79)
2. Clozapine can cause certain white blood cells to drop, which could lead to which of the following: Serious infections and death	53% (47 – 59)	65% (59 – 70)	61% (57 – 64)
3. What are the requirements that a patient must complete to receive Clozapine?			
Have… blood tested before starting treatment with clozapine	87% (83 – 90)	87% (83 – 90)	88% (85 – 90)
During clozapine treatment, …have regular blood tests	97% (94 – 98)	97% (94 – 98)	97% (96 – 99)

Source: adapted by the FDA REMS assessment analyst from tables 86, 87, and 88 from REMS Assessment Report 3, tables 96, 97, and 98 from REMS Assessment Report 4, and tables 49, 50, and 51 from Appendix 13 of REMS Assessment Report 7.
Note: Surveys were not conducted every year; the survey waves for assessment reports 1 and 2 (conducted in 2017 and 2018) used different question wording so results are not presented.
Abbreviations: Abbreviations: CI, confidence interval; FDA, U.S. Food and Drug Administration; n, number of survey respondents; REMS, Risk Evaluation and Mitigation Strategy

3.4 Prescribers Adherence with Safe Use Requirements

3.4.1 Prescribers Documentation That Periodic Monitoring of Patients is Performed to Identify Severe Neutropenia[16]

In 2021, the REMS was modified to require monthly submission of a PSF, regardless of the patient's monitoring frequency. This form captures the ANC result(s) recorded by the prescriber or their designees, the reason ANC result(s) are missing (if applicable), if the patient was monitored as recommended in the prescribing information (i.e., yes or no response), and the patient's monitoring frequency. For patients with neutropenia, the PSF also captures if the prescriber determines that the benefits of continuing clozapine treatment outweigh the risk of neutropenia. A cumulative total of 2,821,436 PSFs were received during the two reporting periods since the PSF was introduced under the REMS. There were 110,730 and 120,943 patients who had at least one PSF submitted for Assessment Reports 6 and 7, respectively. For the 110,730 patients with a PSF in Assessment Report 6 which covers approximately 12 months of PSF use, the median number of PSFs per patient was 10, (range 1-217 PSFs). These data have not been reported to the Agency for Assessment Report 7.

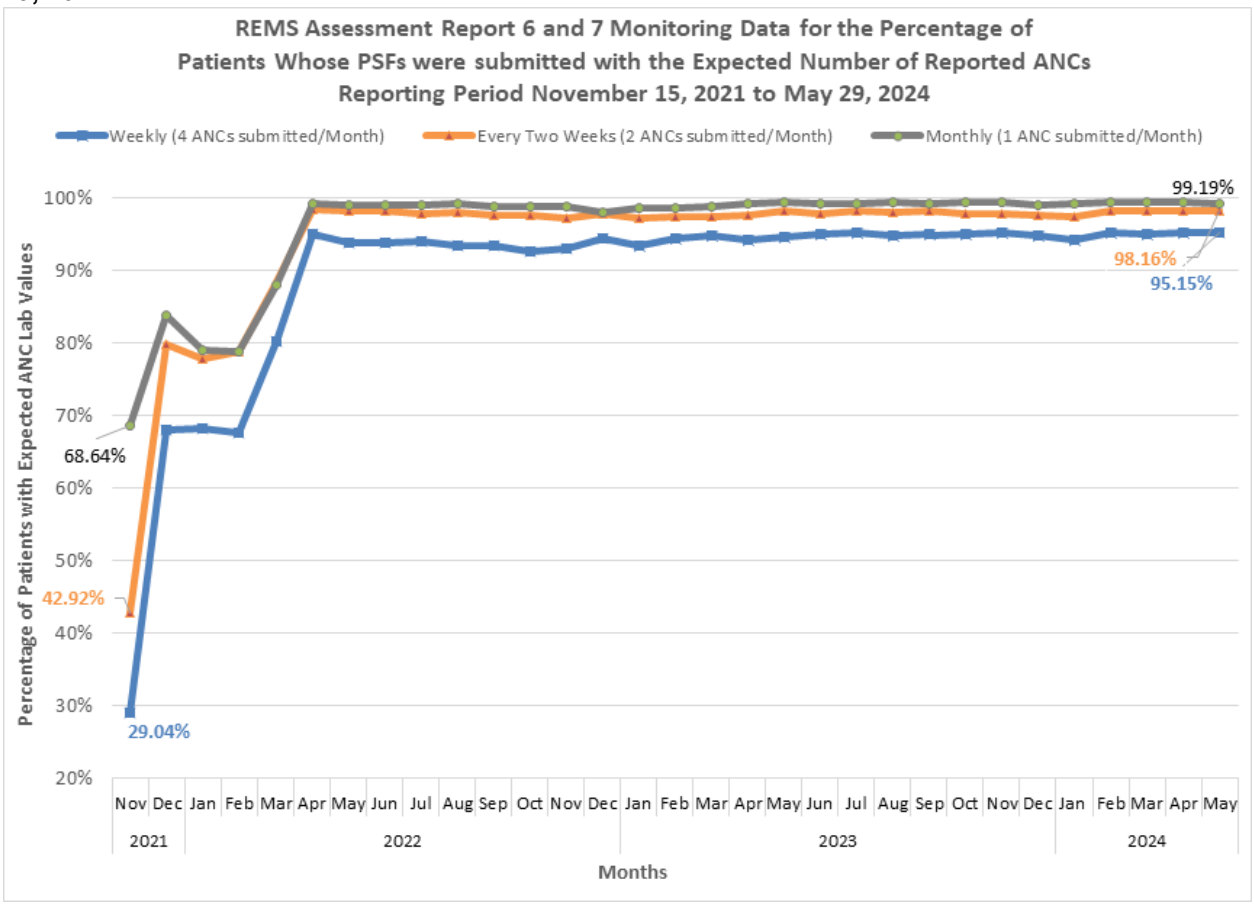
In the sixth, and seventh assessment reports, for those patients who had a PSF submitted to the REMS, approximately 96% of these patients had a PSF submitted in which the prescriber checked "yes,"

[16] Note: The Major Modification to the Clozapine REMS that was approved July 29, 2021 (Supplement 98) revised the third goal from "*ensuring compliance with the monitoring schedule for absolute neutrophil count (ANC) prior to dispensing clozapine" to "ensuring prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia*".

indicating that the patient was being monitored as recommend in the prescribing information. Following receipt of a PSF that indicates the patient is not being monitored as recommended, the Clozapine REMS Contact Center calls the associated prescriber to remind them of the requirement to monitor the patient as recommended.

PSF data suggest high adherence with monitoring of patients' ANCs across the recommended ANC monitoring frequencies. As shown in Figure 3, by April 2022 greater than 90% of patients who had a PSF submitted, regardless of monitoring frequency, had the recommended number of ANC results submitted to the REMS. This trend continued through May 2024 (data cutoff for Assessment 7).

Figure 3. Percentage of Patients, by Month, Whose Patient Status Forms Were Submitted with the Expected Number of Reported ANC Values Per Their Designated Monitoring Frequency During the Clozapine REMS Assessment Report 6 And 7 Reporting Periods, from November 15, 2021, to May 29, 2024



Source: Adapted by the FDA REMS assessment analyst from the Clozapine REMS Assessment Report 6, table 81, and Clozapine REMS Assessment Report 7, table 62. Abbreviation: ANC, absolute neutrophil count

3.4.2 Prescriber Documentation of a Risk-Benefit Assessment When ANC Falls Below the Acceptable Range as Described in the Prescribing Information

When a patient's ANC is between 500 to 999/µL (moderate neutropenia, General Patient Population) or <500/µL (severe neutropenia for General Patient Population and for patients with BEN), the patient's prescriber must provide a treatment rationale to the Clozapine REMS if treatment is to be continued.

After the July 2021 modification, prescribers needed to complete the treatment rationale section of the PSF to authorize continued treatment with clozapine when the ANC falls below the acceptable range. Completion of this section on the PSF requires the prescriber to check a box that the benefits of continuing clozapine treatment outweigh the risk of neutropenia and provide their signature. During the Assessment 6 and 7 reporting periods, 0.03% (901/2,821,436) of the submitted PSFs included a prescriber authorizing a treatment rationale for their patient. Most (93%) of the treatment rationales were for patients categorized as general population. There were 455 and 182 patients who received a treatment rationale during the two reporting periods, respectively. While most of these patients (79% to 82%) received one treatment rationale, there was a range of 1 to 23 treatment rationales per patient submitted.

The FDA does not have sufficient data to determine how many patients had an ANC that fell below the acceptable range because clozapine could be dispensed to patients without submission of a PSF. Therefore, we cannot evaluate the extent to which prescribers documented a treatment rationale.

3.5 Summary of Reported ANCs Consistent with Neutropenia

We do not have an accurate count of how many patients experienced moderate or severe neutropenia due to data integrity issues and insufficient data.

Table 7 provides the total number of unique patients who had at least one ANC test result consistent with neutropenia stratified by mild, moderate, and severe neutropenia reported in each of the seven REMS Assessment Reports. Note the duration of the assessment reporting periods varied across the assessments and the reports should not be directly compared.

Prior to the implementation of the modified REMS in November 2021, the number of patients with severe neutropenia was similar with a range of 94 to 241 patients. In the first assessment reporting period after implementation of the modified REMS (Assessment Report 6), there was a noted increase of 5,467 patients with an ANC test result consistent with severe neutropenia. The CPMG noted in Assessment Reports 6 and 7 that not all of the reported ANC test result entries during these two reporting periods (November 2021 to May 2024) indicated actual neutropenia as their analysis of these lab values suggested that some stakeholders entered the ANC values using the incorrect unit on the PSF (Refer to Section 3.5.1 for more information about the possible erroneous reports).

Table 7. Number of Unique Patients with at Least One ANC Test Result Consistent with Neutropenia

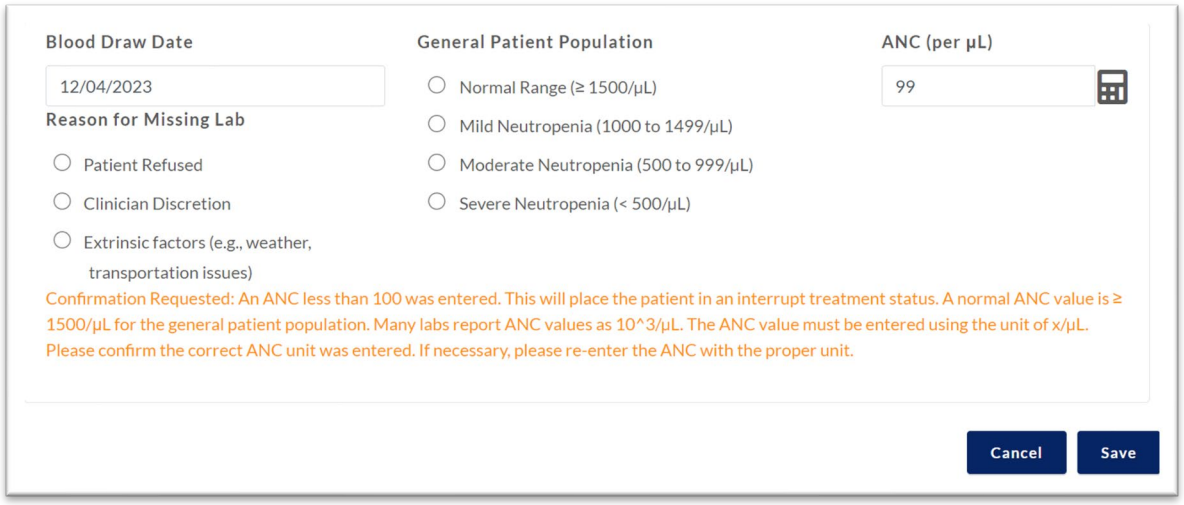
REMS Assessment Report Number	1	2	3		4	5	6[1]	7[1]
Reporting Period	**16Jul16-15Jul17**	**16Jul17-15Jul18**	**16Jul18-27Feb19**	**28Feb19-31Dec19**	**01Jan20-31Dec20**	**01Jan21-15Nov21**	**15Nov21-30Nov22**	**01Dec22-29May24**
Neutropenia								
Mild	3,866	4,039	2,688	3,841	4,438	3,721	5,458	7,199
Moderate/BEN	314	395	264	383	555	447	2,034	1,358
Severe/BEN severe	94	150	96	197	241	176	5,467	1,324
Number of patients who received at least one RDA	N/A	108,308	104,475	112,142	114,214	112,059	104,257	115,298

Source: Adapted from Table 1 from the CPMG response to the Agency's Information Request that was sent on January 13, 2023, Assessment Reports 2-5 for respective RDAs counts, and REMS Assessment Report 7, Page 35 and Table 96.
[1]Analysis of ANC lab values by the CPMG suggested that stakeholders had entered ANC values as 10^3/µL, instead of as cells/µL as required by the REMS. To address this issue, the CPMG updated the REMS Website on March 19, 2022, to require that stakeholders confirm any ANC values entered when less than 100.
Neutropenia definition (ANC value) for General Population Patients: mild (500-1,499/µL); moderate (500-999/µL, severe (less than 500/µL) and for BEN patients: neutropenia (500-999/µL), severe (less than 500/µL).
Limitations of this data REMS Reports 6 and 7 reported that that "not all of these entries indicate neutropenia"; an analysis suggested some stakeholders entered ANC Values using the incorrect unit and REMS data indicates that many of these ANC values were entered incorrectly.
Abbreviations: ANC, absolute neutrophil count; BEN, Benign ethnic neutropenia; CPMG, Clozapine Product Manufacturers Group; N/A, not available; RDA, REMS Dispense Authorization; REMS, Risk Evaluation and Mitigation Strategy

3.5.1 Analysis of Erroneous Reports of Neutropenia in FAERS

The Agency noticed a spike in reporting of neutropenia with clozapine in the FDA Adverse Event Reporting System (FAERS) that occurred shortly after the Clozapine REMS modification was implemented in November 2021. The CPMG also noticed a comparable increase in reporting of neutropenia beginning with REMS Assessment Report 6. The CPMG stated, "It should be noted that not all of these entries indicate neutropenia. Analysis of ANC lab values suggests that some stakeholders entered the ANC value using the incorrect unit. The Clozapine REMS requires the ANC value to be entered in the unit of cells/µL whereas ANC values may have been entered in the unit of 10^3/µL. For example, an ANC value of 8,000 cells/µL is equivalent to 8 x 10^3/µL. The Clozapine REMS requires this ANC value to be entered as 8,000 cells/µL. An ANC value entry of 8 would indicate that this patient has severe neutropenia. To address this, the Clozapine REMS website was update on March 19, 2022, to require the stakeholder to confirm that the value is correct when an ANC value less than 100 is entered." (Figure 4). Despite this update to the website, the Agency continues to receive FAERS reports of neutropenia that appear to be erroneous. Additionally, the Agency is awaiting CPMG's plan to ensure errors in future submissions of neutropenia reports to FAERS are averted.

Figure 4. Alert Added by the CPMG to REMS Website



Source: Clozapine REMS. Available at: http://www.newclozapinerems.com. Accessed October 8, 2024.
Abbreviations: ANC, absolute neutrophil count; CPMG, Clozapine Product Manufacturers Group; REMS, Risk Evaluation and Mitigation Strategy

The Agency submitted multiple information requests to the CPMG between October 2023 and October 2024 asking the CPMG to identify, investigate, and correct or nullify erroneous reports of neutropenia associated with the use of clozapine in FAERS and take further action to ensure errors in future submissions of reports to FAERS are averted. As of August 2024, the CPMG corrected or nullified 380[17] erroneous reports of neutropenia associated with the use of clozapine submitted to FAERS from October 1, 2021, through April 30, 2024; however, they were unable to confirm 5,766 reports of neutropenia submitted to FAERS. The Agency is awaiting further clarification from the CPMG on the reasons they were unable to confirm these reports of neutropenia.

In 2024, the Agency conducted an analysis of FAERS reports to identify if there were erroneous reports of neutropenia possibly impacted by inaccurate reporting of ANCs that the CPMG had not corrected or nullified, given the large spike in reporting noted previously along with the small number of reports corrected or nullified by the CPMG. We searched FAERS for reports of neutropenia-related terms[18] with clozapine received from November 15, 2021, through September 30, 2024. We focused on reports describing an ANC <10 as these were most likely to be erroneous. From our review, we identified 2,512 reports that were likely erroneous reports of neutropenia as they reported an ANC <10 but did not describe any complications of neutropenia (e.g., sepsis) and/or did not describe changes to clozapine therapy commensurate with the clozapine labeling recommendations (e.g., interrupt treatment).

3.6 Establishing Long-Term Safety and Safe Use of Clozapine by Enrolling All Patients Who Receive Clozapine in the Registry

The following is a summary of the safety data on clozapine-induced neutropenia included in the two most recent REMS Assessment Reports (6 and 7). Data from prior Assessment Reports (1-5) are not

[17] May include duplicate reports.
[18] FAERS Search Terms: *Agranulocytosis* (Narrow Standardised Medical Dictionary for Regulatory Activities Query); High Level Term *Neutropenias*; Preferred Terms *Neutrophil count decreased, Neutrophil percentage decreased, Granulocyte count decreased, Granulocyte percentage decreased*.

included in this summary as the adverse event data were reported in aggregate counts and lacked specificity for clozapine-induced neutropenia and patient outcome information.

The PSF was designed to obtain clozapine-induced neutropenia adverse event and outcome data from the prescriber. On each monthly PSF, the prescriber or their designee indicates "no" or "yes" on the form to indicate whether their patient experienced an adverse event due to clozapine-induced neutropenia. The REMS Contact Center then conducts outreach to the prescriber to obtain additional information on the adverse event to gather any known outcomes.

As shown in Table 8, the percentage of patients whose prescriber indicated on the PSF that they had experienced a clozapine-induced adverse event was similar at 0.29% and 0.32% for the two reporting periods. Data suggest that most of these patients (97% to 99%) were adhering to having their ANCs monitored in accordance with their designated monitoring frequency. An exception was for Assessment Report 6 where only 10% of patients adhered to their three times weekly monitoring of ANCs;[19] however, this increased to 87% in Assessment Report 7. Note that these data are not inclusive of all patients who received clozapine as pharmacies were able to dispense without obtaining authorization to dispense clozapine from the REMS during this time.

Table 8. Data from Patient Status Forms (PSF) That Indicated a Clozapine-Induced Adverse Event

Adverse Event and Monitoring Frequency	Assessment Report 6[1] 29 Jul 2021-30 Nov 2022	Assessment Report 7 01 Dec 2022-29 May 2024
Count of Patients with a PSF submitted to the REMS	110,730	120,943
Count of PSFs where an adverse event is indicated	371	439
Count of patients with an adverse event indicated	319	390
Percentage of patients with an adverse event indicated	0.29%	0.32%
Adherence to Monitoring Frequency		
Monthly	98.45%	99.06%
Every two weeks	97.06%	95.81%
Weekly	92.16%	89.67%
Three times weekly	10.34%	87.27%

Source: Adapted from Clozapine REMs Assessment 6 Tables 132 and 133, Assessment Report 7, Tables 113, 114.
[1] The Clozapine Assessment Report 6 stated, "*This REMS Assessment 6 Report includes the modified Clozapine REMS reporting period from July 29, 2021, through November 30, 2022. Data included in this assessment report is from August 2, 2021, through November 30, 2022. The legacy Clozapine REMS was decommissioned on November 15, 2021, with the launch of the modified Clozapine REMS*."
Abbreviations: PSF, Patient Status Form; REMS, Risk Evaluation and Mitigation Strategy

3.6.1 Outcome Data

The patient outcome data for those patients who were reported as having experienced a clozapine-induced neutropenic adverse event on their PSF is insufficient to inform on the long-term safety and safe use of clozapine. Nearly all the reported follow-up information for these patients was reported as "unknown" for both assessment reports. Only 7 patients had reported outcome data out of the 319 and 390 patients who were reported as having experienced a clozapine-induced neutropenic adverse event

[19] According to the clozapine prescribing information, patients experiencing mild neutropenia (general population) must have ANC monitoring three times weekly until ANC ≥1500/µL. Patients with benign ethnic neutropenia with ANC 500-999/µL, must have ANC monitoring three times weekly until ANC ≥1000 or ≥ patient's known baseline.

on their PSF for Assessment Report 6 and 7, respectively.[20] Of these seven patients, the outcome was reported for three as "ongoing" and four were reported as "resolved." Of the four "resolved" cases, two did not state the actual outcome that was observed. Of the remaining two, the narrative for the cases stated that one recovered from "agranulocytosis" and restarted on clozapine without additional detail, and the other case noted that the patient recovered from "… an Ileus that she presumed to be caused by Clozapine." Infection and death were not mentioned in any of the resolved cases.

3.7 Patient Access

As previously noted, when a pharmacist does not receive authorization to dispense because of an overdue PSF, pharmacies can provide a current ANC (within 30 days of the attempted fill) that is within an acceptable range for the patient, provide the prescriber's NPI number to the REMS administrator, then proceed with dispensing. This option in the REMS is referred to as a "Dispense Rationale." A "Transition Dispense Rationale" is another option in the REMS that allowed pharmacies to obtain authorization to dispense clozapine to a non-enrolled patient if they possessed a current ANC lab value that was in an acceptable range. Both of these dispense rationale options allowed for authorization of a clozapine dispense despite not all REMS safe use conditions being met.

Data from the two most recent assessment reports (Assessment Report 6 and 7) indicates that use of the transition and dispense rationales allowed 64,208 patients access to clozapine.

3.8 Data to Inform on Patient Participation in the REMS

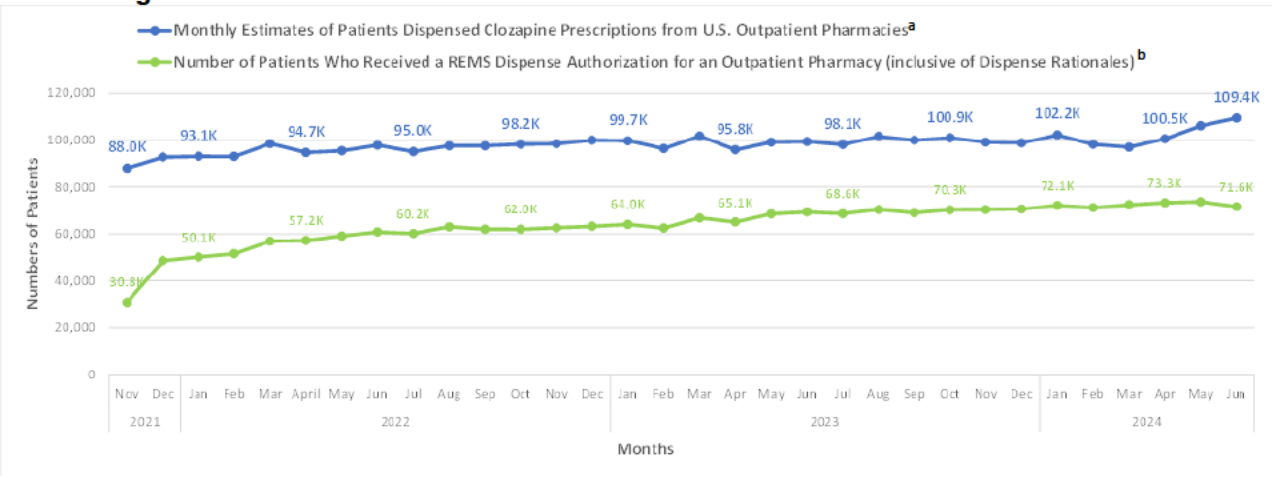
To provide possible context of how many patients were receiving clozapine but not participating in the REMS, the FDA required the CPMG to include in the REMS Assessments a comparison of those patients who had a prescription dispensed from an outpatient retail pharmacy to the number of enrolled patients who received an RDA. Prescription dispenses were identified using the IQVIA Longitudinal Prescription Database. This IQVIA data identified that there were 72,759 and 106,051 patients who had received one or more prescription dispenses for clozapine at a US Retail Pharmacy for the same time period as Assessment Report 6 and Assessment Report 7, respectively. For comparison, there were 104,257 and 115,298 enrolled patients who received at least one RDA for Assessment Report 6 and Assessment Report 7, respectively. The CPMG stated that comparisons of these data are limited by the differences in how the REMS and IQVIA define inpatient and outpatient pharmacies, dispensing in the U.S. prison system is not included in the IQVIA study and receipt of an RDA by the pharmacy does not guarantee that clozapine was dispensed to the patient since the REMS administrator is not notified of whether a patient or caregiver actually picks up the medication.

To further inform on patient participation in the REMS, an analysis of the national outpatient clozapine use patterns was conducted by the FDA from January 1, 1992, through June 30, 2024. As shown in Figure 5, there were an estimated 88,000 patients in November 2021 (the month the REMS was modified) and 109,000 patients in June 2024 with a dispensed clozapine prescription from U.S. outpatient pharmacies (retail, mail-order/specialty, and long-term care). For comparison, the CPMG provided the number of patients per month who had at least one RDA for an outpatient pharmacy from November 2021 to June 2024. There was a range of 30,815 patients (November 2021) to 73,676 patients (May 2024) who received at least one RDA.

[20] The six patients reported in REMS Assessment Report 6 are confirmed as unique patients. However, for one patient reported in the REMS Assessment Report 7, we are unable to confirm if this is a unique patient.

The most recent data for comparison (June 2024) suggests that an estimated 65% of patients who were dispensed clozapine from an outpatient pharmacy were participating in the REMS as evidenced by an RDA. Since February 2023, the estimated patient participation in the REMS ranges between 65% to 75%. However, the use of an RDA does not necessarily indicate that all safe-use conditions of the REMS were met due to enforcement discretion that is still currently in place (see Section 3.6).

Figure 5. Monthly Estimates of Patients Who had a Dispensed Clozapine Prescription from U.S. Outpatient Pharmacies (Internal FDA Analysis) Compared to the Number of Patients Who Received a REMS Dispense Authorization for an Outpatient Pharmacy by Month from November 2021 through June 2024



Source: [a]Symphony Health Metys™, November 2021 through June 2024. Data extracted July 2024. [b]CPMG response to the Agency's October 17, 2023, Information Request that was received on October 19, 2023, and the CPMG response to the Agency's September 10, 2024, Information Request that was received on September 20, 2024.
* Unique patient counts may not be added across time periods, as this could lead to overestimates due to the possibility of double counting patients receiving treatment over multiple periods in the study.
Abbreviation: REMS, Risk Evaluation and Mitigation Strategy

4 Summary of Additional Studies

As mentioned in Section 2, to date the Clozapine REMS has not been fully implemented. Thus, the data that the CPMG has provided in the REMS Assessment reports reflect only data that they have collected through the REMS, which are therefore insufficient to assess prescriber's knowledge or adherence to ANC monitoring or the risk of severe neutropenia and related clinical outcomes, such as infections or death. To fill in these gaps in information, the FDA has conducted a literature review, FAERS review, and additional studies designed and analyzed in collaboration with Brigham and Women's Hospital (BWH studies), Veterans Affairs (VA study), and through the FDA Sentinel System (Sentinel studies).

4.1 Literature Review

Two systematic literature reviews, using PubMed, of articles published through June 25, 2024, found 230 articles addressing the incidence of neutropenia with clozapine use; of these, 14 described studies that provided quantitative estimates of the incidence of severe neutropenia among clozapine users. Thirteen of these studies were conducted in populations where clozapine patients were regularly monitored for severe neutropenia. In the only study prior to the widespread adoption of clozapine monitoring, conducted in Finland, the estimated agranulocytosis incidence was 2.6 cases per 100

person-years of treatment during the first six months of marketing, with roughly half of cases having a fatal outcome (de la Chapelle et al. 1977). Studies conducted in populations where clozapine patients' neutrophil counts were monitored regularly reported a lower incidence of severe neutropenia. The overall cumulative incidence of severe neutropenia among clozapine patients undergoing regular blood monitoring was less than 1% in most studies, ranging from 0.38% to 1.15%. Three non-U.S. studies (Atkin et al. 1996; Toyoda et al. 2021; Kang et al. 2024) and one U.S. study (Alvir et al. 1993) reported cumulative incidence of severe neutropenia within the first year of clozapine use with rates ranging from 0.70% to 0.96%. Though the specific requirements of monitoring programs across the three non-U.S. studies varied by country (United Kingdom, Japan, and South Korea) and study time frame, generally patients were monitored more frequently (e.g., weekly) for the first several months of treatment (usually up to 18 weeks) and less frequently (e.g., biweekly or monthly) thereafter if they had previously maintained normal WBC and ANC. In the U.S. study, patients were monitored more closely (i.e., weekly for the first 6 months, biweekly between Months 7 to 12, and monthly thereafter). The results from our literature reviews found that the cumulative incidence of severe neutropenia among clozapine patients was around 1% in patients undergoing regular monitoring. Incidence would likely be higher without regular hematologic monitoring. Most severe neutropenia cases were found to occur in the 18-weeks following the first clozapine use. However, given methodological limitations, the incidence of severe neutropenia, defined as ANC <500/µL, after one year of clozapine therapy is not clear.

We also reviewed the medical literature to compare neutropenia rates between clozapine and other antipsychotic drugs. Glocker et al. (2023) analyzed data from an observational pharmacovigilance program in Germany, Austria, and Switzerland—Arzneimittelsicherheit in der Psychiatrie (AMSP) from 1993 to 2016, including 333,175 psychiatric inpatients treated with antipsychotic drugs. They identified 124 cases of antipsychotic-induced neutropenia (ANC <1500/µL) and 48 cases of severe neutropenia (ANC <500/µL), corresponding to a cumulative incident rate of 0.37 and 0.14 per 1000 in patients treated with antipsychotic drugs, respectively. Inpatients who were exposed to clozapine had the highest incidence rate of neutropenia of 1.57% (95% CI 1.2-2.0) across 60 cases, followed by perazine 0.52% (95% CI 0.24-1.0) across 8 cases, quetiapine 0.23% (95% CI 0.12-0.4) across 15 cases, olanzapine 0.13% (95% CI 0.06-0.25) across 7 cases, aripiprazole 0.13% (95% CI 0.05-0.45) across 2 cases, risperidone 0.11% (95%CI 0.07-0.25) across 6 cases, prothipendyl 0.06% (95% CI 0-0.32) in 1 case, promethazine 0.06% (95%CI 0-0.3) in 1 case, and haloperidol 0.03% (95% CI 0-0.13) in 1 case.

Using data from the Finnish Care Register for Health Care and the Prescription Register, which together provide data systematically on all healthcare encounters in Finland, Rubio et al. (2024) compared the diagnosis of severe neutropenia during clozapine versus non-clozapine treatment among people diagnosed with schizophrenia or schizoaffective disorder in the entire population in Finland between 1972 and 2014 (42-year observation period). Among 61,769 people identified with schizophrenia or schizoaffective disorder, 14,037 individuals were treated with clozapine and 47,732 individuals treated with non-clozapine antipsychotics. Among 398 individuals diagnosed with severe neutropenia, 231 individuals were treated with clozapine and 167 individuals treated with non-clozapine antipsychotics, which leads to a cumulative incidence of severe neutropenia of 1.37% (95% CI 0.58-3.16) on clozapine and 0.13% (0.04-0.23) on non-clozapine antipsychotics. Among the 398 severe neutropenia cases, 7 (2%) were lethal within 30 days of diagnosis, 4 for clozapine and 3 for non-clozapine antipsychotics, representing a severe neutropenia fatality rate of 2.81 per 10,000 individuals on clozapine, and 0.63 per 10,000 individuals on non-clozapine antipsychotics. In a nested case–control model, Rubio et al. (2024)

matched severe neutropenia cases during clozapine and non-clozapine antipsychotic treatment by sex, age, and time since diagnosis. The risk of severe neutropenia for clozapine decreased over time; however, the risk was persistently higher than in the non-clozapine antipsychotics treatment group Rubio et al. (2024).

To assess the strength of the association between clozapine and neutropenia when compared to other antipsychotic medications, Myles et al. (2019) Myles et al. (2019)identified 20 studies, including 17 randomized controlled trials (RCTs) and 3 retrospective cohort control studies from 1947 through 2018. Different definitions to identify neutropenia were used in these studies (ANC <500/µL, <1000/µL, and 1500/µL). The results of their meta-analysis indicated the risk ratio of neutropenia in clozapine-exposed groups compared to exposure to other antipsychotic medications was 1.45, with 95% CI of 0.87-2.42. The risk ratio of severe neutropenia (ANC <500/µL) was 1.65, with 95% CI of 0.58-4.71.

Our review of this meta-analysis identified a few concerns. Retrospective cohort studies are not comparable to RCTs and should not be combined in meta-analyses. The study also incorrectly assumed that all levels of neutropenia (<500, <100 or <1500/µL) would show the same relative risk and could be analyzed together. A threshold such as 1500/µL is more likely to include false positives, which represents mild neutropenia unrelated to drug treatment that would occur with similar incidence among all patients treated with antipsychotics and push the relative risk toward one. Therefore, we conducted a re-analysis using only data from the RCT studies in this article using random effects Poisson regression to adjust for length of observation and avoid the need for continuity corrections (Division of Psychiatry. Chen Q et al. October 3, 2024). In studies where neutropenia was defined as ANC <1500/µL, the incidence rate ratio of inpatients treated with clozapine compared with non-clozapine antipsychotics was estimated as 1.27 (95% CI 0.64-2.51); in studies with a threshold of <500/ µL (severe neutropenia), the incidence rate ratio was estimated as 6.18 (95% CI 0.74-51.42). Our re-analysis estimated the rate of any neutropenia for non-clozapine antipsychotics to be 98.4 per 1000 person-years (95% CI 30.3-319.2) and severe neutropenia (ANC <500/µL) to be 3.6 per 1000 person-years (95% CI 0.34-39.3). Using the point estimates, the increase in absolute risk of any neutropenia with clozapine compared to other antipsychotics would be 26.6 per 1000 patient years (PY) and 19.7 for severe neutropenia, suggesting that most of the difference between clozapine and other antipsychotics is in the risk for severe neutropenia. Because of the relatively small sample size (1796 person-years of observation for a threshold of 500/µL), our analysis lacked the power to detect a statistically significant difference between neutropenia and severe neutropenia in the incidence rate ratio of clozapine compared to other-antipsychotics, but the results still suggest that clozapine is more likely to result in severe neutropenia than other antipsychotics.

4.2 FDA Adverse Event Reporting System

We searched FAERS to evaluate trends of neutropenia reported with clozapine from January 2017 through September 2024. During this time period, we identified 79 cases of neutropenia reported with clozapine use that were not submitted through the Clozapine REMS Program.[21] Of the 79 cases in this case series, we identified 12 cases reporting mild neutropenia, 31 cases reporting moderate neutropenia, and 34 cases reporting severe neutropenia with clozapine use; 2 cases reported “ANC <1000/µL,” rendering us unable to distinguish between moderate and severe neutropenia. Of the 79

[21] Cases were included that met the definition of mild (ANC 1000-1499/µL), moderate (ANC 500-999/µL), or severe (ANC <500/µL) neutropenia.

cases, we identified 3 fatal cases, 24 cases of non-fatal hospitalization (neutropenia was the reason for admission in 12 cases), and 3 cases of emergency department visits. We assessed causality for death as possible for two fatal cases because we had sufficient information on temporality with the onset of neutropenia during clozapine treatment. In one of these cases, the patient was admitted to the hospital for febrile neutropenia, approximately 1 month following clozapine initiation, with an ANC of 0 and was reported to have died from multi-organ failure 10 days following admission. The second patient, who had been on clozapine for 9 years, was admitted to the hospital with sepsis and found to have an ANC of 280/uL and gram-negative rods on blood culture. The patient died a little over 24 hours after admission. We could not assess the causality for the remaining fatal case due to the lack of information on latency from the onset of neutropenia during clozapine treatment. Overall, our review of FAERS reports for mild, moderate, or severe neutropenia with clozapine not submitted by the Clozapine REMS Program identified few reports relative to the number of neutropenia reports provided by the CPMG in their information request responses and REMS Assessment reports.

Additionally, we conducted a high-level overview of 11,610 FAERS world-wide reports coded with the serious outcome of death associated with clozapine from January 2015 through September 2023. Nearly 9 years of reports revealed that neutropenia was described in a low proportion of these fatal reports. In U.S.-only reports of fatalities, only 3% mention neutropenia. Nearly half of the domestic fatal reports were not coded with any adverse events other than death, which precludes assessment of the cause of death. Upon review of the domestic fatal reports describing neutropenia, most were in the context of concurrent malignancy or infection.

4.3 Brigham and Women's Hospital and Harvard Medical School Studies

In collaboration with FDA, BWH conducted multiple studies utilizing a multi-modal approach to evaluate the impact of REMS and to understand how REMS programs have operated in practice. Clozapine was one of the 11 drugs included in these quantitative and qualitative studies (Sarpatwari et al. 2021).

4.3.1 Neutropenia-Related Hospitalization among Clozapine Initiators Compared to Olanzapine Initiators

The purpose of this study was to evaluate the risk of neutropenia observable in claims data following treatment initiation with clozapine versus olanzapine in a hospital setting. This was a cohort study nested in longitudinal administrative claims data from Optum's deidentified Clinformatics Data Mart (2004-June 2022), Merative Marketscan (2003-2022), and Medicaid (2000-2018) databases. The study cohort comprised new users of clozapine and olanzapine (oral formulation only), with new use defined as no dispensing of clozapine or olanzapine (any formulation) in the prior 6 months. Initiators were required to be at least 18 years old and to have continuous insurance plan enrollment, a recorded diagnosis of schizophrenia or schizoaffective disorder, and at least 1 dispensing of a different antipsychotic (not clozapine or olanzapine) in the prior 6 months. Two neutropenia-related outcomes were assessed: a hospitalization with an ICD-9 or ICD-10 code for neutropenia in any discharge diagnosis position (broad definition); and a hospitalization with the code in the primary position (narrow definition). Patients were followed from the day of the first dispensing of the drug until the first occurrence of one of the following outcomes: death, end of insurance enrollment, end of data, admission to a nursing facility or hospice, filling a prescription for the other drug, or drug discontinuation (defined as a gap of greater than 30 days following the end of days' supply without a refill). To address potential confounding, BWH performed 1:1 propensity score matching using 101

baseline covariates. Kaplan-Meier survival analyses were used to assess the cumulative incidence over time. The incidence rate (IR) of neutropenia per 1,000 PYs with 95% confidence intervals (CIs) and the corresponding incidence rate ratios (IRR) were estimated at 6 months, 1 year, 2 years, and 3 years post-initiation, as well as over the entire follow-up.

The unmatched cohort included 21,718 clozapine initiators and 212,083 olanzapine initiators, whereas the matched cohort comprised 16,873 clozapine and olanzapine initiators each. In the matched analysis, the median follow-up time was 175 days (interquartile range [IQR: 43-640 days) for clozapine initiators and 146 days (IQR: 60-498 days) for olanzapine initiators. At 6 months, the IR was 5.89 per 1,000 PYs (95% CI: 4.17-8.33) for clozapine and 2.72 per 1,000 PYs (95% CI: 1.64-4.51) for olanzapine using the broad definition, corresponding to an IRR of 2.17 (95% CI: 1.17-4.00). Using the narrow definition, there were 12 events, and the IR was 2.21 per 1,000 PYs (95% CI: 1.25-3.89) for clozapine; and the IR was 0.18 per 1,000 PYs (95% CI: 0.03-1.29) for olanzapine, corresponding to an IRR of 12.18 (95% CI: 1.58-93.71). The IRRs attenuated with longer follow-up and were 1.36 (95% CI: 0.84, 2.18) under the broad definition and 4.13 (95% 1.19-14.36) under the narrow definition when considering the entire follow-up period. These IRRs were based on a total of 43 events in the clozapine group and 28 events in the olanzapine group for the broad definition; and 14 and <11 events[22] respectively for the narrow definition. Refer to section 10.2.1 for additional information on results of this study.

Results from this study found that clozapine initiators were at an elevated risk of neutropenia-related hospitalization relative to olanzapine initiators; and the relative risk was seen highest in the first 6 months. The absolute risk of neutropenia-associated hospitalization for clozapine initiators, however, was low. Although the absolute risk was also highest in the first 6 months, it was still seen beyond 5 years.

There are several study limitations. First, there was no information on ANC test results; therefore, the severe neutropenia outcome definition only relied on the diagnosis code of hospital admission with an ICD-9-CM or ICD-10 code for neutropenia. To improve the accuracy of outcome event estimation, the narrow definition for neutropenia was limited to the primary position of the discharge diagnosis, which may have higher positive predictive value and specificity for the diagnosis code of neutropenia and may provide confidence that the neutropenia cases identified are true cases(Bush et al. 2018; Zikos et al. 2019). The study was unable to evaluate different levels of neutropenia, such as mild, moderate, or severe neutropenia because of the lack of ANC test results. Second, increased frequency of ANC monitoring may lead to detection bias. Third, patients may have more days' supply (stockpiling) than what was reflected in the claims data; therefore, not all patients may get refills within 30 days after expiration of their days' supply. If a patient did not have a refill within 30 days or if there were missing data on clozapine prescriptions that were dispensed for a patient (this may be less likely given all the patients in this study were insured), this may lead to shortened recorded treatment duration, which in turn can result in missed outcomes during the treatment period using an as-treated method. Events that resulted in death before hospital admission are likely to be under-ascertained; this could have resulted in an underestimate of the neutropenia risk. Our study further did not assess adherence with REMS requirements, precluding answering whether the increased risk of neutropenia-related hospitalization in the first 6 months was due to events occurring despite adherence to the REMS or occurring owing to non-adherence to REMS requirements. Finally, the results might not be generalizable to patients who

[22] Counts less than 11 were suppressed under the Data Use Agreement for use/access of the Medicaid data.

receive clozapine but are not insured. It is possible that patients without health insurance are more susceptible to both testing and treatment nonadherence.

4.3.2 Prevalence and Frequency of ANC Monitoring in Claims Data in Patients Initiating Clozapine

The purpose of this study was to assess the prevalence and frequency of ANC monitoring in patients starting clozapine. BWH and FDA conducted a cohort study of clozapine initiators using the same three administrative claims databases described in Section 4.3.1, Optum (January 1, 2004, to March 31, 2022), Marketscan (2003 to 2020), and Medicaid (2000 to 2018). Patients were included if they had at least 6 months of continuous insurance enrollment. The study evaluated the proportion of patients with at least 1 ANC test in the 30 days prior to clozapine initiation and the frequency of ANC testing (per 30 days) in the first 6 Months of treatment, Months 7 to 12 of treatment, and Year 2 of treatment.

Among 62,003 clozapine initiations, 63% were preceded by ANC testing within 31 days. During the first 6 months of treatment when a patient is supposed to have weekly testing, among patients who continued to receive clozapine refills (N=52,217), the median testing rate was 2.1 (IQR: 0.3-3.8) tests per 30 days. During months 7-12 when a patient is supposed to have biweekly testing, the median testing rate was 1.6 (IQR: 0.3-2.5) tests per 30 days. During year 2 of treatment when a patient is supposed to have monthly ANC tests, the mean median testing rate was 1.1 (IQR: 0.5-1.9) tests per 30 days. Refer to section 10.2.2 for additional information on results of this study.

Results from this study found that ANC monitoring was performed at a lower-than-expected rate prior to clozapine initiation and during the first 6 months of treatment but was mostly in line with REMS requirements thereafter.

The same limitations described in 4.3.1 also apply in this study. In addition, information on the occurrence of ANC testing could be missing from claims data, further underestimating the true testing rate.

4.3.3 Survey of Physicians' Experiences and Perspectives Prescribing Clozapine for Psychiatric Disorders

The purpose of this survey was to understand physicians' perceptions of and experiences with the Clozapine REMS. This national survey had 57 closed-field questions, and the questionnaire was administered to 750 physicians who prescribed clozapine in 2021 or 2022. These questions used 5-point Likert scales and were arranged around 3 topics: (1) the prescriber certification process, (2) the process for initiating a patient on clozapine, and (3) the safe use requirement. Gender, race, practice specialty, practice setting, practice region, professional time in clinical practice, years since graduation from medical school, and number of patients prescribed clozapine in the past 3 years were also solicited. Refer to section 10.2.2 for additional information on the methodology.

Of 196 respondents (response rate=30%), most reported that the information provided during certification was clear (179, 92%) and contained useful drug information (145, 75%), and that the paperwork associated with required blood testing facilitated physician-patient conversation (102, 53%). Most respondents wanted certification materials to include all clinically important risks (179, 89%) and benefits (139, 72%), and reported frequent delays in medication access owing to required blood testing (116, 60%). Two-thirds of respondents agreed that the positives of the certification process (123, 64%) and blood testing requirements (129, 68%) outweighed the negatives. Negative REMS perceptions were

less common among physicians in practice longer (≥35 versus <15 years since medical school: OR =0.28, 95% CI =0.10-0.80) and non-Asian, non-White versus White physicians (OR =0.08, 95% CI 0.01-0.73). Refer to section 10.2.2 for additional information on the results.

Results from the survey found that most physicians were satisfied with the clozapine REMS Program, highlighting the clarity of the testing information and usefulness of the drug information disseminated as part of the certification process as well as the patient-physician discussion facilitated by the safe use requirements.

There are several study limitations. First, as with all surveys, the study was subject to participation, recall, and response biases. Specifically, it is possible that physicians who did not feel strongly about the Clozapine REMS were less likely to participate, that respondents' memory of the certification process was poor, and that respondents felt pressured to respond in certain ways. We sought to reduce this bias by inviting a random sample of physician prescribers, limiting participation to physicians who had prescribed clozapine in 2021 or 2022, and ensuring the confidentiality of responses. Second, responses were also impacted by the COVID-19 public health emergency, during which time the FDA exercised enforcement discretion as to REMS-required testing. Finally, the views of non-prescribers were not included, which may have overestimated the positive perceptions of the program reported in our survey, given that some physicians with highly negative perceptions may avoid prescribing the drug altogether.

4.4 FDA Sentinel Distributed Database Studies

4.4.1 Adherence to ANC Monitoring

The purpose of this study was to assess clozapine users' adherence to ANC monitoring requirements. A descriptive analysis was conducted using claims data from private and public insurers, which included four national commercial insurers, Medicare fee for service, and Medicaid in the Sentinel Distributed Database (SDD). The study period was January 1, 2010, to April 30, 2023, stratified into three periods based on modifications to the REMS program: January 1, 2010, to September 30, 2015 (period one), October 1, 2015, to December 31, 2019 (period two), January 1, 2020, to April 30, 2023 (period three). New clozapine episodes were identified among a cohort of individuals at least 12 years of age who were enrolled in health plans with medical and drug coverage in the 30 days prior to their first dispensing of clozapine (index date). Clozapine episodes of use were defined as periods during which a patient was taking clozapine, identified by National Drug Codes, date of dispensing, and days' supply from outpatient dispensing data. New use was defined as no evidence of a clozapine dispensing (washout) in the 30 days prior to an index dispensing. We included a secondary cohort where new use was defined using a 6-month washout period. This was done as a sensitivity analysis to identify patients that were more likely to be true "new users" (i.e., more treatment-naïve). This is a subset of the main cohort.

ANC monitoring was identified based on a procedure code for a relevant laboratory test. Adherence to ANC monitoring was evaluated using three different definitions: 1) evidence of at least one ANC test in the 30 days prior to initiating clozapine, 2) the number of ANC tests per month (rate), and 3) requiring the number of days between ANC tests (gaps) to be below a specific threshold. ANC monitoring was assessed for individual episodes of clozapine use, for three different episode durations based on ANC monitoring requirements: Months 0 to 6, Months 7 to 12, and Months 13 to 24.

In this analysis, we identified 81,656 clozapine episodes in period one, 83,877 clozapine episodes in period two, and 41,487 clozapine episodes in period three. A majority of clozapine episodes were among Medicare beneficiaries (87.0% in period one, 52.4% in period two, and 64.3% in period three). The proportion of episodes from patients covered by Medicaid was 5.7% in period one, 41.1% in period two, and 21.9% in period three. The proportion of episodes from patients covered by commercial insurers was 7.3% in period one, 6.5% in period two, and 13.9% in period three.

Prior to initiating clozapine, the proportion of episodes that had at least one ANC test in the prior 30 days was 69.1% in period one, 65.2% in period two, and 63.4% in period three.

We evaluated adherence during clozapine episodes of use based on the number of ANC laboratory tests per month, among those who had at least one observed ANC laboratory test. During the first 6 months of treatment when we expect to observe approximately four ANC laboratory tests per month, the median (IQR) number of monthly ANC tests was 2.3 (IQR 1-4) per month in period one, 2.1 (IQR 1-4) per month in period two, and 1.6 (IQR 1-4) per month in period three. However, 16% in period one, 20% in period two, and 22% in period 3 had no observed ANC monitoring during the first 6 months of treatment and were not included in the calculation of monthly rate. During Months 7-12 of clozapine use when we expect to observe approximately two ANC laboratory tests per month, the median (IQR) number of monthly ANC tests was 1.8 (IQR 1-3) in period one, 1.6 (IQR 1-2) in period two, and 1.3 (IQR 1-2) in period three. During Months 13-24 of clozapine use when we expect to observe at least one ANC laboratory test per month, the median (IQR) number of monthly ANC tests was 1.3 (IQR 1-2) in period one, 1.2 (IQR 1-2) in period two, and 1.1 (IQR 1-2) in period 3. In the secondary cohort with new use defined using a 6-month washout period, the median (IQR) number of ANC tests in the first 6 months of clozapine use was higher: 3.8 (IQR 2-4) per month in period one, 3.5 (IQR 2-4) per month in period two, and 3.1 (IQR 1-4) per month in period three. Although these data reflect the frequency of ANC laboratory tests observed per month, these data do not inform if the timing of monitoring was performed as described in labeling.

To better understand the timing of monitoring, we also assessed the time between ANC claims. During Months 0 to 6 of treatment, we expect the length of time, or "gaps" between ANC laboratory tests to be approximately 7 days. To allow for a small grace period, adherence to labeling was defined as ANC laboratory tests $\leq$10 days apart. This reflects nearly perfect adherence, since all observed gaps during a clozapine episode were required to be 10 or fewer days apart. During Months 0-6, only 10.1% of clozapine episodes in period one, 8.6% of clozapine episodes in period two, and 7.2% of clozapine episodes in period three had all gaps between observed ANC tests ≤10 days. It is important to note that, if any two ANC laboratory tests were more than 10 days apart during Months 0-6, that clozapine episode would not have been deemed as adherent in this analysis. Given the low adherence observed, the definition of adherence was loosened to allow for gaps between ANC screenings of up to 33 days. However, even with loosening the definition of adherence, only 41.1% of clozapine episodes in period one, 37.9% of clozapine episodes in period two, and 35.7% of clozapine episodes in period three had all gaps between observed ANC tests ≤33 days.

During Months 7-12 and 13-24 of clozapine use we expect gaps between ANC laboratory tests to be approximately 14 days and 30 days, respectively. Allowing for small grace periods, adherence to labeling was defined as ANC laboratory tests ≤17 days apart during Months 7-12 and ≤33 days apart during Months 13-24. During Months 7-12, 17.8% of clozapine episodes in period one, 14.6% of clozapine episodes in period two, and 12.6% of clozapine episodes in period three had all gaps between observed

ANC tests ≤17 days. During Months 13-24, 34.9% of clozapine episodes in period one, 29.0% of clozapine episodes in period two, and 28.7% of clozapine episodes in period three had all gaps between ANC tests ≤33 days. A single gap between observed ANC laboratory tests >17 days or >33 days, respectively, would result in a clozapine episode being identified as non-adherent.

In the secondary cohort with new use defined using a 6-month washout period, adherence was somewhat higher. During Months 0-6, 16.7% of clozapine episodes in period one, 13.4% of clozapine episodes in period two, and 12.4% of clozapine episodes in period three had all gaps between observed ANC tests ≤10 days. Loosening the definition of adherence to allow for gaps between ANC screenings of up to 33 days (within Months 0-6 of clozapine use), 46.1% of clozapine episodes in period one, 42.8% of clozapine episodes in period two, and 41.4% in period three had all gaps between observed ANC tests ≤33 days.

This analysis provides two metrics to evaluate adherence to ANC monitoring while taking clozapine using claims data. Assessing the number of ANC laboratory tests per month (rate) suggests that many patients were monitored, but we are unable to determine if the timing of monitoring is occurring as described in labeling. For various reasons patients may have ANC laboratory tests that are clustered during the month versus occurring weekly as required in Months 0-6, and this cannot be determined by assessing the monthly rate. Therefore, this metric may overestimate adherence. The second metric that assesses the gaps between claims for ANC monitoring, may underestimate reasonable adherence to monitoring ANC values as clozapine episodes with any two laboratory tests that were further apart than the defined time period would not be considered adherent to ANC monitoring. A limitation of this study is the possibility of missed ANC monitoring that occurs in a setting where payment for services are bundled (i.e., inpatient and institutional settings) since this study captures ANC monitoring based on billed laboratory tests in claims data.

In summary the results from this study found that many patients are monitored but not according to the labeling, particularly in the first six months of treatment. After six months of treatment, adherence to ANC monitoring is somewhat improved with less frequent monitoring requirements. Approximately 20% of patients do not appear to have any monitoring performed.

4.4.2 Descriptive Cross-Sectional Analysis Comparing Subset Population with Available ANC Test Results to Source Sentinel Distributed Database Clozapine Population

The purpose of this study was to describe and compare demographic, clinical, and health care utilization characteristics among the clozapine user population captured in the SDD with and without linked ANC test results. This claims-based analysis used data from 13 data partners, of which 8 had ANC test results available for some patients. Of note, most captured ANC test results occurred in the outpatient setting. Medicare and Medicaid beneficiaries were not included in the 8 data partners because ANC test results are not available. The study included new clozapine users, defined as no prior dispensing of clozapine in the 30 days prior, with a clozapine dispensing from January 1, 2010, to July 8, 2024, who were at least 12 years of age, and had medical and drug coverage for at least 183 days prior to their initial dispensing of clozapine. We also compared demographic characteristics, clinical characteristics and health care utilization and medication characteristics among individuals with and without complete linkage of ANC test results.

From the 13 SDD partners, we identified 164,971 episodes of new clozapine use among 105,067 unique patients. In the subset analysis among the eight SDD partners with at least some linked ANC test results,

we identified 10,473 episodes of new clozapine use among 6,698 unique patients. This represents over 90% population loss when linked to available ANC test results. Additionally, only 2,223 clozapine episodes of the 164,971 eligible clozapine episodes in the SDD had complete ANC test information. Compared to the new clozapine users captured in the 13 SDD data partners, completely linked individuals in the eight data partners were less likely to have a schizophrenia diagnosis recorded in claims[77.9 versus 85.2%, standardized mean differences (SMD)=0.188], had a lower average number of ambulatory visits [mean (SD)=13.8(13.9) versus 19.3(23.3), SMD =0.287], and had fewer dispensed prescriptions [mean(SD)=25.2 (21.8) versus 31.1 (27.3), 0.239]. Unlike the mostly publicly insured clozapine users in the whole SDD, the subset of clozapine users within the eight data partners with ANC test results were privately insured patients and could be slightly healthier with fewer prescriptions and ambulatory visits. A limitation of this analysis was the inability to describe characteristics not captured in health administrative claims that could impact neutropenia risk and ANC monitoring adherence, such as mental illness severity or sociodemographic characteristics. Refer to section 10.3.1 for additional information on this study.

4.4.3 Neutropenia and Monitoring in a Subset Population with Available ANC Test Results: a Patient Episode Profile Retrieval (PEPR) Analysis

The purpose of this study is to calculate rates of varying levels of neutropenia occurring during the first 6 months of treatment and describe frequency and timing of ANC monitoring among patients in the 8 SDDs with linkage to ANC test results. We conducted a line-by-line review of all claims for individual patients (also known as a Patient Episode Profile Retrieval (PEPR)), to provide descriptive information on ANC monitoring among new clozapine users. The cohort included new clozapine episodes, defined as a clozapine dispensing from January 1, 2010, to January 1, 2020, without a dispensing in the 30 days prior, having the same number of ANC test results as was billed or ordered, were at least 12 years of age at the initial dispensing, and were enrolled in health plans with medical and drug coverage for at least 30 days prior to their initial dispensing of clozapine. Individuals were followed for 6 months, until treatment discontinuation, or until loss of insurance coverage, whichever happened first. Neutropenia events were identified by diagnosis code or ANC test result. For events identified by diagnosis code, we searched ANC test results the week prior and subsequent to the date of the diagnosis code to confirm the neutropenic event and classify the neutropenic event's severity. Among clozapine episodes with multiple neutropenia events, only the most severe event was captured. If multiple events of the same severity occurred, only the first event was captured.

The study sample included 2,223 clozapine episodes with 760.3 total years at risk for neutropenia. Fifty-three neutropenia cases were identified: six episodes with ≥1 ANC test result indicating severe neutropenia, nine clozapine episodes with an ICD-10-CM diagnosis code for severe neutropenia but without a corroborating ANC test result, six episodes with ≥1 ANC test result indicating moderate neutropenia, and 32 clozapine episodes with ≥1 ANC test result indicating a mild neutropenic event. The event rate for severe neutropenia (based on ANC test results) was 8 per 1,000 person years at risk (95% confidence interval=4 to 18 per 1,000 person years).

To protect patient privacy, the data holders do not share with FDA proportions and numbers for counts less than five. Among individuals with ANC test-confirmed severe neutropenia, no cases of severe infection 30 days prior or 30 days subsequent to the neutropenic events were identified. However, about half of the cases did have cancer and/or evidence of ongoing chemotherapy. Table 20 summarizes finding on monitoring behavior from the PEPR. Around half of severe cases had an ANC test in 7 days, 14

days, or 30 days prior to their neutropenic event. In individuals with monitoring, all showed evidence of a severe downward trend in ANC test results prior to the severe laboratory result. The downward trend varied with some occurring quickly (over the course of 1 or 2 weeks) and others more slowly (occurring over several weeks to months). At least one case of severe infection treated with antibiotics was identified. Most had evidence of multiple continued clozapine dispensings after the severe neutropenia test result.

Among individuals with ANC test-confirmed moderate neutropenia, none had evidence of chemotherapy or filgrastim 30-days prior or subsequent to an event. Unlike the ANC test-confirmed severe neutropenia group, monitoring was less likely to occur at weekly intervals in the moderate group. Less than half had evidence of ANC monitoring 7 or 14 days prior to their moderate neutropenic event. More than half had monitoring in the 30-days prior. Similar to the monitoring findings for cases of confirmed severe neutropenia, all showed evidence of a downward trend prior to their moderate laboratory result, though this trend occurred quickly in some (over the span of a 1 to 2 weeks) and more slowly in others (over the course of several weeks or months). Most appeared to discontinue clozapine treatment after the event. Among mild neutropenia cases (N=32), half had evidence of monitoring the 7 days prior to their neutropenic event. A majority of mild neutropenia cases had evidence of monitoring 14 days and 30 days prior to their event (68.8% and 90.6%, respectively). We note that no moderate or mild cases had evidence of cancer and/or evidence of ongoing chemotherapy.

This study showed that neutropenia is occurring among clozapine patients during the first six months of treatment. Selecting a potentially non-representative sample is a major limitation of this analysis; individuals without ANC monitoring or without complete capture of ANC test result data represent a significant majority of clozapine users in the SDD. We also note that diagnosis codes for neutropenia did not appear to correspond with ANC test results; 9 of 10 severe neutropenia cases with a diagnosis code for severe neutropenia had no corroborating ANC test result. Refer to section 10.3.2 for additional information on the results.

4.4.4 Descriptive Electronic Medical Chart Review to Describe Neutropenia Events among a Medicare and Medicaid Insured Population

The purpose of this study was to describe ANC monitoring, neutropenia-related outcomes (hospitalizations), and subsequent clozapine discontinuation within the first 6-months of clozapine treatment among a Medicare and Medicaid insured population using a data source with access to inpatient medical records including ANC test results. We used Medicare and Medicaid claims and unstructured and structured electronic health records (EHR) from Massachusetts General Brigham (MGB) affiliated facilities. The cohort included new clozapine episodes, defined as a clozapine dispensing from 2000 to 2020 without a dispensing in the 30 days prior, with at least one record at an MGB affiliated facility, among individuals at least 12 years of age at the initial dispensing, and who were enrolled in a Medicare or Medicaid medical and drug coverage for at least 30 days prior to their initial dispensing of clozapine. Standardized extraction sheets were created a priori to ensure accurate and consistent capture of concepts from structured and unstructured data. Captured concepts included neutropenia-related information, indication-related information, and additional information about clozapine use. To ensure accurate capture of neutropenic events, we cross-referenced information abstracted from the medical records with ANC laboratory results and diagnostic codes. Events identified from diagnosis codes without corroborating information in the medical records or ANC lab results were considered not true cases.

Initially, we identified 2,525 incident clozapine episodes and 39 neutropenia events within 180 days of starting clozapine. Six cases of neutropenia were available for in-depth EHR review. Sixteen diagnosis-defined cases had no medical records 3 months prior and 6 months subsequent to the neutropenic event for review, thirteen diagnosis-defined cases were not corroborated with medical records or ANC test results the week prior or subsequent to the event, and four laboratory-defined cases had no medical records or ANC test results available to corroborate diagnoses in the week prior and subsequent to the event. Clozapine was recorded as the suspected cause of neutropenia in all six cases. In one out of six episodes, neutropenia was recorded to have led to a serious infection (bacteremia) requiring inpatient management. No deaths were identified. No mention of monitoring plans and no records of adherence to ANC testing or guidelines were available in the medical records. This study suggested that neutropenia does appear to occur among clozapine exposed patients. Major limitations of this study included the loss to attrition and lack of available data on ANC monitoring. Refer to section 10.3.3 for additional information on the results.

4.5 Veterans Affairs Study

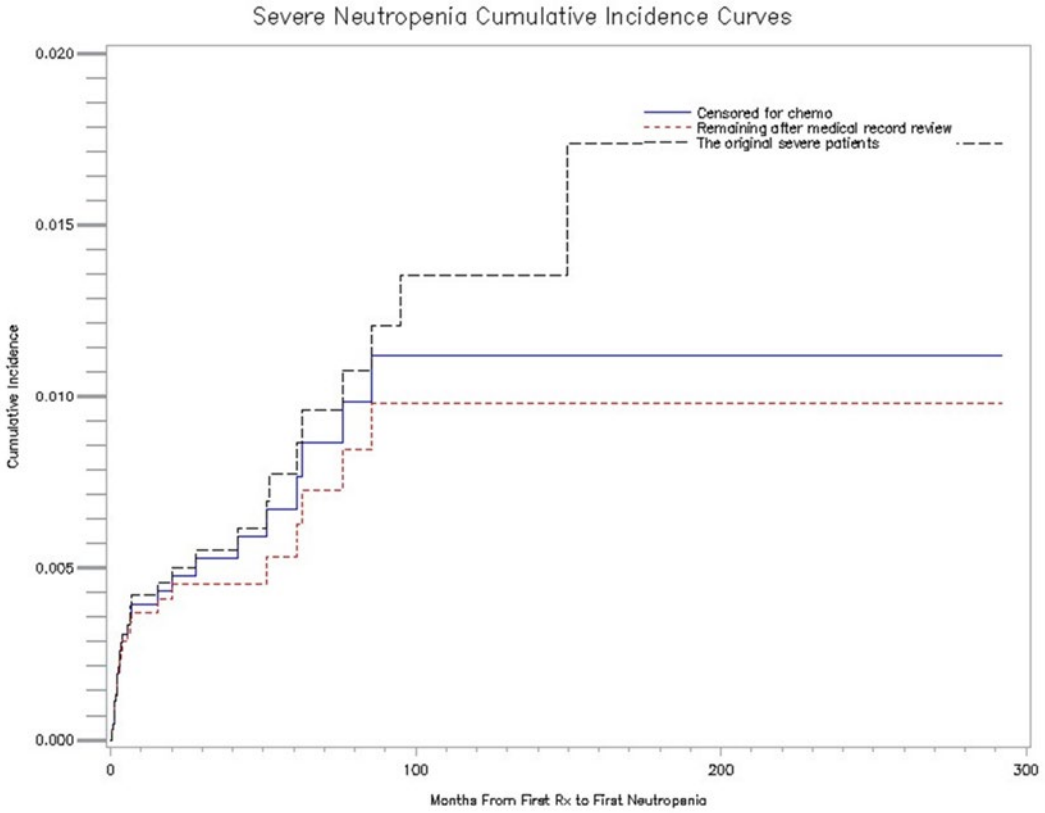
The purpose of this study was to evaluate risks of neutropenia and severe neutropenia following initiation of clozapine use and over time, including periods of clozapine discontinuation and rechallenge. Using longitudinal outpatient prescription data and serial outpatient/inpatient ANC data from the VA health system, new users of clozapine were followed during 1999-2023 for the development of severe neutropenia (ANC <500/µL). The cohort included new users of clozapine defined as no dispensing of clozapine in the prior 12 months, patients must have a clozapine prescription from October 1, 1999, to September 30, 2023, at least one year of VA service before clozapine initiation, and known sex, age, veteran status. Clinical outcomes associated with neutropenia, including deaths, were captured. ANC test results were obtained from VA Corporate Data Warehouse and clinical information was obtained from chart reviews, which is still ongoing at this time.

This cohort included 6,488 patients followed on clozapine for up to 23 years. Nearly 60% of patients had one episode of continuous clozapine use, with 40% having ≥2 episodes. During follow-up, 32 patients developed severe neutropenia during their first episode of use, with an additional 16 patients developing severe neutropenia during a subsequent episode. After censoring four patients from the cohort who were treated with cancer chemotherapy, there were 28 patients with severe neutropenia. During medical chart review, three additional patients were removed due to two patients with a probable lab error and one patient with active cancer as the most likely cause of neutropenia, leaving 25 patients with severe neutropenia.

Using Kaplan-Meier methods and based on the total of 32 severe neutropenic events, the cumulative incidence of severe neutropenia per 1000 patients during the first episode of use was 4.2 (95% confidence interval (CI) 2.6-6.5) at 1 year, 7.8 (95% CI 4.8-11.9) at 5 years, 13.5 (95% CI 8.4-20.9) at 8 years, and 17.4 (95% CI 9.5-29.3) from 13-23 years. The cumulative incidence remained steady from 13-23 years, most likely due to the small sample after 13 years with no additional cases observed. After censoring four patients treated with cancer chemotherapy, medical chart review identified two patients with a probable lab error and one patient with active cancer as the most likely cause of neutropenia, leading to 25 severe neutropenia cases remaining. A Kaplan-Meier analysis based on these 25 events yielded cumulative incidence estimates per 1000 patients of 3.7 (95% CI 2.3-5.9) at 1 year, 5.3 (95% CI

3.2-8.5) at 5 years, and 9.8 (95% CI 5.6-16.0) at 8 years and beyond. The sample size remaining on clozapine beyond 8 years was low. Refer to the Kaplan-Meier plot in Figure 6.

Figure 6. Kaplan-Meier plot showing cumulative incidence of severe neutropenia during the first episode of continuous clozapine use including all patients, and with censoring for cancer chemotherapy, and after medical record review of cases, from the Veterans Affairs health system, FY2000-FY2023.



Source: Adapted from the VA.

Using life-table methods, interval-specific incidence rates per 1000 person-years were estimated during the first episode of clozapine use. Based on 32 cases of severe neutropenia, the incidence of severe neutropenia was highest during the first 3 months of clozapine use (9.6), and somewhat lower during months 3-6 (4.1) and 6-9 (3.6). There were no events during months 9-12. From 1-5 years, the incidence rate was approximately 1 per 1000 person-years, from 5-8 years, 1.9 per 1000 person years, and from 8-13 years, 0.4 per 1000 person years. The number of patients remaining on treatment beyond 8 years was low (n=686, 10.5% of initiators) and beyond 13 years, was very low (n=268, 4.1% of initiators). Based on 25 cases of severe neutropenia, the pattern of risk with clozapine was similar to that observed with the 32-case analysis. Risk of severe neutropenia was highest during the first 3 months (8.9 per 1000 person years) and somewhat lower during months 3-6 (4.1) and months 6-9 (2.4). The risk was still evident during years 5-8 (1.6 per 1000 person years). As above, the cohort number remaining on clozapine was low beyond 8 years of follow-up.

During the first episode of continuous clozapine use, there were two deaths that were likely attributable to clozapine-induced neutropenia.

This study is not yet complete. Data regarding inpatient clozapine use must still be incorporated into the analysis, which, based on preliminary work, will probably lead to the identification of one or two additional cases of severe neutropenia.

The results from the VA study found that the cumulative incidence of severe neutropenia among clozapine patients was around 0.4% during the first year of treatment The risk was highest during the first 3 months, with somewhat lower risk between 3-9 months. Risk continued to accrue through at least 8 years of continuous use. Beyond 8 years, the cohort sample size was low, reducing our statistical power to observe additional cases even if the risk of severe neutropenia continued. Study strengths included comprehensive follow-up, accessible serial ANC values for most patients, and the ability to review detailed medical records, which provided important details about case-patients that could not be obtained from electronic laboratory or prescription data. Study limitations include pharmacy records not showing brief interruptions in clozapine therapy that don't result in missed prescription fills, and generalizability may be limited because the VA healthcare delivery system may differ from healthcare delivery elsewhere in the US the patient population was predominantly male, with high comorbidity burden.

5 Updated Assessment on Severe Neutropenia and Related Clinical Outcomes

The data indicate that clozapine can cause severe neutropenia, though estimates of its frequency vary. Perhaps because of this variability and the overall relatively low risk of developing severe neutropenia, there are conflicting perceptions among the public about the incidence of severe neutropenia with clozapine.,[23][24] Some perceive the risk as low and believe that it aligns with the risk of severe neutropenia observed with other drugs that are approved without a REMS, that the risk is greatest in the first several months of treatment, and that the risk is unlikely to result in fatal outcomes. The purpose of conducting an updated risk assessment is to assess the cumulative incidence of severe neutropenia over time with clozapine use as well as any related clinical outcomes, such as death and infection, that result from severe neutropenia. FDA conducted several activities to assess the risk, including 1) a review of the biomedical literature, 2) a review of adverse event reports in FAERS, 3) studies analyzing data from FDA's Sentinel System, 4) a pharmacoepidemiological study in collaboration with researchers from BWH, and 5) a pharmacoepidemiological study conducted in collaboration with the Department of Veterans Affairs (VA) as described in Section 4. This section provides FDA's overall assessment of the risk of severe neutropenia and related clinical outcomes.

5.1 What Was Known about Clozapine-Induced Severe Neutropenia, 1989-1998

When Clozaril was first approved in the United States in 1989, clozapine-induced severe neutropenia had an estimated cumulative incidence at 1 year of approximately 1.3%. This incidence was based on the occurrence of severe neutropenia in 15 U.S. cases out of 1,743 patients exposed to Clozaril during its clinical testing prior to domestic marketing. Furthermore, before widespread adoption of ANC

[23] The Angry Moms. https://www.theangrymoms.com/.

[24] National Alliance on Mental Illness. https://www.nami.org/NAMI/media/NAMI-Media/PDFs/FINAL11-30_Clozapine-REMS-Program-Updates_Indiv-Families.pdf.

monitoring, of the 112 cases of severe neutropenia reported worldwide in association with Clozaril use as of December 31, 1986, 35% were fatal (Clozaril Prescribing Information, 1989).

By 1998, knowledge about Clozaril-induced severe neutropenia was more widespread, and close monitoring of WBC counts was more widely practiced. As of August 21, 1997, with weekly monitoring in place, the percent of severe neutropenia cases that were fatal had declined to 3% (19 of 585 cases of severe neutropenia) (Clozaril Prescribing Information, March 3, 1998). These data support that ANC monitoring reduces fatalities with clozapine-induced severe neutropenia.

Furthermore, according to the 1998 label (Clozaril Prescribing Information, March 3, 1998 label), "a hematologic risk analysis was conducted based upon the available information in the Clozaril® National Registry (CNR) for U.S. patients. Based upon a cut-off date of April 30, 1995, the incidence rates of severe neutropenia, based upon a weekly monitoring schedule, rose steeply during the first two months of therapy, peaking in the third month. Among Clozaril patients who continued the drug beyond the third month, the weekly incidence of severe neutropenia fell to a substantial degree. After 6 months, the weekly incidence of severe neutropenia declined still further, however, never reaches zero."

5.2 What is Known About Clozapine-Induced Severe Neutropenia Now

As reflected in Section 4, our additional studies collectively reflect about 20 years of data from different types of healthcare delivery systems and insurance coverage. Together these studies capture inpatient and outpatient settings, hospitals and other integrated delivery care networks, private insurances, and public insurers such as Medicare and Medicaid. See Table 9.

Table 9. Comparison of Study Period, Settings, Clinics, and Insurance Across Four Studies

Comparison Parameters	BWH	PEPR	Medical Chart Review	VA
Study period	2000-2022	2010-2020	2000-2020	1999-2023
Type of settings	Inpatient	Primarily outpatient	Primarily inpatient	Outpatient
Type of clinics	Hospital	Integrated delivery care networks	Mass General Brigham and affiliates: academic medical centers, community settings	VA healthcare database: academic medical centers, community settings
Type of insurance	Private, Medicaid	Private	Medicare, Medicaid	Pending

Source: Table created by FDA risk management analyst.
Abbreviations: BWH, Brigham and Women's Hospital; PEPR: Patient Episode Profile Retrieval; VA, veterans affairs

Of all the studies conducted to update our assessment of the risk of clozapine-induced severe neutropenia, the VA study provides the most reliable estimates. The VA is a large integrated healthcare system comprising 1,193 outpatient sites across the United States (Veterans Health Administration). Due to the nature of the integrated health care system, there is near completeness of ANC data, long term follow-up data, and comprehensive clinical, pharmacy, and laboratory data.

As noted in Section 4.1, three non-U.S. studies (Atkin et al. 1996; Toyoda et al. 2021; Kang et al. 2024) and one US study (Alvir et al. 1993) reported cumulative incidence of severe neutropenia within the first year of clozapine use with rates ranging from 0.70% to 0.96%.

As described in Section 4.5, the cumulative incidence of severe neutropenia was 0.4% at 1 year in the VA database and 0.8% from the Alvir study in the United States (Alvir et al. 1993). Both estimates from the VA study and the literature are lower than the cumulative incidence of 1.3% at 1 year that was reported

with the 1989 labeling. Table 10 lists the incidence of severe neutropenia and death at two time points.[25]

Table 10. Comparison of the Incidence of Severe Neutropenia and Death From 1989-1998 and 2024.

Outcome	1989-1998	2024
Severe neutropenia	From the 1989 label: • The ANC of less than 500/μL has been estimated to occur in association with clozapine use at a cumulative incidence of 1.3%.	From the VA study: • The cumulative incidence was 0.4% at 1 year. • Lower cumulative incidence may be due to greater adherence to ANC monitoring and discontinuing clozapine for mild and moderate neutropenia in the VA population. From the literature review: • The cumulative incidence was 0.8% at 1 year
Death	From the 1989 label: • Of the 112 cases of neutropenia reported worldwide in association with clozapine use as of December 31, 1986, 40 cases (35%) were fatal before widespread adoption of monitoring. From the 1998 label: • As of August 21, 1997, with weekly monitoring, there were 585 cases of severe neutropenia and of those cases 18 (3%) were fatal.	From the VA study: • Out of 48 cases of neutropenia identified in the VA system from 1999-2023, 2 (4.1%) were fatal.

Source: FDA created from data as cited above.,
Abbreviations: ANC, absolute neutrophil count; VA, veterans affairs

The lower cumulative incidence reported in the VA study may be due to greater adherence to ANC monitoring as well as discontinuation of clozapine among mild and moderate neutropenia cases before they progressed to severe neutropenia. Of the 6,488 patients on clozapine in the VA study, there were 2 fatal cases (4.1%). One case was due to clozapine-induced neutropenia and one case was likely due to clozapine-induced neutropenia. The VA study fatality rate is similar to the fatality rate of 3% associated with clozapine[26] under weekly monitoring observed in 1997.

In summary, consistent with what we knew about clozapine-induced severe neutropenia between 1989 and 1998, severe neutropenia is a serious risk of clozapine use, and frequent ANC monitoring can mitigate severe neutropenia and neutropenia-related deaths. The risk of neutropenia is greater for clozapine than it is for other antipsychotic drugs. The VA study suggests that incidence of severe neutropenia is highest during the first 3 months of clozapine use, and somewhat lower during Months 3-9. There were 0 events during Months 9-12. However, risk persists beyond 13 years, though at a lower rate. Our updated assessment of the risk, including data from the VA study as well as data from the Sentinel and BWH studies, led FDA to conclude that the risk of severe neutropenia remains the same – it

[26] Prior to 1997, Clozaril was the only clozapine product approved. The restricted distribution program required weekly monitoring to detect neutropenia.

is greatest with clozapine in the first 6 months of treatment and, beyond that timepoint, it never reaches zero across the studies conducted. This is consistent with the currently approved clozapine label, which states that the risk is greatest in the first 18 weeks of clozapine initiation. Additionally, our assessment confirms that frequent ANC monitoring remains necessary to identify neutropenia early so that healthcare providers can intervene and may prevent progression to more severe cases. Very few deaths related to clozapine-induced neutropenia were found in the retrospective observational studies we conducted.

6 Updated Healthcare Gap Assessment

As currently designed, the Clozapine REMS addresses two care gaps: (1) knowledge of the risk of severe neutropenia and the need for ANC monitoring in the prescribing population and (2) ensuring that ANC monitoring of patients occurs. Clozapine has been approved for almost 40 years and the landscape of healthcare delivery has changed significantly since clozapine was first approved in 1989. The purpose of FDA conducting an updated care gap assessment is to determine whether gaps in knowledge and behavior in the prescribing population persist.

6.1 Knowledge and Training

For the first care gap, we sought to understand if practitioners understand the risk and the appropriate actions that need to occur if neutropenia is detected. The updated assessment evaluated prescriber survey data; examined available non-REMS training, guidelines, and resources; and assessed the extent to which education on the risk of severe neutropenia and the need for ANC monitoring with clozapine is incorporated in the healthcare delivery system today.

In 1989, clozapine was the first antipsychotic product approved that had a boxed warning for severe neutropenia and requirements for weekly WBC monitoring. Monitoring for and managing neutropenia would not have been common for psychiatrists practicing at the time clozapine was approved. Lack of prescriber knowledge about the risk of clozapine-induced severe neutropenia, the need for ANC monitoring, and management of neutropenia would have presented a healthcare gap for the prescribing population in 1989.

The Agency has now performed an updated assessment to ascertain if this healthcare gap still exists today. This updated assessment examined educational resources that are currently available for prescribers of clozapine as well as the extent to which psychiatry training incorporates monitoring for and managing severe neutropenia associated with clozapine use.

6.1.1 Evaluation of Prescriber and Pharmacist Knowledge

REMS Assessment survey data has shown sustained knowledge among healthcare providers who are participating in the REMS about the risk of severe neutropenia associated with clozapine use and the need for ANC monitoring. Since 2017, four surveys evaluating prescriber and pharmacist knowledge have been completed as part of the REMS Assessments. Collectively, 1,116 certified prescribers and 1,109 pharmacists from certified pharmacies have been surveyed.

BWH and FDA conducted a survey as described in section 4.3.3. Although 17% of physicians reported that they could not recall well the certification process that allowed them to begin to prescribe clozapine, more than 97% of physicians recalled the certification process provided information on severe neutropenia.

Data from the VA and the Sentinel Studies supports that prescribers who may or may not be certified in the REMS, are knowledgeable about the risk and management of neutropenia. The VA study provided information on how prescribers were managing patients with mild and moderate neutropenia. In the VA study, when mild or moderate neutropenia is identified some healthcare providers are discontinuing clozapine, monitoring ANC to see if ANC returns to baseline, and restarting clozapine in some cases. This practice of discontinuing clozapine for mild neutropenia is more conservative than what is recommended in the approved labeling. In addition, in a national survey of 97 clozapine prescribers at the VA (Moody and Eatmon 2019) indicated prescribers were knowledgeable with an average clozapine knowledge assessment score of 85.6%. The knowledge assessment included questions on indication, dose, baseline ANC requirements, ANC monitoring requirements, and adverse events. This study is limited by small sample size and lack of generalizability of the results.

In the medical chart review in the Sentinel study, all six episodes of neutropenia recorded clozapine discontinuation following neutropenia. Management strategies consisted of prophylactic anti-infectives and/or granulocyte colony stimulating factors. Data from the VA and Sentinel studies suggest that prescribers' understanding of clozapine-induced severe neutropenia risk and management is supported by the actions that they are taking in patients who develop neutropenia. Additionally, since clozapine's approval in 1989, additional antipsychotic medications, including olanzapine, risperidone, and quetiapine (the most frequently prescribed antipsychotics used for the treatment of resistant schizophrenia), have been approved with labeling that includes a warning and precaution for the class risk of leukopenia, neutropenia, and agranulocytosis (DEPI consult response. Drug utilization. Ramzan, et al. September 10, 2024). This means that today's prescribers are likely to be more familiar with the risk of neutropenia as well as the need to monitor and manage this risk across antipsychotic medications.

Collectively, our evaluation suggests that today's clinicians, including those who may not be participating in the REMS, are knowledgeable about the risk of clozapine-induced severe neutropenia and the need for ANC monitoring. Today's clinicians prescribe a number of antipsychotics which are associated with neutropenia, and their experience with monitoring and managing neutropenia goes beyond clozapine.

6.1.2 Landscape Analysis of Resources and Training Outside of the REMS

We wanted to understand what resources and training are available outside of the REMS that contribute to prescriber knowledge about how to monitor for and manage clozapine-induced severe neutropenia. We also wanted to understand how widely they are accessed by prescribers.

Regarding the treatment of schizophrenia, there are a number of books, scientific studies, review articles, and guidelines published on the treatment and management of this condition with antipsychotics. We identified and reviewed nine different treatment guidelines for schizophrenia to determine the extent to which monitoring for neutropenia is addressed. Eight of the nine guidelines include recommendations for using clozapine. Although most focus on efficacy, including clozapine's place in therapy, six guidelines also include varying amounts of information on neutropenia and the need to monitor for neutropenia. For example, the American Psychiatric Association "Practice Guideline for the Treatment of Schizophrenia" was first published in 1997 and updated in 2004 and 2020 (Association 1997; Lehman et al. 2004; American Psychiatric Association ; Keepers et al. 2020), and all three editions include information about the risk of neutropenia as well as ANC monitoring recommendations. The American Academy of Child and Adolescent Psychiatry's 2013 "practice parameter for the assessment and treatment of children and adolescent with schizophrenia" includes

focused information on using clozapine and includes ANC monitoring recommendations (McClellan and Stock 2013). We also identified two books identified through prescriber surveys via the REMS assessment reports, The Clozapine Handbook (2019) and Maudsley's Prescribing Guidelines in Psychiatry (2022), that include extensive information about the management of patients on clozapine. Furthermore, information on the safe use of clozapine has been incorporated in several common electronic resources used for clinical decision support and drug information such as UpToDate, Micromedex, and Medscape.

The BWH and FDA's national survey study of 196 physicians who have prescribed clozapine showed that the survey respondents ranked clinical decision support tools (e.g., UpToDate, Micromedex, ePocrates) the highest for usefulness in contributing to their understanding of the risk of neutropenia. "Studies and other articles published in medical journals" and "prescribing information" ranked second and third, respectively. Information collected through the REMS assessment knowledge surveys also indicates that prescribers seek information about clozapine and monitoring neutropenia from resources outside of the REMS (e.g., Medscape, Micromedex, and UpToDate).

To understand if and to what extent clozapine and monitoring for neutropenia are incorporated into psychiatric medical training, we contacted the Accreditation Council for Graduate Medical Education (ACGME, which sets and monitors professional medical education standards for accredited residencies and fellowships), The American College of Psychiatrists (ACP, which administers the Psychiatry Resident In-Training Examination (PRITE) to psychiatry residents annually during their residency training), and the American Board of Psychiatry and Neurology (ABPN, which administers the psychiatry board certification examination to promote and assess the competence of psychiatrists and neurologists). We gathered the following information from these organizations:

- **ACGME** Psychiatry Common Program Requirements: These standards require accredited programs to provide residents exposure to the management and treatment using appropriate pharmacologic, psychotherapeutic, and social rehabilitative interventions for "all major psychiatric disorders in the current standard diagnostic statistical manual" which includes schizophrenia. In addition, residents and fellows are required to attend 70% of regularly scheduled didactic sessions that are coordinated with their concurrent clinical experiences. The specific curriculum is established by the local residency/fellowship program within the framework of the ACGME's Common Program Requirements. Curricular components must also meet the requirements of the relevant specialty board, which are informed by the current standard of practice determined by the appropriate specialty society. There are approximately 300 ACGME-accredited psychiatry residencies (AMA 2024) in the United States educating approximately 7500 residents and fellows. This information from ACGME suggests that psychiatry residencies and fellowships include training on management of schizophrenia; however, we were unable to determine the extent to which information about clozapine and its risk of neutropenia is incorporated across programs.
- **ACP**: ACP confirmed that all US psychiatry residents take the PRITE exam annually. In reviewing the 300-question exam, there have been two to four questions that involve clozapine on the exam annually in 2021, 2022, and 2023. ACP also administers the Psychiatrists In-Practice Examination (PIPE) as a continuing education exercise. This exam also includes one or more questions involving clozapine. This information from ACP suggests that psychiatry residencies and fellowships include training on management of schizophrenia; however, we were unable to determine the extent to which information about clozapine and its risk of neutropenia is incorporated across programs.

- **ABPN**: ABPN confirmed there are questions in the certification examination "question bank" about clozapine and there is a place for these questions on their exam content outline. However, we were unable to determine the extent to which information about clozapine and its risk of neutropenia is included in any given examination. Psychiatrists studying for board certification may study the safe use of clozapine given the possibility of a clozapine-related exam question.

We note that published studies of surveys conducted among psychiatrists and psychiatry residents were mixed. One survey of 164 psychiatry residents found only one-third of respondents reported that their residency had a *dedicated* clozapine clinic (Singh et al. 2020). Only 18% of survey respondents felt very comfortable initiating clozapine and 41% felt somewhat comfortable. Almost 40% of respondents cited limited experience and inadequate training in clozapine use. Similarly, 22% of survey respondents in a study published by Cotes et al. (2022) received formal training during residency. In contrast, a study by Leung et al. (2019) reported more than 80% of survey respondents, from nine US sites and one Canadian site, believed they had adequate training and education in clozapine management. Limitations across these studies include a small sample size and lack of generalizability of the results.

In summary, our evaluation suggests that the knowledge gap has likely narrowed due to the availability of resources available beyond the educational materials in the Clozapine REMS. Unlike in 1989, experience with managing antipsychotic medication-associated neutropenia, including clozapine-induced neutropenia, is incorporated into today's medical training for psychiatrists.

6.2 Adherence to ANC Monitoring

For the second care gap, we sought to understand the extent to which ANC monitoring is performed. As previously mentioned, monitoring for and managing neutropenia typically would not have been routinely performed by psychiatrists practicing prior to US approval of clozapine in 1989 and, therefore, created a gap in safe use behavior (monitoring and management of neutropenia) in the prescribing population. Since 1989 the healthcare landscape has changed, and we would expect that monitoring is now a routine part of practice. Because the Clozapine REMS has never been fully implemented and we cannot rely on REMS assessment data alone to determine adherence to ANC monitoring, there remains uncertainty regarding whether prescribers are monitoring as required in the prescribing information and REMS. An analysis of prescribers' adherence to ANC monitoring as described in the prescribing information was done by evaluating REMS assessment reports, conducting a literature review, and evaluating the findings from FAERS, BWH studies, and Sentinel studies(refer to Section 4 for more details of these studies). We evaluated a variety of sources, gathering information on prescribers participating in the REMS and outside of the REMS to provide a robust picture of the extent to which ANC monitoring is routinely performed.

Despite not all REMS requirements being fully implemented, we estimate approximately 65% to 75% of patients receiving clozapine had at least one REMS dispense authorization at any given month (refer to Section 3.8 for more details), suggesting that the majority of stakeholders are participating in the REMS. Among the stakeholders participating in the REMS who submitted a PSF, data from the REMS assessment report (refer to Section 3 for more details) showed high adherence with ANC monitoring throughout treatment. The adherence with the monitoring requirements gradually increased over the first 6 months after the implementation of the July 2021 modification, to exceed 90% adherence for all monitoring frequencies.

Data from the additional studies support that ANC monitoring is occurring. However, in months 0-6 after treatment is started, it appears to be happening less frequently than the required weekly monitoring as

described in the prescribing information, and some patients may be initiating treatment without a baseline ANC being obtained in the prior 30 days. For example, for the first 6 months of treatment, where we would expect 4 ANC tests in a month for new clozapine users, we observed a median of 2.1 ANC tests per month in the BWH study and 3.1 ANC tests per month in the Sentinel analysis. The second analysis in Sentinel looking at time periods between ANC tests showed that 10% or less of clozapine episodes had perfect adherence to the monitoring frequency and when loosening the definition of adherence, adherence only increased to 41%. In both studies, approximately 63% of clozapine users had a baseline ANC prior to initiating clozapine, leaving about 37% of clozapine users without a baseline ANC. In contrast, for patients on treatment for 6 to 12 months and for those on treatment for beyond 1 year, adherence to ANC monitoring was consistent with the monitoring frequency outlined in the prescribing information.

These findings from BWH and Sentinel studies have to be interpreted carefully given the study limitations, which could underestimate adherence to monitoring given the strict definitions chosen to align with the prescribing information, definition of a new clozapine user, and these studies rely on claims data. Furthermore, we are unable to determine whether these studies represent findings from providers who were or were not actively participating in the clozapine REMS.

Additionally, we searched the medical literature for case reports published between January 1, 2017, and December 31, 2022, to assess adherence to ANC monitoring practices as recommended in the clozapine prescribing information. We identified 14 articles that included individual patient cases that detailed clozapine management by the provider in response to ANC results. According to the literature, providers typically followed clozapine labeling recommendations,[27] but these cases may not be generalizable because most (n=8) of these cases involve clozapine management in complex scenarios (e.g., concurrent cancer treatment). Detailed descriptions of the frequency of ANC monitoring after a moderate or severe neutropenia event were not provided for all cases. It should be noted that the findings of the literature review may reflect publication bias, wherein authors may only publish information related to positive practices or outcomes.

As mentioned before, during the COVID-19 pandemic, the FDA guidance for industry and health care professionals *Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency* allowed health care providers prescribing and/or dispensing drugs approved with REMS that are subject to laboratory testing or imaging to consider whether there were compelling reasons not to complete the REMS-required laboratory testing or imaging studies during the PHE. Some clozapine clinics relaxed ANC monitoring to every three months in patients for whom monthly ANC test results were required (Nichols et al. 2020).

Lastly, we attempted to assess adherence to monitoring through FAERS reports. We searched FAERS for cases of neutropenia[28] with clozapine received from January 2017 through September 2024. Most cases reviewed (77%, 61 of 79) did not provide adequate information to draw any conclusions. Of the 13 cases with sufficient information, 85% (n=11) described ANC monitoring consistent with the prescribing information but these cases may not be generalizable because some involve clozapine management in

[27] For the cases that included clozapine management prior to 2015 (4 of 14), we evaluated clozapine management in the context of the labeling recommendations at the time.

[28] FAERS Search Terms: *Agranulocytosis* (Narrow Standardised Medical Dictionary for Regulatory Activities Query); High Level Term *Neutropenias*; Preferred Terms *Neutrophil count decreased, Neutrophil percentage decreased, Granulocyte count decreased, Granulocyte percentage decreased*.

complex scenarios (e.g., colony-stimulating factor treatment). Additionally, we are unable to determine whether these reports represent findings from providers who were or were not actively participating in the Clozapine REMS, nor can we rely on these cases to estimate the rate of adherent monitoring happening in the general prescriber population.

Multiple data sources were analyzed to assess ANC monitoring. Although each data source has limitations, the data are consistent across all studies which supports that monitoring is occurring; however, adherence to monitoring is poorer when the monitoring frequency is weekly. None of the additional studies were able to inform the contribution of the REMS on adherence to the monitoring requirements. Thus, we do not know the impact that the REMS has on ANC monitoring behavior in prescribers of clozapine.

7 Data on Burden and Access

FDA is aware of concerns about the burden associated with the Clozapine REMS and the potential impact it has on patient access. Since 2015, the Agency has received numerous direct communications from healthcare providers, patients, caregivers, Congress, professional organizations, and patient advocacy groups[29] about the burden of the REMS and its impact on patient access to clozapine. FDA has purposefully chosen not to require full implementation of the REMS in order to minimize negative impact on patient access and decrease the likelihood of treatment disruption. Data reported by the CPMG from the two most recent REMS assessment reports suggest that over 45,000 patients per year could have had their clozapine treatment withheld or delayed if all REMS safe use requirements were enforced.

Before exploring barriers to clozapine treatment, we sought to ascertain what current access to clozapine is using epidemiology and drug utilization data. While clozapine will not be appropriate for every patient with treatment-resistant schizophrenia, data indicate that clozapine use in these patients is low. Approximately 814,000 to 1.2 million people may be diagnosed with treatment-resistant schizophrenia in the U.S. (Diniz et al. 2023) Drug utilization data indicate just under 148,000 people were dispensed a clozapine outpatient prescription in the United States in 2023. Based on these data, this translates to approximately 12-18% of *potential* people with treatment-resistant schizophrenia may be treated with clozapine. Further evidence of under-utilization has been documented through U.S. VA and U.S. Medicaid claims with only approximately 5-10% of potential patients receiving clozapine (Stroup et al. 2014; Emerson 2023).

Next, we explored possible barriers to clozapine treatment beginning with barriers related to the REMS. BWH and FDA conducted a national survey among physicians who prescribe clozapine (N =196 physicians), which found that most respondents (150, 77%) agreed ANC monitoring was clinically necessary; almost 60% also agreed that the safe use requirements in the REMS have caused a delay in their patients receiving clozapine compared to 34% agreeing that insurance issues have often caused delay. Only one-third of the physicians surveyed agreed insurance issues are more burdensome than the safe use requirements for most patients. Interestingly, two-thirds of respondents agreed that the positives of the certification process (64%) and blood testing requirements (68%) outweighed the negatives. Negative REMS perceptions were less common among physicians in practice longer (≥35 years). Similarly, participants in a focus group (n=7) noted the value of monitoring but also noted that

[29] Examples of patient advocacy groups include Team Daniel Running for Recovery from Mental Illness and The Angry Moms.

missed doses were more detrimental than missed ANC monitoring (Cooke et al. 2023). In addition, participants also cited administrative inefficiencies with the REMS website and paperwork (Cooke et al. 2023). A white paper published by the National Association of State Mental Health Program Directors concluded clozapine is underused due to a variety of barriers related to the lack of prescriber knowledge and confidence, special monitoring requirements, administrative factors, and lack of preparation by health systems. Although the REMS adds administrative burden, it is important to keep in mind that intensive monitoring is necessary when using clozapine, whether or not such monitoring is required to be documented through the REMS. The need for monitoring, coordination of care and support associated with monitoring for neutropenia as well as monitoring for other adverse events and adherence to treatment would remain part of treating patients with clozapine regardless of the REMS.

There are also barriers to using clozapine that are cited in the medical literature that are not directly related to the REMS. Farooq et al. (2019) published a systematic review of barriers to using clozapine in treatment-resistant schizophrenia. Fifteen articles met their inclusion criteria, including international and domestic studies. The article cited inadequate knowledge of or experience with clozapine use as a leading clinician-related factor. In addition, the need for intense monitoring, serious side effects, perception that patients may not adhere to treatment, difficulties obtaining blood work, staff resources, and fragmentation of care were also cited by clinicians. More patient-centered factors included refusal by patients to do blood testing and the burden of regular blood work. Concern about other side effects as well as patient intolerance to clozapine may also restrict the use of clozapine. Further, in addition to REMS-related barriers, Cooke et al. (2023) noted that the burden of ANC monitoring and other challenges with coordination of care may cause physicians to avoid use of clozapine in patients who are homeless. A white paper published by the National Association of State Mental Health Program Directors concluded clozapine is also underused due to "negative prescriber attitudes" and "inadequate understanding or acknowledgement of clozapine's unique nature by policy makers and payers." Finally, literature suggests that Black patients are disproportionally affected by access issues compared to White patients (Williams et al. 2020; Barry et al. 2024). The authors did not analyze the rationale behind this trend but noted that benign ethnic neutropenia (BEN) may potentially cause reluctance in prescribing clozapine for Black patients, despite BEN not demonstrating an increased risk for developing severe neutropenia (Williams et al. 2020) and changes to the prescribing information to accommodate for lower monitoring thresholds for patients with BEN.

We also note that two of the articles mentioned inadequate training or exposure to clozapine (Love et al. 2016; Farooq et al. 2019). However, the studies cited by Farooq et al. (2019) were all from outside the U.S. Our evaluation indicates that there are resources and training available for practitioners in the U.S. Practitioners who treat patients with clozapine cite widely available clinical decision support tools as their primary source of information. Further, study authors advocate for increased training through residency programs rather than other mechanisms (e.g., REMS) (Freudenreich et al. 2013; Singh et al. 2020). With regard to the other factors cited by clinicians and patients, they are not likely to resolve with changing the REMS to reduce burden or eliminating the REMS completely and they contribute to significant health disparity for persons with schizophrenia (Tiihonen et al. 2009; Cahoon et al. 2013; Farooq et al. 2019; Vermeulen et al. 2019).

In summary, the reported underutilization of clozapine is due to a variety of reasons including the administrative burden created by the REMS. These barriers to treatment coupled with the risk

assessment outlined in Section 6 provide important context with which to evaluate possible changes to the Clozapine REMS.

8 Summary of FDA's Re-Evaluation of the REMS

Around the time of clozapine's approval in 1989, there was limited information on the risk of severe neutropenia from clinical trial data in United States and the healthcare environment was different than what it is today. Unlike clozapine, other antipsychotics approved at the time were not associated with the need for frequent ANC monitoring. General knowledge about monitoring and managing neutropenia was limited among psychiatrists. Obtaining a complete CBC with ANC wouldn't have been routinely performed by psychiatrists practicing at the time. Thus, additional strategies beyond labeling were necessary to educate healthcare providers and ensure that they completed the necessary ANC monitoring for patient safety.

Our updated assessment of the risk of clozapine-induced severe neutropenia confirms that what we know about the risk today is consistent with the currently approved labeling. Over the past 30 years, the agency has updated the labeling as more information about the risk and management of clozapine-induced severe neutropenia have evolved. What the data clearly demonstrate is that ANC monitoring has reduced fatalities associated with clozapine-induced severe neutropenia; thus, ANC monitoring is an important component of clinical care when treating patients with clozapine.

We revisited the two healthcare gaps that the Clozapine REMS is addressing. The first healthcare gap is *lack of widespread knowledge of the risk of severe neutropenia and need for frequent ANC monitoring.* Our updated gap assessment demonstrated that, despite some literature that suggests that inadequate training in or exposure to using clozapine remains a barrier to prescribing clozapine, generally today's providers have greater knowledge about the risk of clozapine-induced severe neutropenia and the need to monitor ANC compared to prescribers in 1989. Furthermore, training on management of patients who are prescribed clozapine is more broadly integrated into training and education for prescribers today than it was in 1989. There are also a variety of available resources outside of the REMS including practice guidelines for the treatment of schizophrenia and several common electronic resources used for clinical decision support.

For the second healthcare gap, *ANC monitoring wouldn't typically have been performed by psychiatrists practicing at the time*, we found evidence of ANC monitoring. Despite the REMS not being fully enforced since its initial approval in 2015, ANC monitoring is being performed, although less than what is recommended in labeling and the REMS, for the first 6 months. Unfortunately, what our updated healthcare gap assessment could not inform is the contribution of the REMS on adherence to the monitoring requirements. Thus, we do not know the impact that the REMS has on ANC monitoring behavior in prescribers of clozapine.

The question remains whether the REMS is still necessary to educate providers on the risks of clozapine and the need for ANC monitoring and ensure that healthcare providers perform ANC monitoring.

There are several factors to consider when re-evaluating whether the clozapine REMS is necessary to ensure the benefits of clozapine outweigh the risk of neutropenia. First, the REMS has been operating under enforcement discretion since shortly after approval, under which the Agency does not object to dispensing to patients without verifying safe use conditions in the REMS. It is unclear the extent to which the REMS itself is contributing to ensuring ANC monitoring is performed and reducing the risk of

severe neutropenia. Despite patients undergoing ANC monitoring less frequently than recommended in the label (especially in the first six months of treatment), very few cases of death and hospitalizations were seen in the studies we conducted. Second, clozapine has been approved for almost 40 years. The knowledge gap has narrowed while the availability of resources and practice guidelines has grown. Third, there are burden and access issues in patients with schizophrenia resulting in significant health disparities (Tiihonen et al. 2009; Cahoon et al. 2013; Farooq et al. 2019; Vermeulen et al. 2019), though not all can be attributed to the REMS. Fully implementing the REMS may result in more burden than what we are seeing today. The burden of the REMS must be weighed against the benefits of clozapine, which is currently the only treatment approved for treatment-resistant schizophrenia and it is also effective in reducing suicidality. Lastly, there are other healthcare gaps that contribute to burden and impact patient access to clozapine that will continue to exist regardless of whether the REMS is changed or eliminated to reduce burden. For example, healthcare provider's comfort and familiarity around prescribing clozapine as it is associated with other serious adverse effects, patient difficulty in accessing psychiatric care, fragmentation of services that should be coordinated (e.g., transition from inpatient to outpatient, insurance coverage), or rising costs of healthcare services will impact patient access to clozapine. Furthermore, changing or eliminating the REMS does not remove the need for prescribers to monitor ANCs.

Modifications to a REMS could include changes regarding how a requirement is implemented, the removal of specific requirements or even eliminating the REMS. It's important to consider how the REMS requirements are connected when considering modifications to the REMS. The elements in the Clozapine REMS are not exclusive of one another and in combination, if fully implemented, would form a closed system. For example, the pharmacy is responsible for confirming that the prescriber is trained by verifying he/she is certified, the patient is enrolled and has been monitored appropriately. If pharmacy certification was removed, none of the requirements would be able to be enforced. For example, it would not be possible to ensure that prescribers are trained and certified prior to prescribing clozapine or that monitoring was performed. Also consider, if we removed the requirement to document that ANC monitoring was performed, this would essentially also remove the patient registry, as no ANC test results would be collected under the REMS.

Based on the data gathered, the current state of ANC monitoring and the REMS requirements, and understanding the limitations with these studies, we observed very few cases of death associated with clozapine despite imperfect adherence to monitoring for neutropenia.

The Agency is seeking your input on possible changes to the REMS, including elimination of the program, to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of clozapine.

Specifically, we look forward to your input on the following:

- 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 ANC monitoring?
- How reassured or concerned are you that current and potential clozapine healthcare providers will perform ANC monitoring without the requirements of the REMS?
- 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?

- Is the requirement to educate healthcare providers on the risk of severe neutropenia and the need for ANC monitoring through the REMS necessary to ensure safe use?

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10 Appendix

10.1 ANC Monitoring per Clozapine Prescribing Information

Table 11. General Patient Population: Treatment Recommendations Based on ANC Monitoring

ANC Level	Treatment Recommendation	ANC Monitoring Frequency
Normal range (≥1500/μL)	• Initiate treatment • If treatment interrupted: – <30 days, continue monitoring as before – ≥30 days, monitor as if new patient	• Weekly from initiation to 6 months • Every 2 weeks from 6 to 12 months • Monthly after 12 months
Discontinuation for reasons other than neutropenia For more information, see Section 2.4 of the prescribing information		
Mild Neutropenia (1000 to 1499/μL)*	• Continue treatment	• Three times weekly until ANC ≥1500/μL • Once ANC ≥1500/μL, return to patient's last "Normal Range" ANC monitoring interval**
Moderate Neutropenia (500 to 999/μL)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine induced neutropenia • Resume treatment once ANC ≥1000/μL	• Daily until ANC ≥1000/μL, then • Three times weekly until ANC ≥1500/μL • Once ANC ≥1500/μL, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval**
Severe Neutropenia (less than 500/μL)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC ≥1000/μL, then • Three times weekly until ANC ≥1500/μL • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1500/μ

Source: adapted from Clozapine Prescribing Information Table 2
* Confirm all initial reports of ANC less than 1500/μL with a repeat ANC measurement within 24 hours
** If clinically appropriate
Abbreviation: ANC, absolute neutrophil count

Table 12. BEN Patient Population: Treatment Recommendations Based on ANC Monitoring

ANC Level	Treatment Recommendation	ANC Monitoring Frequency
Normal BEN range (Established ANC baseline ≥1000/μL)	• Initiate treatment • If treatment interrupted: – <30 days, continue monitoring as before – ≥30 days, monitor as if new patient	• Weekly from initiation to 6 months • Every 2 weeks from 6 to 12 months • Monthly after 12 months
Discontinuation for reasons other than neutropenia For more information, see Section 2.4 of the prescribing information		
BEN Neutropenia (500 to 999/μL)*	• Recommend hematology consultation • Continue treatment	• Three times weekly until ANC ≥1000/μL or ≥ patient's known baseline • Once ANC ≥1000/μL or at patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval.**
Severe neutropenia (less than 500/μL)*	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC ≥500/μL, then • Three times weekly until ANC ≥ patient's baseline • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1000/μL or at patient's baseline

Source: adapted from Clozapine Prescribing Information Table 3
* Confirm all initial reports of ANC less than 1500/μL with a repeat ANC measurement within 24 hours
** If clinically appropriate
Abbreviations: ANC, absolute neutrophil count; BEN, benign ethnic neutropenia

10.2 Additional Information for the Brigham and Women's Hospital (BWH) and Harvard Medical School Studies

10.2.1 Neutropenia-Related Hospitalization Among Clozapine Initiators in the United States

Objective

To evaluate the risk of severe neutropenia following treatment initiation with clozapine versus olanzapine, an alternative, second-generation antipsychotic often used for treatment-resistant schizophrenia.

Methods

We conducted a retrospective cohort study based on three longitudinal administrative claims data: Optum's de-identified Clinformatics Data Mart (2004-2022), Merative Marketscan (2003-2022), and Medicaid (2000-2018). The study cohort comprised new users of clozapine and olanzapine (oral formulation only), with new use defined as no dispensing of clozapine or olanzapine (any formulation) in the prior 6 months. Initiators were required to be at least 18 years old and to have continuous insurance plan enrollment, a recorded diagnosis of schizophrenia or schizoaffective disorder, and at least 1 dispensing of a different antipsychotic (not clozapine or olanzapine) in the prior 6 months.

For baseline characteristics, we searched for the encoded diagnoses and procedures within 6 months before the index date.

Outcome measures: The main definition for the severe neutropenia: hospitalization with an ICD-9-CM or ICD-10-CM codes for neutropenia in the primary position ("narrow definition"). The secondary definition of neutropenia-related outcomes: hospitalization with an ICD-9-CM or ICD-10-CM code for neutropenia in any position ("broad definition"). We assume the narrow definition captures patients hospitalized due to neutropenia; since we neither had ANC test results nor chart review to support the accuracy of the coding.

As the primary analysis, "as-treated" method, patients were followed from the day after the index date until the neutropenia-related hospitalization, death, end of insurance enrollment, end of data, admission to a nursing facility or hospice, filling a prescription for the other exposure group, or drug discontinuation (defined as a gap of greater than 30 days following the end of days' supply without a refill), whichever occurred first. The sensitivity analysis was based on the intent-to-treat (ITT) method; where patients were not censored for drug discontinuation.

To account for possibly inhomogeneous risk profiles among patients who received the two different antipsychotic drugs, a 1:1 propensity score (PS) matching was established, including age, sex, year of index, and all clinically relevant baseline comorbidities (total 101 baseline covariates). Balance for each matching was evaluated using risk differences, ensuring absolute standardized mean differences between covariates were less than 0.1. Kaplan-Meier survival analyses were used to assess the cumulative incidence over time. The IR of severe neutropenia per 1,000 person-years with 95% confidence intervals (CIs) and the corresponding IRRs were estimated at 6 months, 1 year, 2 years, and 3 years post-initiation, as well as over the entire follow-up.

Among clozapine initiators, we also evaluated IR for those who had a baseline ANC testing 30 days prior to or on the index data (adherent to REMS requirement) versus those who did not (nonadherent).

Results

The unmatched cohort included 21,718 clozapine initiators and 212,083 olanzapine initiators, whereas the matched cohort comprised 16,873 clozapine and olanzapine initiators each. Mean (SD) ages at the time of therapy initiation were 38.0 (13.7) and 39.2 (13.6) years for clozapine and olanzapine cohort, respectively; 54.9% and 54.3% were male. More than 80% of patients had public insurance. On average, 2 other antipsychotics were used during the 180 days prior to the index date, with 41% used quetiapine. A quarter of patients had a drug use disorder during baseline period. The rate of neutropenia-causing medications was 11% and 24% for both drugs assessed 30 days and 180-31 days prior to the index date, respectively (Table 13).

As-Treated Analysis

In the matched analysis, the median follow-up time was 175 days (interquartile range: 43-640 days) for clozapine initiators and 146 days (60-498 days) for olanzapine initiators for the as-treated analysis. At 6 months, using the narrow definition, there were 12 and <11 cases[30] in the clozapine and olanzapine cohort, respectively. The IR was 2.21 per 1,000 PYs (95% CI: 1.25-3.89) for clozapine and 0.18 per 1,000

[30] Counts less than 11 were suppressed under the Data Use Agreement for use/access of the Medicaid data.

PYs (95% CI: 0.03-1.29) for olanzapine, corresponding to an IRR of 12.18 (95% CI: 1.58-93.71). The IR was 5.89 (95% CI: 4.17-8.33) for clozapine and 2.72 (95% CI: 1.64-4.51) per 1,000 PYs for olanzapine using the broad definition, corresponding to an IRR of 2.17 (95% CI: 1.17-4.00).

At one year, using the narrow definition, the IR was 1.32 (95% CI: 0.75-2.33) for clozapine and 0.23 (95% CI: 0.06-0.92) per 1,000 PYs for olanzapine, corresponding to an IRR of 5.77 (95% CI: 1.29-25.76). At two years, the IR was 0.86 (0.49-1.52) and 0.16 (0.04-0.63) per 1,000 PYs for the two drugs, corresponding to an IRR of 5.50 (1.23-24.55). At three years, the IR was 0.7 (0.40-1.24) and 0.13 (0.03-0.52) per 1,000 PYs for the two drugs, corresponding to an IRR of 5.40 (1.21-24.13).

The IRRs attenuated with longer follow-up and were 4.13 (95% 1.19-14.36) under the narrow definition and 1.36 (95% CI: 0.84, 2.18) under the broad definition, when considering the entire follow-up. These IRR were based on a total of 14 and 3 events respectively for the narrow definition, and 43 events in the clozapine group and 28 events in the olanzapine group for the broad definition (Table 14).

Intent-to-Treat (ITT) Analysis

ITT analysis yielded similar results as the as-treated analysis; for both the narrow and broad definitions at the four time points post-initiation. In the matched analysis, the median follow-up time was 507 (IQR: 90 to 1414) and 566 (IQR: 147 to 1525) days for clozapine and olanzapine cohort for the ITT analysis. At 6 months, using the narrow definition, the IRs were 2.19 (95% CI: 1.30 to 3.69) and 0.15 (0.02 to 1.04) per 1,000 PYs for the two drugs, corresponding to an IRR of 14.86 (1.95 to 113.03).

The IRRs attenuated with longer follow-up and was 5.03 (95% CI: 1.71 to 14.78) under the narrow definition and 1.49 (1.02 to 2.16) under the broad definition, when considering the entire follow-up. These IRRs were based on a total of 19 and <11[31] events respectively for the two drugs under the narrow definition; and 66 and 47 events under the broad definition (Table 15).

REMS Adherers Versus Nonadherers

Among clozapine initiators, the mean (SD) follow-up times were 1.40 (2.29) and 1.46 (2.35) years for those who had a baseline ANC testing 30 days prior to or on the index date (adhere to REMS requirement) versus those who did not (non-adherence). Using the narrow definition, the IRs were 0.26 (95% CI: 0.10 to 0.70) and 0.70 (0.39 to 1.26) per 1,000 PYs for the adherers and non-adherers group, respectively, and yielded an IRR 0.38 (0.12 to 1.19). Using the broad definition, the IRs were 1.05 (0.65 to 1.72) and 1.90 (1.33 to 2.71) per 1,000 PYs for the adherers and non-adherers group, respectively, and yielded an IRR 0.56 (0.30 to 1.02).

Discussion

Our analysis of three U.S. health claims databases of patients on clozapine revealed that clozapine was associated with significantly worse outcomes in terms of severe neutropenia compared to olanzapine. In addition, having baseline ANC testing (fulfill the baseline monitoring requirement) was marginally associated with improved patient outcomes compared to outcomes for patients who did not have baseline ANC testing.

[31] Counts less than 11 were suppressed under the Data Use Agreement for use/access of the Medicaid data.

The majority of the severe neutropenia events (neutropenia-related hospitalization) occurred within the first 6 months of clozapine initiation.

There are several study limitations. First, we do not have information on ANC test results; therefore, the severe neutropenia outcome definition is based only on the diagnosis code of hospital admission with an ICD-9-CM or ICD-10 code for neutropenia. To improve the accuracy of outcome event estimation, the narrow definition for the severe neutropenia was limited to the primary position, which is a specific diagnosis of neutropenia and agranulocytosis. Further validation would require chart review and ANC testing results. Second, the study is unable to evaluate clinical outcomes, such as mild or moderate neutropenia and agranulocytosis, without ANC test results. Third, low ANC counts would necessitate more frequent testing, which may lead to detection bias. Forth, patients may have more days' supply (stockpiling) than what was reflected in the claims data; therefore, patients may not be included in the follow up and, thus, may miss outcomes during the treatment period. All patients in our study were insured, either through private or public insurance; thus, missing data on clozapine dispensings are unlikely. Finally, the results might not be generalizable to patients who receive clozapine but are not insured. It is possible that patients without health insurance are more susceptible to both testing and treatment nonadherence.

Table 13. Patient Characteristics at the Time of Clozapine Initiation, Matched Cohort, 2000 to 2020

Covariate	Clozapine*	Olanzapine*	SMD
N	16,873	16,873	
Demographics			
Age (in years); mean (SD)	38.0 (13.7)	39.2 (13.6)	.090
Age Groups; N (%)			
18-54	14621 (86.65)	14643 (86.78)	.004
55-64	1875 (11.11)	1880 (11.14)	.001
65-74	245 (1.45)	228 (1.35)	-.009
75+	132(0.78)	122 (0.72)	-.007
Sex; N (%)			
Male	9259 (54.87)	9167 (54.33)	-.011
Female	7614 (45.13)	7706 (45.67)	.011

Covariate	Clozapine*	Olanzapine*	SMD
Calendar time (Index Year); N (%)			
2000	449 (2.66)	446 (2.64)	-.001
2001	750 (4.44)	667 (3.95)	-.024
2002	654 (3.88)	636 (3.77)	-.006
2003	927 (5.49)	880 (5.22)	-.012
2004	914 (5.42)	918 (5.44)	.001
2005	819 (4.85)	850 (5.04)	.009
2006	1048 (6.21)	1042 (6.18)	-.001
2007	940 (5.57)	941 (5.58)	.000
2008	1009 (5.98)	1069 (6.34)	.015
2009	1111(6.58)	1115 (6.61)	.001
2010	952 (5.64)	933 (5.53)	-.005
2011	944 (5.59)	1036 (6.14)	.023
2012	1011 (5.99)	1033 (6.12)	.005
2013	1005 (5.96)	1044 (6.19)	.010
2014	929 (5.51)	962 (5.71)	.002
2015	791 (4.69)	779 (4.62)	-.003
2016	609 (3.61)	561 (3.32)	-.016
2017	650 (3.85)	638 (3.78)	-.004
2018	698 (4.14)	683 (4.05)	-.005
2019	181(1.07)	195 (1.16)	.009
2020	184 (1.09)	158 (0.94)	-.015
2021	185 (1.10)	170 (1.01)	-.009
2022	113 (0.67)	117 (0.69)	.002
Region; N (%)			
Midwest (NorthCentral in MARKETSCAN)	5224 (30.96)	5385 (31.91)	.020
Northeast	3839 (22.75)	3867(22.92)	.004
South	4304 (25.51)	4255 (25.22)	-.007
West	3489 (20.68)	3353 (19.87)	-.020
Unknown / Other	17 (0.10)	13 (0.08)	-.007
Insurance type			
Commercial	3012 (17.85)	2975 (17.63)	-.006
Public	13861 (82.15)	13898 (82.37)	.006

Covariate	Clozapine*	Olanzapine*	SMD
Prior use of antipsychotic therapy (not including the index date); N (%)			
Number of different antipsychotic drugs used during baseline; Mean (SD)	1.9 (0.9)	1.9 (1.0)	-.010
Aripiprazole	3463 (20.52)	3466 (20.54)	.000
Asenapine	378 (2.24)	412 (2.44)	.013
Brexpiprazole	62 (0.37)	65 (0.39)	.003
Cariprazine	124 (0.73)	117 (0.69)	-.005
Chlorpromazine	1152 (6.83)	1123 (6.66)	-.007
Fluphenazine	1598 (9.47)	1579 (9.36)	-.004
Haloperidol	4918 (29.15)	4928 (29.21)	.001
Iloperidone	203 (1.20)	184 (1.09)	-.010
Loxapine	389 (2.31)	351 (2.08)	-.016
Lumateperone	14 (0.08)	12 (0.07)	-.004
Lurasidone	787 (4.66)	761 (4.51)	-.007
Mesoridazine	19 (0.11)	22 (0.13)	.006
Molindone	52 (0.31)	45 (0.27)	-.007
Paliperidone	1735 (10.28)	1729 (10.25)	-.001
Perphenazine	698 (4.14)	677 (4.01)	-.007
Pimavanserin	22 (0.13)	23 (0.14)	.003
Pimozide	19 (0.11)	16 (0.09)	-.006
Prochlorperazin	103 (0.61)	117 (0.69)	.010
Quetiapine	6970 (41.31)	6964 (41.27)	-.001
Risperidone	6742 (39.96)	6710 (39.77)	-.004
Thioridazine	118 (0.70)	113 (0.67)	-.004
Thiothixene	323 (1.91)	308 (1.83)	-.006
Trifluoperazine	182 (1.08)	141 (0.84)	-.025
Ziprasidone	2688 (15.93)	2685 (15.91)	-.001
Concomitant initiation of other antipsychotic therapy; N (%)			
Number of different antipsychotic drugs used on index date; Mean (SD)	0.2 (0.5)	0.2(0.5)	-.020
Aripiprazole	267 (1.58)	284 (1.68)	.008
Asenapine	16 (0.09)	17 (0.10)	.003
Brexpiprazole	<11	<11	.012
Cariprazine	<11	<11	.005
Chlorpromazine	148 (0.88)	141 (0.84)	-.004
Fluphenazine	206 (1.22)	203 (1.20)	-.002
Haloperidol	804 (4.77)	829 (4.91)	.007
Iloperidone	<11	<11	.000
Loxapine	27 (0.16)	22 (0.13)	-.008
Lurasidone	41 (0.24)	39 (0.23)	-.002
Mesoridazine	<11	<11	-.008
Molindone	<11	<11	-.020
Paliperidone	121 (0.72)	105 (0.62)	-.012
Perphenazine	82 (0.49)	81 (0.48)	-.001
Pimavanserin	<11	<11	.000
Pimozide	<11	<11	.000
Prochlorperazin	<11	<11	-.012
Quetiapine	798 (4.73)	742 (4.40)	-.016
Risperidone	693 (4.11)	691 (4.10)	-.001
Thioridazine	<11	<11	.005
Thiothixene	32 (0.19)	30 (0.18)	-.002
Trifluoperazine	15 (0.09)	<11	-.011
Ziprasidone	217 (1.29)	210 (1.24)	-.004

Covariate	Clozapine*	Olanzapine*	SMD
Neutropenia-related conditions (assessed during 30 days prior to index date)			
Neutropenia	136 (0.81)	85 (0.50)	-.038
Pneumonia	202 (1.20)	210 (1.24)	.004
Hospitalization with infection	740 (4.39)	733 ram (4.34)	-.002
Crohn's disease	13 (0.08)	19 (0.11)	.010
Rheumatoid arthritis	38 (0.23)	48 (0.28)	.010
Lupus	13 (0.08)	15 (0.09)	.003
Aplastic anemia	<11	<11	.000
Neutropenia treatment	<11	<11	-.014
Neutropenia-causing medications	1871 (11.09)	1867 (11.07)	-.001
Neutropenia-related conditions (assessed during 180 -31 days prior to index date*)*			
Neutropenia	94 (0.56)	83 (0.49)	-.010
Pneumonia	488 (2.89)	514 (3.05)	.009
Hospitalization with infection	1345 (7.97)	1343 (7.96)	.000
Crohn's disease	28 (0.17)	22 (0.13)	-.010
Rheumatoid arthritis	71 (0.42)	72 (0.43)	.002
Lupus	20 (0.12)	17 (0.10)	-.006
Aplastic anemia	<11	22 (0.13)	.027
Neutropenia-causing medications	4027 (23.87)	4092 (24.25)	.009
Other comorbidities			
Dementia	713 (4.23)	734 (4.35)	.006
Parkinson’s disease	426 (2.52)	421 (2.50)	-.001
Bipolar and anxiety disorders	8815 (52.24)	8936 (52.96)	.014
Drug use disorder	4420 (26.20)	4370 (25.90)	-.007
Ischemic heart disease	723 (4.28)	737 (4.37)	.004
Acute kidney injury	311 (1.84)	301 (1.78)	-.005
Chronic kidney disease	333 (1.97)	329 (1.95)	-.001
Liver disease	910 (5.39)	899 (5.33)	-.003
Combined comorbidity score	1.7 (1.4)	1.7 (1.4)	.000
Prior use of medications			
Trihexyphenidyl	833 (4.94)	819 (4.85)	-.004
Benztropine	7933 (47.02)	7982 (47.31)	.006
Other Parkinson’s disease medications	411 (2.44)	413 (2.45)	.001
Dementia medications	369 (2.19)	373 (2.21)	.001
Antidepressants	10,210 (60.51)	10,101 (59.86)	-.013
Anticonvulsants	9113 (54.01)	9185 (54.44)	.009
Lithium	2872 (17.02)	2906 (17.22)	.005
Benzodiazepines	8509 (50.43)	8510 (50.44)	.000
Other anxiolytics/hypnotics	3768 (22.33)	3727 (22.09)	-.006
Barbiturates	81 (0.48)	95 (0.56)	.011

Covariate	Clozapine*	Olanzapine*	SMD
Healthcare utilization (assessed over 180 days prior to initiation and including the index date unless otherwise specified); Mean (SD)			
Number of hospitalizations	1.4 (2.4)	1.3 (2.3)	-.030
Number of ER visits	2.2 (4.0)	2.2 (3.5)	.010
Number of outpatient visits	2.7 (3.9)	2.7 (4.0)	.000
Number of unique drugs dispensed	11.6 (6.4)	11.6 (7.0)	.010
Number of hospitalizations with psychiatric diagnosis	1.1 (1.8)	1.0 (2.0)	-.030
Number of outpatient visits with psychiatric diagnosis	1.5 (2.8)	1.5 (3.1)	.000
Number of hospitalizations in 30 days prior to initiation and including the index date	0.4 (1.0)	0.5 (0.9)	.030
Number of hospitalizations with psychiatric diagnosis in 30 days prior to initiation and including the index date	0.4 (0.8)	0.4 (0.9)	-.010
Number of outpatient visits with psychiatric diagnosis in 30 days prior to initiation and including the index date	0.3 (0.8)	0.3 (0.8)	.050
Office visits with psychiatric diagnosis in 180 days prior to initiation and including the index date; N (%)	7356 (43.60)	7330 (43.44)	-.003

Source: Generated from the study results.

Abbreviations: N, number of patients, SMD, standardized mean differences

*Counts less than 11 were suppressed under the Data Use Agreement for use/access of the Medicaid data

Table 14. Risk of Severe Neutropenia: As-Treated Analysis

	Narrow Definition: Inpatient Diagnosis of Neutropenia in Primary Position				Broad Definition: Inpatient Diagnosis of Neutropenia in Any Position			
	Before Matching		After Matching		Before Matching		After Matching	
Treatment Interval	Clozapine (N=21,718)	Olanzapine (N=212,083)	Clozapine (N=16,873)	Olanzapine (N=16,873)	Clozapine (N=21,718)	Olanzapine (N=212,083)	Clozapine (N=16,873)	Olanzapine (N=16,873)
Follow-up; Median (IQR) in days	155 (37-611)	148 (60-505)	175 (43-640)	146 (60-498)	155 (37-611)	148 (60-504)	175 (43-640)	146 (60-497)
Full follow-up								
Events; N	15	23	14	<11	46	244	43	28
IR per 1000 person-years (95% CI)	0.48 (0.29-0.8)	0.08 (0.05-0.12)	0.56 (0.33-0.94)	0.13 (0.04-0.42)	1.48 (1.11-1.98)	0.87 (0.76-0.98)	1.71 (1.27-2.30)	1.26 (0.87-1.82)
IRR (95% CI)	5.94 (3.10-11.38)		4.13 (1.19-14.36)		1.72 (1.25-2.35)		1.36 (0.84-2.18)	
6 months								
Events; N	13	<11	12	<11	34	104	32	15
Cumulative Incidence; %	0.09 (0.05-0.15)	0.003 (0.001-0.007)	0.1 (0.06-0.17)	0.007 (0.0008-0.04)	0.22 (0.15-0.30)	0.07 (0.05-0.08)	0.25 (0.18-0.36)	0.11 (0.06-0.18)
IR per 1000 person-years (95% CI)	1.92 (1.11-3.30)	0.07 (0.03-0.17)	2.21 (1.25-3.89)	0.18 (0.03-1.29)	5.01 (3.58-7.02)	1.48 (1.22-1.80)	5.89 (4.17-8.33)	2.72 (1.64-4.51)
IRR (95% CI)	26.90 (9.59-75.47)		12.18 (1.58-93.71)		3.38 (2.30-4.98)		2.17 (1.17-4.00)	
1 year								
Events; N	13	<11	12	<11	36	139	34	21
Cumulative Incidence; %	0.09 (0.05-0.15)	0.009 (0.005-0.02)	0.1 (0.06-0.17)	0.02 (0.005-0.09)	0.24 (0.17-0.34)	0.11 (0.09-0.13)	0.29 (0.20-0.40)	0.22 (0.13-0.34)
IR per 1000 person-years (95% CI)	1.15 (0.67-1.99)	0.09 (0.05-0.17)	1.32 (0.75-2.33)	0.23 (0.06-0.92)	3.2 (2.31-4.43)	1.26 (1.07-1.49)	3.75 (2.68-5.25)	2.41 (1.57-3.70)
IRR (95% CI)	12.73 (5.58-29.03)		5.77 (1.29-25.76)		2.54 (1.76-3.66)		1.56 (0.90-2.68)	
2 years								
Events; N	13	13	12	<11	39	184	37	22
Cumulative Incidence; %	0.09 (0.05-0.15)	0.02 (0.008-0.03)	0.1 (0.06-0.17)	0.02 (0.005-0.09)	0.29 (0.20-0.39)	0.2 (0.17-0.24)	0.34 (0.24-0.47)	0.24 (0.15-0.37)
IR per 1000 person-years (95% CI)	0.75 (0.44-1.30)	0.08 (0.05-0.14)	0.86 (0.49-1.52)	0.16 (0.04-0.63)	2.26 (1.65-3.10)	1.14 (0.99-1.32)	2.66 (1.93-3.68)	1.73 (1.14-2.63)
IRR (95% CI)	9.34 (4.33-20.16)		5.50 (1.23-24.55)		1.98 (1.40-2.80)		1.54 (0.91-2.61)	

	Narrow Definition: Inpatient Diagnosis of Neutropenia in Primary Position				Broad Definition: Inpatient Diagnosis of Neutropenia in Any Position			
	Before Matching		After Matching		Before Matching		After Matching	
Treatment Interval	Clozapine (N=21,718)	Olanzapine (N=212,083)	Clozapine (N=16,873)	Olanzapine (N=16,873)	Clozapine (N=21,718)	Olanzapine (N=212,083)	Clozapine (N=16,873)	Olanzapine (N=16,873)
3 years								
Events; N	13	14	12	<11	42	207	39	23
Cumulative Incidence; %	0.09 (0.05-0.15)	0.02 (0.01-0.03)	0.10 (0.06-0.17)	0.02 (0.005-0.09)	0.36 (0.25-0.51)	0.27 (0.23-0.32)	0.40 (0.28-0.58)	0.27 (0.17-0.43)
IR per 1000 person-years (95% CI)	0.61 (0.36-1.06)	0.07 (0.04-0.12)	0.7 (0.40-1.24)	0.13 (0.03-0.52)	1.99 (1.47-2.69)	1.07 (0.93-1.23)	2.29 (1.67-3.13)	1.5 (1.00-2.26)
IRR (95% CI)	8.49 (3.99-18.07)		5.40 (1.21-24.13)		1.86 (1.33-2.59)		1.53 (0.91-2.55)	

Source: Generated from the study results.

Abbreviations: CI, confidence Interval; IR, incidence rate; IRR, incidence rate ratio; N, number of patients

Table 15. Risk of Severe Neutropenia: Intent-To-Treat Analysis

	Narrow Definition: Inpatient Diagnosis of Neutropenia in Primary Position				Broad Definition: Inpatient Diagnosis of Neutropenia in Any Position			
	Before Matching		After Matching		Before Matching		After Matching	
Treatment Interval	Clozapine (N=21,718)	Olanzapine (N=212,083)	Clozapine (N=16,873)	Olanzapine (N=16,873)	Clozapine (N=21,718)	Olanzapine (N=212,083)	Clozapine (N=16,873)	Olanzapine (N=16,873)
Follow-up; Median (IQR) in days	482 (71-1393)	566 (160-1430)	507 (90-1414)	566 (147-1525)	480 (70-1390)	564 (159-1427)	506 (90-1410)	563 (146-1523)
Full follow-up								
Events; N	20	65	19	<11	76	525	66	47
IR per 1000 person-years (95% CI)	0.35 (0.23-0.54)	0.11 (0.08-0.13)	0.42 (0.27-0.65)	0.08 (0.03-0.22)	1.34 (1.07-1.67)	0.85 (0.78-0.93)	1.45 (1.14-1.84)	0.97 (0.73-1.29)
IRR (95% CI)	3.33 (2.01-5.49)		5.03 (1.71-14.78)		1.56 (1.23-1.99)		1.49 (1.02-2.16)	
6 months								
Events; N	15	<11	14	<11	43	138	39	16
Cumulative Incidence; %	0.09 (0.05-0.15)	0.005 (0.003-0.01)	0.11 (0.06-0.18)	0.007 (0.0008-0.04)	0.25 (0.19-0.34)	0.08 (0.07-0.09)	0.29 (0.21-0.40)	0.11 (0.07-0.18)
IR per 1000 person-years (95% CI)	1.87 (1.13-3.10)	0.1 (0.05-0.20)	2.19 (1.30-3.69)	0.15 (0.02-1.04)	5.35 (3.97-7.22)	1.59 (1.35-1.88)	6.1 (4.46-8.35)	2.36 (1.44-3.85)
IRR (95% CI)	17.99 (7.87-41.10)		14.86 (1.95-113.03)		3.36 (2.39-4.74)		2.59 (1.45-4.63)	

	Narrow Definition: Inpatient Diagnosis of Neutropenia in Primary Position				Broad Definition: Inpatient Diagnosis of Neutropenia in Any Position			
	Before Matching		After Matching		Before Matching		After Matching	
Treatment Interval	Clozapine (N=21,718)	Olanzapine (N=212,083)	Clozapine (N=16,873)	Olanzapine (N=16,873)	Clozapine (N=21,718)	Olanzapine (N=212,083)	Clozapine (N=16,873)	Olanzapine (N=16,873)
1 year								
Events; N	15	20	14	<11	47	215	42	26
Cumulative Incidence; %	0.09 (0.05-0.15)	0.01 (0.008-0.02)	0.11 (0.06-0.18)	0.02 (0.004-0.06)	0.29 (0.21-0.38)	0.13 (0.12-0.15)	0.32 (0.24-0.43)	0.20 (0.14-0.29)
IR per 1000 person-years (95% CI)	1.02 (0.62-1.69)	0.13 (0.08-0.20)	1.2 (0.71-2.02)	0.16 (0.04-0.64)	3.2 (2.41-4.26)	1.36 (1.19-1.56)	3.59 (2.66-4.86)	2.1 (1.43-3.08)
IRR (95% CI)	5.71 (3.05-10.70)		7.40 (1.68-32.58)		2.35 (1.72-3.23)		1.71 (1.05-2.79)	
2 years								
Events; N	15	28	14	<11	51	316	46	29
Cumulative Incidence; %	0.09 (0.05-0.15)	0.02 (0.01-0.03)	0.11 (0.06-0.18)	0.02 (0.004-0.06)	0.32 (0.24-0.42)	0.23 (0.20-0.25)	0.37 (0.27-0.49)	0.23 (0.16-0.34)
IR per 1000 person-years (95% CI)	0.6 (0.36-1.00)	0.11 (0.07-0.15)	0.7 (0.42-1.19)	0.1 (0.02-0.38)	2.04 (1.55-2.69)	1.19 (1.06-1.32)	2.32 (1.74-3.09)	1.38 (0.96-1.99)
IRR (95% CI)	5.71 (3.05-10.70)		7.40 (1.68-32.58)		1.72 (1.28-2.31)		1.68 (1.05-2.67)	
3 years								
Events; N	15	35	14	<11	58	391	50	33
Cumulative Incidence; %	0.09 (0.05-0.15)	0.03 (0.02-0.04)	0.11 (0.06-0.18)	0.02 (0.004-0.06)	0.41 (0.31-0.53)	0.32 (0.29-0.35)	0.43 (0.32-0.57)	0.30 (0.20-0.42)
IR per 1000 person-years (95% CI)	0.46 (0.28-0.76)	0.1 (0.07-0.14)	0.54 (0.32-0.91)	0.07 (0.02-0.29)	1.78 (1.37-2.30)	1.13 (1.02-1.25)	1.93 (1.46-2.54)	1.2 (0.85-1.69)
IRR (95% CI)	4.54 (2.48-8.31)		7.42 (1.69-32.63)		1.57 (1.19-2.07)		1.61 (1.03-2.49)	

Source: Generated from the study results.

Abbreviations: CI, confidence Interval; IR, incidence rate; IRR, incidence rate ratio; N, number of patients

10.2.2 Prevalence and Frequency of ANC Testing in Patients Initiating Clozapine in the United States

Objective

To assess the prevalence and frequency of hematologic testing in patients initiating clozapine.

Methods

Data came from three U.S. national claims databases: a public health insurance program, Medicaid database (2000 to 2018); and two commercial health insurance databases: Optum's de-identified Clinformatics® Data Mart database (2004 to March 31, 2022); and the Merative Marketscan database (2003 to 2020). Individuals who initiated clozapine with at least 6 months of continuous insurance enrollment and no clozapine use were included.

Main outcome: (1) Proportion of study individuals with at least 1 hematologic test prior to clozapine initiation; and (2) frequency of testing (N tests per 30 days) per patient during Months 0-6, 7-12, and 13-24 from the index date. Tests were identified based on billing and revenue codes; patients hospitalized during the assessment period were assumed to receive testing. Patients could contribute multiple clozapine initiation episodes.

Results

We identified a total of 62,003 clozapine initiations in 54,169 individuals eligible for inclusion in the study, with 51,738 (84%) represented by the Medicaid population. Mean age at the time of therapy initiation was 36 years (SD 15); 57% were male. Most patients 46,569 (75%) used at least one other antipsychotic during the 6 months prior to clozapine initiation. A quarter of patients (15,417; 25%) were hospitalized within 30 days before the start of therapy; 13,094 (21%) had a concurrent diagnosis code for a drug use disorder. Mean days' supply for the initial clozapine prescription was 12.7 days (SD 9.8), with a median of 7 days (IQR: 7-14).

Testing Prevalence Prior to Initiation

About two-thirds (38,754; 63%) of initiations had claims-based evidence of a hematologic test within 31 days prior to clozapine initiation. This number increased to 43,876 (71%) when the baseline period was extended to 60 days prior to clozapine initiation. The proportion of patients with claims for any WBC test was higher (67% within 31 days and 75% within 60 days) than when the test definition was restricted to WBC differential (Table 16). With the further addition of an ER visit to the definition, 70% had a test within 31 days and 78% had a test within 60 days (Table 16). Results were similar between Medicaid and MarketScan enrollees; Optum Clinformatics enrollees had a slightly higher observed prevalence of testing (data not shown).

Testing Prevalence and Frequency During Treatment

Out of 62,003 patients initiating clozapine, 52,217 (84%) had at least one refill within 30 days following the end of the days' supply of the initial clozapine dispensing and were thus eligible for the analysis of testing frequency during treatment. During the first assessment period, covering the first 6 months, these patients stayed on treatment and under follow-up for a mean of 133 days (SD 64, median 182 days) and had a mean of 12.6 (SD 9.2; median 10, IQR: 5-22) clozapine dispensings with mean of 10

days' supply (SD 7.2; median 7 days; IQR:7-7). During this period, the mean number of tests per patient per 30 days was 2.2 (SD 1.8; median 2.1, IQR: 0.3-3.8), and 10,263 (20%) patients had no claims-based evidence of ANC testing (Table 16 and Table 17). With the most expanded definition of a test (code or hospitalization or ER visit), the mean testing rate per patient per 30 days was 2.7 (SD 2.3). Optum enrollees had the highest testing rate (mean 2.4; median 2.6, IQR: 0.8-4.0).

There were 28,428 patients still on treatment and under follow-up on Day 183 of treatment, and therefore, eligible for the second post-initiation assessment period (Months 7-12, covering days 183-365 of treatment). The mean number of clozapine dispensings during this period was 11.5 (SD 7.0; median 11, IQR: 6-15) with a mean days' supply of 13 days (SD 8; median 14, IQR: 7-14). The mean and median rates of testing during the 7-12 month period were 1.7 tests (SD 1.4) and 1.6 tests (IQR: 0.3-2.5) per patient per 30 days; 5,605 (20%) patients had no claims-based evidence of testing (Table 16 and Table 17).

There were 19,718 patients still on treatment and under follow-up on Day 366, and therefore, eligible for the analysis of testing during Months 13-24 (days 366-731 of treatment). During this period, patients received a mean of 16.2 dispensings (SD 11.7; median 14, IQR: 9-23) with the mean days' supply across all clozapine dispensings of 17 days (SD 9; median 14, IQR: 7-28). The mean rate of testing during Months 13-24 of treatment was 1.3 tests (SD 1.1) per patient per 30 days; 2,939 (15%) patients had no claims-based evidence of testing (Table 16 and Table 17).

Sensitivity Analyses

Out of 62,003 clozapine initiations, 1555 (3%) patients had no medical claims during the 180-day baseline period prior to clozapine initiation. Sensitivity analyses on 60,448 individuals with evidence of medical claims yielded similar results: with the main definition of a test, 64% of individuals initiating clozapine had evidence of a test within 31 days prior to initiation (73% had a test within 60 days prior to initiation); the mean testing rate after clozapine initiation was 2.2 (SD 1.8) tests per patient per 30 days during days 1-182; 1.7 (SD 1.4) tests per patient per 30 days during Months 7-12, and 1.3 (SD 1.1) tests per patient per 30 days during Months 13-24 of treatment.

Discussion

In this study of more than 60,000 clozapine initiations covering 2000-2022, we observed that about 30% of patients had no claims-based evidence of hematologic testing within 60 days prior to clozapine initiation. Most patients' initial clozapine prescription consisted of a 7-day supply. Among those obtaining refills, the mean rate of testing after clozapine initiation was 2.2 tests per 30 days during the first 6 months of treatment, less than the goal of 4 tests per 30 days. Observed testing rates were in line with REMS requirements during Months 7-12 (2 test per month) and 13-24 (1 test per month) of treatment.

In this study of individuals initiating clozapine in the United States, ANC hematologic testing recorded in claims data was completed at a lower-than-expected rate prior to clozapine initiation and during the first 6 months of treatment but was mostly in accordance with REMS requirements thereafter. The impact of these findings on the occurrence of severe neutropenia is not known.

The data and the study have two limitations. First, information on the occurrence of ANC testing could be missing from the claims data, therefore underestimating the true testing rate. Second, the data lack

information on laboratory values; patients with low ANC would require more frequent testing. Third, missing data on clozapine dispensings are unlikely, although possible if patients paid for the drug out-of-pocket rather than through insurance. All patients in the study were insured; thus, the results might not be generalizable to patients who receive clozapine but are not insured. It is possible that patients without health insurance are more susceptible to both testing and treatment nonadherence.

Table 16. Prevalence of ANC Testing Before and After Clozapine Initiation

	Before Treatment Initiation		After Treatment Initiation		
Test Definition	-31 to 0 Days (n=62003) n (%)	-60 to 0 Days (n=62003) n (%)	Days 1-182 (n=52217) n (%)	Days 183-365 (n=28428) n (%)	Days 366-731 (n=19718) n (%)
Main*	38754 (62.5)	43876 (70.8)	41954 (80.3)	22823 (80.3)	16779 (85.1)
Sensitivity					
Any WBC, revenue code, or hospitalization	41544 (67.0)	46116 (74.4)	43808 (83.9)	23836 (83.8)	17276 (87.6)
Any WBC, revenue code, hospitalization, or ER visit	43362 (69.9)	48263 (77.8)	44853 (85.9)	24322 (85.6)	17637 (89.4)

Source: Generated from the study results.
*Main definition included CPT codes for WBC differential or a hospitalization
Abbreviations: ER, emergency room; n, number of tests; WBC, white blood count

Table 17. Frequency of Hematologic Testing After Clozapine Initiation

Test Definition/Measure	Day 1-182 (n=52217) n Tests per 30 Days	Day 183-365 (n=28428) n Tests per 30 Days	Day 366-731 (n=19718) n Tests per 30 Days
Main*			
Testing rate per 30 days, mean (SD)	2.2 (1.8)	1.7 (1.4)	1.3 (1.1)
Testing rate per 30 days, median (IQR)	2.1 (0.3, 3.8)	1.6 (0.3, 2.5)	1.1 (0.5, 1.9)
Sensitivity, any WBC test, revenue codes (chemistry or hematology), or hospitalization			
Testing rate per 30 days, mean (SD)	2.6 (2.2)	2.0 (1.8)	1.5 (1.4)
Testing rate per 30 days, median (IQR)	2.6 (0.8, 4.1)	2.0 (0.7, 2.6)	1.2 (0.7, 2.0)
Sensitivity, any WBC test, revenue codes (chemistry or hematology), hospitalization, or ER visit			
Testing rate per 30 days, mean (SD)	2.7 (2.3)	2.1 (1.9)	1.6 (1.5)
Testing rate per 30 days, median (IQR)	2.8 (0.9, 4.1)	2.0 (0.8, 2.8)	1.3 (0.8, 2.1)

Source: Generated from the study results.
* Main definition included CPT codes for WBC differential or a hospitalization
Abbreviations: ER, emergency room; IQR, interquartile range (25th to 75th percentile); n, number of tests; SD, standard deviation; WBC, white blood count

10.2.3 A National Survey of Physicians' Experiences and Perspectives Prescribing Clozapine for Psychiatric Disorders

Objective

To understand how the Clozapine REMS Program has impacted clinical practice.

Methods

Survey Instrument and Recruitment

We created and tested a survey instrument with 57 closed-field questions using 5-point Likert scales around three topics: (1) the prescriber certification process, (2) the process for initiating a patient on clozapine, and (3) the safe use requirement. From IQVIA, we purchased contact information for 750 randomly drawn US-based physicians recorded as having prescribed clozapine in 2021 or 2022.

Analyses

The response rate was calculated using the American Association of Public Opinion Research third standard definition (American Association for Public Opinion Research 2023). Responses from partially completed surveys were included, with descriptive statistics for each question calculated based on the number of received responses.

Multivariable logistic regression modeling was used to examine predictors of physicians dissatisfied with the Clozapine REMS program. For this model, a negative perception variable was constructed based on "somewhat disagree" or "strongly disagree" responses to either 1 of 2 statements: "overall, the positives of the provider certification process for clozapine outweigh the negatives" and "overall, the patient safe use requirements for clozapine outweigh the negatives." Covariates in the model included gender, race, practice specialty, practice setting, practice region, professional time in clinical practice, years since graduation from medical school, and the number of patients prescribed clozapine in the past 3 years.

The Mass General Brigham Institutional Review Board and the FDA's Research Involving Human Subjects Committee approved the study. Analyses were performed using SAS v. 9.4.

Results

In total, 196 physicians (30% response rate) returned a partially or fully completed survey. Most were male (129, 67%), White (124, 63%), or Asian (48, 25%); most were psychiatrists (165, 86%); and most practiced in an outpatient group setting (88, 45%) (Table 18).

Perceptions of Clozapine Risk

A majority of respondents (115, 64%) ranked severe neutropenia as the biggest concern among four drugs risks: (1) severe neutropenia, (2) orthostatic hypotension, bradycardia, or syncope, (3) pulmonary embolism, and (4) seizure. One-fourth (43, 24%) ranked orthostatic hypotension, bradycardia, or syncope first.

Prescriber Certification

Of the physicians responding to the survey, 83% reported they recall "very well" to "Slightly well" the certification process that allowed them to begin to prescribe clozapine. Although 17% reported they could not recall well, more than 97% of respondents reported the certification process provided information on the risk of severe neutropenia.

About two-thirds (123, 64%) of respondents agreed that the positives of the certification process outweighed the negatives. A similar proportion (128, 66%) agreed it was reasonable that certification

was required to prescribe clozapine and not for other drugs they used to treat schizophrenia, while half (99, 51%) found completing the certification process easy (Figure 7). Almost all (179, 92%) respondents agreed that the certification process clearly explained the testing required of patients taking clozapine, and three-fourths (145, 75%) agreed it provided useful information about the drug, including on the risk of severe neutropenia (190, 97%).

When asked how the certification process could be improved, over two-thirds of respondents agreed that educational materials should include information on all clinically important risks of clozapine (172, 89%) and a summary of how well clozapine is expected to work (139, 72%).

Blood Testing Requirement

As with the certification process, two-thirds (129, 68%) of respondents agreed that the positives of the safe use requirement for clozapine—blood testing—outweighed the negatives. Three-fourths (150, 77%) agreed that the safe use requirement was clinically necessary, and half (102, 53%) agreed that paperwork associated with the safe use requirement facilitated discussion about clozapine with patients (Figure 8). Almost all respondents reported discussing the risk of severe neutropenia with patients always or almost always (171, 88%) or most of the time (9, 5%). Over half (118, 61%) of respondents reported that their patients always or almost always adhered to the blood testing schedule set forth in the REMS program, and over one-quarter (56, 29%) most of the time.

However, almost half (85, 44%) of respondents reported that testing under the Clozapine REMS Program was somewhat or very hard, with majorities agreeing that the safe use requirement was burdensome for patients (135, 71%) and often caused a delay in patients receiving clozapine (115, 60%).

Multivariable Analysis

In the multivariable model, a negative perception of the Clozapine REMS program was associated with two variables: years since medical school and race. Respondents in practice longer were less likely to have a negative view (≥35 versus <15 years since medical school: odds ratio [OR]=0.28, 95% confidence interval (CI)=0.10 to 0.80]); as were non-white, non-Asian respondents compared to white respondents (OR =0.08, 95% CI 0.01-0.73).

Discussion

In this national survey, two-thirds of physician prescribers of clozapine who responded agreed that the positive features of the Clozapine REMS Program outweighed the negatives. Underlying this perspective, a majority of physicians ranked neutropenia as the foremost clozapine risk, while a larger proportion identified positive elements of each REMS component. Two-thirds of respondents agreed that the blood testing outweighed the negatives; and three-fourths agreed it was clinically necessary. A large majority of physicians also agreed that the blood testing requirement often caused a delay in patients receiving their medication.

As with all surveys, our study was subject to participation, recall, and response biases. Specifically, it is possible that physicians who did not feel strongly about the Clozapine REMS Program were less likely to participate, that respondents' memory of the certification process was poor, and that respondents felt pressured to respond in certain ways. We sought to reduce this bias by inviting a random sample of physician prescribers, limiting participation to physicians who had prescribed clozapine in 2021 or 2022, and ensuring the confidentiality of responses. Responses were also impacted by the COVID-19 public

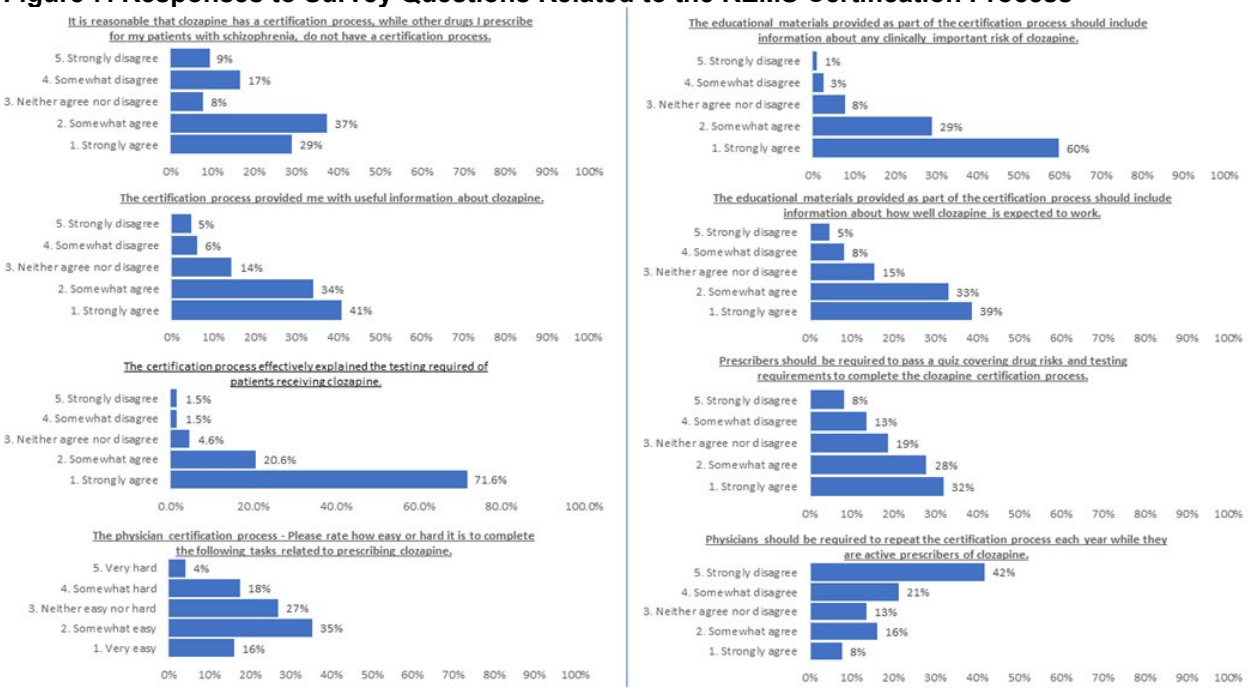
health emergency, during which time the FDA exercised enforcement discretion as to REMS-required testing. Additionally, the views of non-prescribers were not included, which may have overestimated the positive perceptions of the program reported in our survey, given that some physicians with highly negative perceptions may avoid prescribing the drug altogether.

Table 18. Participant Demographics

Characteristic	N	%
Gender		
Male	129	66.8
Female	59	30.6
Prefer not to answer	5	2.6
Race		
White	124	63.3
Black	8	4.1
Asian	48	24.5
American Indian or Alaska Native	1	0.5
Native Hawaiian or other Pacific Islander	1	0.5
Prefer not to answer	15	7.7
Ethnicity		
Hispanic/Latino/Spanish origin	6	3.1
Years since medical school graduation		
<15 years	31	16.0
15-24 years	33	17.0
25-34 years	38	19.6
35 years or more	92	47.4
Specialty		
Psychiatry	165	85.9
Internal medicine	18	9.4
Neurology	7	3.6
Geriatrics	2	1.0
In what clinical settings do you prescribe clozapine? (multiple answers permitted)		
Outpatient clinic (solo practice)	35	17.9
Outpatient (group practice)	88	44.9
Community hospital (non-military/VA)	33	16.8
Academic hospital (non-military/VA)	28	14.3
Military or VA hospital	1	0.5
Other	58	29.6
What percentage of your professional time is spent in direct patient care?		
<80%	38	19.6
80-89%	46	23.7
90-99%	65	33.5
100%	45	23.2
Number of patients to whom prescribed in past 3 years		
1-10 patients	90	46.2
11-20 patients	41	21.0
21 or more patients	64	32.8

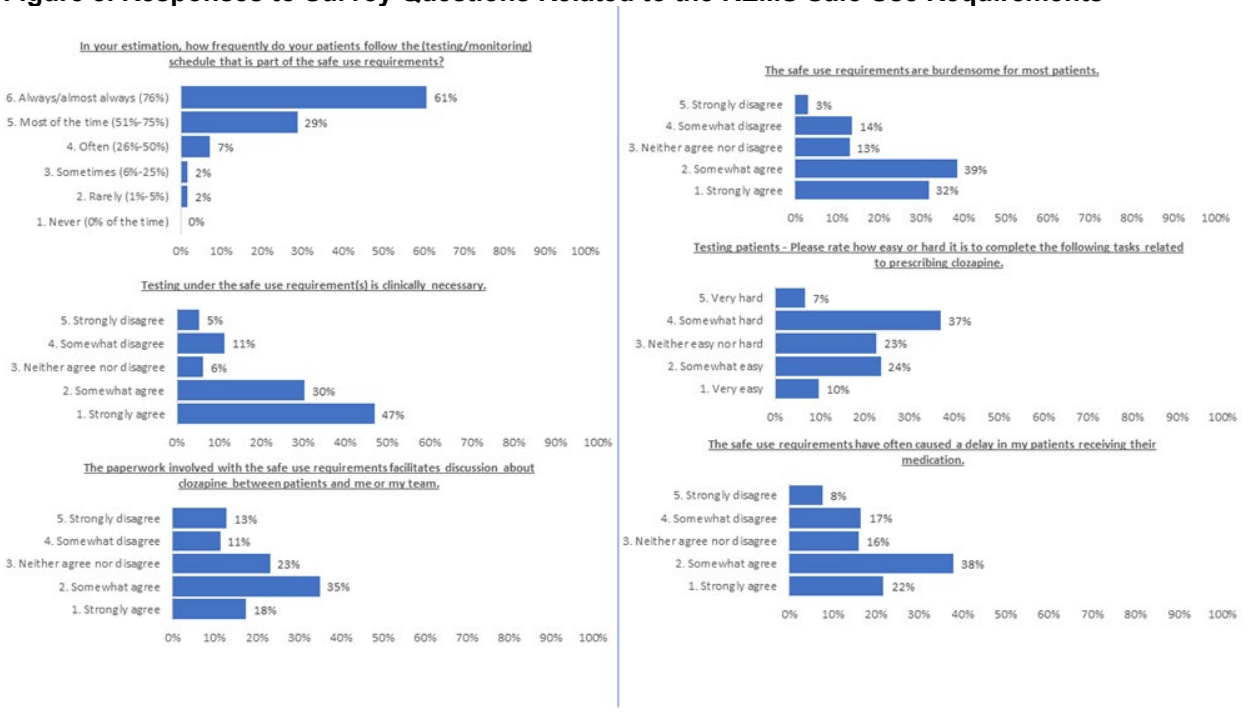
Source: Generated from the survey results.
Percentages are based on the number of responses to the question
Abbreviations: CI; confidence interval; N, number of patients; VA, veterans affairs

Figure 7. Responses to Survey Questions Related to the REMS Certification Process



Source: Generated from the survey results.
Percentages are based on the number of responses to the question.
Abbreviation: REMS, Risk Evaluation and Mitigation Strategy

Figure 8. Responses to Survey Questions Related to the REMS Safe Use Requirements



Source: Generated from the survey results.
Percentages are based on the number of responses to the question.
Abbreviation: REMS, Risk Evaluation and Mitigation Strategy

10.3 Additional Information for Sentinel Distributed Database Studies

10.3.1 Descriptive Cross-Section Analysis Comparing Subset Population With Available ANC Test Results to Source Sentinel Distributed Database Clozapine Population

The first descriptive cross-sectional analysis compared demographic and clinical characteristics of incident clozapine users from 13 SDD partners with the subset of clozapine new users with complete concordance of ANC test results with billed ANC screenings among data partners with any linked ANC test results (8 SDD partners had at least some linked ANC test data available). The Sentinel Distributed Database is a curated database composed of U.S.-based data partner sites that include large national insurers and integrated delivery care networks (Sentinel 2010). Each Data Partner has medical and prescription drug data, including inpatient and outpatient diagnoses and procedures, and retail and mail order prescription records (Behrman et al. 2011). Complete concordant clozapine incident users had the same number of billed ANC screenings in claims as linked ANC test results. We defined incident or new use as no evidence of clozapine dispensing in the previous 30 days. An additional sensitivity analysis defined incident use as no clozapine dispensings in the 183 days prior to the initial clozapine dispensing. Inclusion criteria included a clozapine dispensing from January 1, 2010, to July 8, 2024, age of at least 12 years at the initial dispensing, and enrollment in health plans with medical and drug coverage for at least 183 days prior to their initial dispensing of clozapine. Demographic characteristics (age, sex, and year of index dispensing), clinical characteristics (diagnoses of anxiety, bipolar disorder, cardiovascular disorders, chronic kidney disease, chronic obstructive pulmonary disorder (COPD), depressive disorder, diabetes, post-traumatic stress disorder (PTSD), schizophrenia or schizoaffective disorder, substance use disorder, Crohn's disease, rheumatoid arthritis, chronic immune hepatitis, and systemic lupus erythematosus), and health care utilization and medication characteristics (mean number of ambulatory encounters, emergency room encounters, inpatient encounters, filled prescriptions, and unique drug classes dispensed) were captured in the 183 days prior to the initial index prescription.

From the 13 SDD partners, we identified 164,971 episodes of new clozapine use among 105,067 unique patients. In the subset analysis among the 8 SDD partners with at least some linked ANC test results, we identified 10,473 episodes of new clozapine use among 6,698 unique patients. Only 2,223 new clozapine use episodes among 1,595 unique patients had complete concordance. Table 19 summarizes some demographic, clinical and health care utilization, and medication characteristics among clozapine's new users in the 13 SDD population and the subset population with complete concordance. Compared to the 13 SDD population, the complete concordant subset had fewer episodes associated with a schizophrenia diagnosis (77.9 versus 85.2%, SMD =0.188), had a lower average of ambulatory visits [mean (SD)=13.8(13.9) versus 19.3(23.3), SMD =0.287], and had fewer dispensed prescriptions [mean (SD)=25.2 (21.8) versus 31.1 (27.3), 0.239]. Findings were similar in the sensitivity analysis with the 183-day washout definition for incident use.

Table 19. Select Demographic, Clinical, and Health Care Utilization and Medication Characteristics Among Clozapine Incident Users With a 30-Day Washout Period Among 13 Data Partners and the Subset Population With Complete Concordance

Characteristics	13-Data Partners	8 Data Partners With Linked ANC Test Data	Standardized Mean Difference (SMD)
Total episodes	164,10,473	10,473	
Age, mean (SD)	45.6 (14.8)	46.3 (16.5)	0.045
Female sex, %	41.1	44.6	0.072
Comorbidities, percentage			
Schizophrenia	85.2	77.9	0.188
Bipolar disorder	36.3	38.4	0.043
Depressive disorder	33.6	35.3	0.035
Rheumatoid arthritis	4.1	5.2	0.052
Health care utilization, mean (SD)			
Ambulatory	19.3 (23.3)	13.8 (13.9)	0.287
Inpatient	0.6 (1.2)	0.7 (2.1)	0.058
Prescriptions	31.1 (27.3)	25.2 (21.8)	0.239
Unique drugs	9.0 (6.1)	8.5 (5.9)	0.083

Source: Generated from study results.
Abbreviations: ANC, absolute neutrophil count; SD, standard deviation; SMD, standardized mean difference

10.3.2 Neutropenia and Monitoring in a Subset Population With Linked ANC Test Results: a Patient Episode Profile Retrieval (PEPR) Analysis

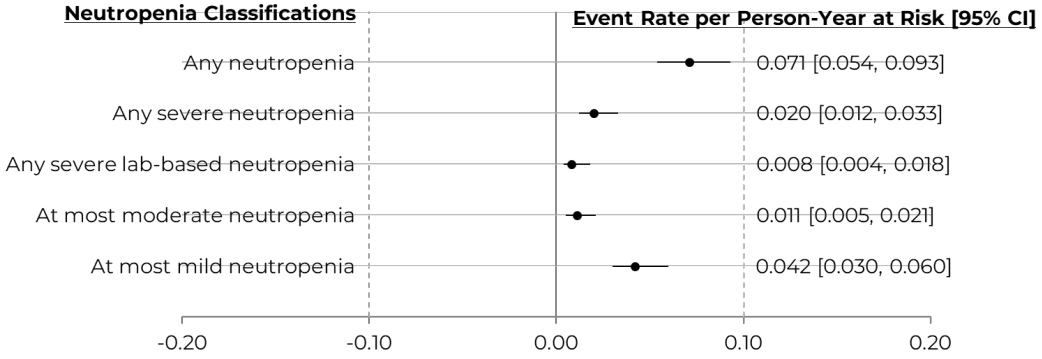
This study was a health administrative claims and ANC tests linked analysis that calculated rates of varying severity levels of neutropenia and included a PEPR, or line-by-line review of claims, to provide descriptive information on ANC monitoring among incident clozapine users. The cohort included new clozapine episodes, defined as a clozapine dispensing from January 1, 2010, to January 1, 2020, without a dispensing in the 30 days prior, with complete concordance of ANC tests and screenings billed, and that involved patients who were at least 12 years of age at the initial dispensing and were enrolled in health plans with medical and drug coverage for at least 30 days prior to their initial dispensing of clozapine. A clozapine episode was further defined as starting on the day of the initial clozapine dispensing and continuing for 6 months, until loss of medication or prescription insurance coverage, or until 60 days after the last clozapine dispensing, whichever came first. Individuals with no evidence of ANC screening were excluded. Complete concordance was defined as the same number of ANC screenings billed in claims as captured by ANC test results data. Five neutropenia outcomes were assessed during the follow-up period: (1) any severe neutropenia defined as an ANC test result of 0 to ≤0.5 K/µL or an ICD-10-CM diagnosis code for agranulocytosis (D70.2), (2) severe neutropenia by lab only defined as an ANC test result of 0 to 0.5K/µL without a corroborating diagnosis code, (3) severe neutropenia by diagnosis code only defined as an ICD-10-CM diagnosis code for agranulocytosis without a corroborating ANC test result, (4) moderate neutropenia defined as an ANC test result of >0.5 to ≤1.0 K/µL, and (5) mild neutropenia defined as an ANC test result of >1.0 to ≤1.5 K/µL. Among clozapine episodes with multiple neutropenia events, only the most severe event was captured. If multiple events of the same severity occurred, only the first event was captured. Among episodes identified as associated with a neutropenic event, we conducted a line-by-line evaluation to describe monitoring prior to events, the sequalae of other neutropenic events prior to this most severe event, timing of neutropenic event after the initial clozapine dispensing, neutropenic treatments, and serious infections or other potential causes of the neutropenic event.

From the SDD data partners with available ANC test results (8 of the 13 SDD data partners), a total of 12,640 clozapine episodes were identified. Only 2,223 clozapine episodes with 760.3 total years at risk for neutropenia had complete concordance. Of note, only a small minority of ANC test results were from the inpatient setting. Fifty-three neutropenia cases were identified: six episodes with ≥1 ANC test result indicating severe neutropenia, nine clozapine episodes with an ICD-10-CM diagnosis code for agranulocytosis, six episodes with ≥1 ANC test result indicating moderate neutropenia, and 32 clozapine episodes with ≥1 ANC test result indicating a mild neutropenic event. Eight of the nine cases of severe neutropenia identified by diagnosis code did not have an ANC test result indicating a severe diagnosis. Risks of neutropenia during the follow up period are summarized by various neutropenia classifications in Figure 9. The event rate for severe lab-based neutropenia was 8 per 1,000 person years at risk (95% confidence interval=4 to 18 per 1,000 person years).

To protect patient privacy, numbers and proportions when counts are less than 5 are not reported. Among individuals with lab-confirmed severe neutropenia, no cases of severe infection 30 days prior or 30 days subsequent to the neutropenic events were identified. About half of the cases did have cancer and/or evidence of ongoing chemotherapy. Table 20 summarizes the findings on screening behavior from the PEPR. About half of severe cases had a screening 7 days, 14 days, or 30 days prior to their neutropenic event. When we looked at ANC test results prior to the severe laboratory result, a steady decline in values across tests was noticed. The time course of the downward trend varied with some occurring quickly (over the course of a week) and slower in others (occurring over several weeks to months). Most had evidence of multiple continued clozapine dispensings after the severe neutropenia lab result. Among cases with lab-confirmed moderate neutropenia, none had evidence of chemotherapy or filgrastim 30 days prior or subsequent to an event. At least one case of severe infection treated with antibiotics was identified. Relative to the lab-confirmed severe neutropenia group, screening was less likely to occur at weekly intervals in the moderate group. Less than half had evidence of ANC screening 7 or 14 days prior to their moderate neutropenic event. More than half had screening in the 30 days prior. All showed evidence of a downward trend prior to their moderate laboratory result, though this trend occurred quickly in some (over the span of a week or two) and more slowly in others (over the course of several weeks or months). Most appeared to discontinue clozapine treatment after the event. Among mild neutropenia cases (N=32), half had evidence of screening the month prior to their neutropenic event. A majority of mild neutropenia cases had evidence of screening 14 days and 30 days prior to their event (68.8% and 90.6%, respectively).

The primary limitation of this study was the small sample size and substantial loss to attrition. The selection of individuals into the study required at least one billed screen to determine concordance between billed and captured ANC test results. Thus, individuals included are those who appear to be monitored at least somewhat routinely. Individuals without screening or without complete concurrence of billed and captured ANC test data constitute a substantial proportion of the population and were not captured in this study. As well, it was noted that laboratory data captured in this study were primarily from the outpatient setting. Inpatient billings and the corresponding ANC test results are likely missing. This might mean that this study is missing severe neutropenic cases in individuals without outpatient, or routine, monitoring.

Figure 9. Neutropenia Event Rates Per Person-Year at Risk and 95% Confidence Intervals Among Clozapine Users With A Neutropenic Event During Their First 6 Months Of Therapy



Source: Generated from study results.
Abbreviation: CI, confidence interval

Table 20. Screening Behavior Among Clozapine Episodes With Concordant ANC Test Results and Neutropenia Events, by Neutropenia Severity

Neutropenia Severity	Evidence of ANC Screen in 7 Days Prior	Evidence of at Least One ANC Screen 14 Days Prior	Evidence of at Least One ANC Screen in 30 Days Prior
Severe (N=6)	Around half*	Around half*	Around half*
Moderate (N=6)	Less than half*	Less than half*	More than half*
Mild (N=32)	16/32, 50.0%	22/32, 68.8%	29/32, 90.6%

Source: Generated from Study results.
* Numbers and proportions when counts are less than 5 cannot be reported for privacy reasons.
Abbreviations: ANC, absolute neutrophil count; N, number of patients

10.3.3 Descriptive Electronic Medical Chart Review to Describe Neutropenia Events Among a Medicare and Medicaid Ensured Population

This study linked Medicare and Medicaid claims and unstructured and structured electronic health records (EHR) from Massachusetts General Brigham (MGB) affiliated facilities to describe various clinical features of neutropenia occurring during the first six months of clozapine treatment. The cohort included incident clozapine episodes, defined as a clozapine dispensing from 2000 to 2020 without a dispensing in the 30 days prior, with at least one record at an MGB affiliated facility, among individuals at least 12 years of age at the initial dispensing, and who were enrolled with Medicare or Medicaid medical and drug coverage for at least 30 days prior to their initial dispensing of clozapine. MGB facilities included two large academic teaching hospitals, three specialty hospitals, seven community hospitals, as well as multiple outpatient clinics, urgent care, and specialty clinics. The unstructured data from one mental health specialty hospital was not available because of patient privacy concerns. Fee-for-service Medicare data from 2007 to 2020 and Massachusetts Medicaid data from 2000 to 2018 were used to identify dates and patients with neutropenia events during their first 6 months of clozapine use. Both specific and non-specific neutropenia codes were used to identify cases for EHR extraction (ICD-9-CM 288.0, 288.9; ICD-10-CM D70.8, D70.9, D70.2). EHR data 1 week prior and subsequent to the neutropenic event were then extracted for review. Standardized extraction sheets with several concepts and definitions were created a priori to ensure accurate and consistent capture of concepts from structured and unstructured data. Captured concepts included neutropenia-related information (potential causes including evidence of malignancy, past history of neutropenia, treatment for neutropenia including discontinuation of clozapine treatment, development of infections), ANC monitoring-related information (ANC values with current neutropenia event, reports on monitoring

before and after event) indication related information (indication for clozapine, efficacy of clozapine for treatment, alternative agents used), and additional information about clozapine use (treatment initiation, dosing, previous treatment episodes).

We identified 2,525 incident clozapine episodes and 39 neutropenia events within 180 days of starting clozapine among Medicare and Medicaid beneficiaries with some record at an MGB affiliated facility. After excluding cases with no MGB medical records in the 3 months prior and 6 months subsequent to the neutropenic event (N=16 cases), no mention of neutropenia in structured of unstructured medical records or ANC test results in the week prior or subsequent to a neutropenic diagnosis (N=13), and exclusion of ANC laboratory confirmed neutropenia cases without any medical records for extraction (N=4), we yielded six cases of neutropenia for in-depth EHR review. Clozapine was recorded as the suspected cause of neutropenia in all six cases. No other causes were mentioned or considered in structured and unstructured medical records reviewed. All six episodes recorded clozapine discontinuation following neutropenia; no additional details regarding treatment switch or dose change were found. Management strategies for neutropenia included prophylactic antibiotics and/or filgrastim treatment. In one out of six episodes, neutropenia was recorded to have led to a serious infection (bacteremia) requiring inpatient management. No deaths were identified. All cases occurred in patients with primarily schizophrenia or bipolar disorders. There was no mention of symptom control with clozapine in reviewed records. No mention of monitoring plans and no records of adherence to ANC testing or guidelines were available in the medical records.

The primary limitation of this analysis was the very small sample size and the lack of information on ANC monitoring.

10.4 List of Approved Clozapine Products

Table 21. List of Approved Clozapine Products

Product	NDA/ANDA	Application Holder
Clozaril	NDA 019758	Heritage Life
Versacloz	NDA 203479	Tasman Pharma
Clozapine	ANDA 090308	Barr Labs Inc
Clozapine	ANDA 202873	Accord Healthcare
Clozapine	ANDA 206433	Aurobindo Pharma
Clozapine	ANDA 075713	Sun Pharma Industries Inc
Clozapine	ANDA 201824	Mylan
Clozapine	ANDA 075417	Mylan
Clozapine	ANDA 074949	Ivax (Subsidiary of Teva Pharmaceuticals)
Clozapine	ANDA 076809	Ivax (Subsidiary of Teva Pharmaceuticals)

Source: Table generated by the FDA risk management analyst.
Abbreviations: ANDA, Abbreviated New Drug Application; NDA, New Drug Application

10.5 Clozapine REMS Document

For information on the requirements of the Clozapine REMS if it was fully implemented, please refer to the Clozapine REMS Document and other program information available at REMS@FDA.com

10.6 Drug Utilization Database Descriptions

IQVIA National Prescription Audit™

National Prescription Audit (NPA) is the industry standard source of national prescription activity for all pharmaceutical products. It measures demand for prescription drugs, including dispensed pharmaceuticals to consumers across three unique channels: retail, mail service, and long-term care pharmacies. From the selected pharmacies, IQVIA collects new and refilled prescription data daily. Data can be analyzed and stratified by patient age, patient gender, co-payment, and four methods of payment: cash, commercial third party, Medicare Part D, and Medicaid. NPA is used to address a variety of research topics examining pharmaceuticals, especially investigations that focus on prescription drug utilization, prescription size, average consumption, and more than 90 prescriber specialty groupings representing over 170 specialties. NPA represents and captures over 94% of all outpatient prescription activity in the US and covers all products, classes, and manufacturers. Although the NPA provides data at a national level, NPA provides data that is at a more granular geographic level of detail. Data are available in IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly.

Symphony Health Metys™

Powered by IDV® Metys™ is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point – all while delivering insights faster than any other tool in the industry. Metys™ accesses over 60 terabytes of automatically included weekly and monthly data, reflecting our breadth of patient-level data and advancements in machine learning. The dispensed prescriptions in the sample represent approximately 85% of all U.S. retail prescriptions, 74% of all U.S. mail order prescriptions, 73% of all U.S. specialty prescriptions, and 50% of all U.S. Long Term Care prescriptions. The retail, mail order, specialty, and long-term care prescriptions are projected to the national level. In addition, the database captures approximately 96% of pharmaceutical distribution into non-retail outlets in the U.S. The non-retail data is not projected to the national level. Metys™ Managed Markets metrics, such as rejections and reversals are calculated using a 50% sample of pharmacy adjudicated claims projected to the national level.