DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

BRIEFING DOCUMENT

CLOZAPINE REMS

MEETING DATE: 19 NOVEMBER 2024

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

ACCORD HEALTHCARE, INC.

AUROBINDO PHARMA USA, INC.

DR. REDDY'S LABORATORIES, INC.*

HLS THERAPEUTICS (USA), INC.

MYLAN INC., A VIATRIS COMPANY

SUN PHARMACEUTICAL INDUSTRIES, INC.

TASMAN PHARMA, INC.

TEVA PHARMACEUTICALS USA, INC.

*Exiting REMS Participant

TABLE OF CONTENTS

LISTING OF IN-TEXT TABLES

LISTING OF IN-TEXT FIGURES

KEY TERMS AND ABBREVIATIONS

Key Terms/ Abbreviations	Definitions and Notes
AE	adverse event
ANC	absolute neutrophil count
ANDA	Abbreviated New Drug Application
API	Application Programming Interface
BEN	benign ethnic neutropenia
CNR	Clozaril National Registry
CPMG	Clozapine Product Manufacturers Group
CPMS	Clozaril Patient Monitoring System
ETASU	Elements to Assure Safe Use
FAQs	Frequently Asked Questions
FDA	Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
HCP	healthcare provider
KA	Knowledge Assessment
KAB	Knowledge, Attitude, and Behavior
KPI	Key Performance Indicator
LRx	Longitudinal Prescriptions
LTC	long-term care
NA	not applicable
NDA	New Drug Application
NNRMF	National Non-Rechallenge Master File
ODT	orally disintegrating tablet
PCN	Pharmacy Claims Network
PDA	Predispense Authorization
PEF	Patient Enrollment Form
PI	Prescribing Information
PSF	Patient Status Form
PV	Pharmacovigilance
RDA	REMS Dispense Authorization
REMS	Risk Evaluation and Mitigation Strategy
TRS	treatment-resistant schizophrenia
US	United States
WBC	white blood cell

1.0 EXECUTIVE SUMMARY

1.1 Introduction

Clozapine is a serotonin-dopamine antagonist that belongs to the atypical antipsychotic drug class and was first approved by the United States (US) Food and Drug Administration (FDA) in 1989 for treatment-resistant schizophrenia (TRS). It is also approved for reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder. Clozapine is the only licensed therapy for those with TRS and the only medication with strong evidence of efficacy in TRS.[1-3]

The use of clozapine has been associated with severe neutropenia, which is defined as an absolute neutrophil count (ANC) <500 cells/µL. Severe neutropenia occurs in a small percentage of patients taking clozapine; however, neutropenia is associated with an increased risk of serious and potentially fatal infections. Therefore, early detection is important.

Risk management requirements for clozapine have evolved over the past 35 years to an FDA-required Risk Evaluation and Mitigation Strategy (REMS) that manages the risk of severe neutropenia, which can lead to serious infections and death. The Clozapine REMS is a single shared patient registry with requirements for prescribers, pharmacists, patients, and wholesalers-distributors. The initial Clozapine REMS was developed by the Clozapine REMS Sponsors in collaboration with the FDA and was approved on 15 September 2015. The current Modified Clozapine REMS was approved on 29 July 2021.

Due to challenges with transitioning from Legacy REMS (15 September 2016 – 15 November 2021) to Modified REMS (29 July 2021 – 29 May 2024) and to ensure continuity of care, the FDA initiated enforcement discretion on 19 November 2021, which allowed pharmacists to dispense without obtaining a REMS Dispense Authorization (RDA) and for wholesalers-distributors to ship to uncertified pharmacies. In November 2022, additional FDA enforcement discretion permitted inpatient pharmacies to dispense a quantity of clozapine upon discharge consistent with the patient's monitoring frequency.

There are currently 8 sponsor companies with at least 1 approved New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) for a clozapine product: Accord Healthcare, Inc., Aurobindo Pharma USA, INC., Dr. Reddy's Laboratories, Inc., HLS Therapeutics (USA), Inc., Mylan Inc., a Viatris Company, Sun Pharmaceutical Industries, Inc., Tasman Pharma, Inc., and Teva Pharmaceuticals USA, Inc. These sponsor companies are collectively referred to as the Clozapine Product Manufacturers Group (CPMG).

The purpose of this briefing document is to support the joint meeting of the Drug Safety and Risk Management Advisory Committee and Psychopharmacologic Drugs Advisory Committee with the FDA to review the Clozapine REMS and consider changes that would reduce the burden on patients, pharmacies, and prescribers and maintain the safe use of clozapine.

1.2 Goals and Objectives of Clozapine REMS

The goal of the Clozapine REMS is to mitigate the risk of severe neutropenia associated with the use of clozapine. The objectives of the Clozapine REMS are to:

1. Educate prescribers and pharmacists about the risk of severe neutropenia and appropriate monitoring requirements.

2. Inform patients about the risk of severe neutropenia and appropriate monitoring requirements.
3. Ensure prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia.
4. Ensure the prescriber documents a risk-benefit assessment when ANC falls below the acceptable range as described in the prescribing information.
5. Establish long-term safety and safe use of clozapine by enrolling all patients who receive clozapine in the registry.

1.2.1 Key Components for Safe Use of Clozapine

The Clozapine REMS is required by the FDA to ensure the benefits of clozapine outweigh the risk of severe neutropenia.

The Clozapine REMS Sponsors must ensure that healthcare providers (HCPs), patients, pharmacies, and wholesalers-distributors comply with the required Elements to Assure Safe Use (ETASU) and additional requirements. These include:

- HCPs who prescribe clozapine must be certified in the REMS.
- A patient must be enrolled in the REMS by a prescriber or prescriber designee.
- On a monthly basis, prescribers must document and submit the ANC results, monitoring frequency, and appropriateness for continuing treatment for each patient via the Patient Status Form (PSF).
- Prescribers, prescriber designees, and pharmacists may document and submit individual ANC lab values outside of the PSF process.
- Pharmacies that dispense clozapine must be certified in the REMS.
- Pharmacies are required to obtain an RDA to dispense each clozapine prescription online or by calling the Contact Center.

Additional requirements:

- A certified pharmacy is required to confirm their authorized representative every 2 years.
- Ensure the PSF is received for each patient enrolled in the REMS. If the form is not received within 31 days of the date of the last PSF, the Clozapine REMS must contact the prescriber for the form.
- Wholesalers-distributors must register and ensure clozapine is distributed only to certified pharmacies.

1.3 Clozapine REMS Assessment Results

The CPMG is required to complete and submit REMS Assessment Reports every 18 months from the approval of the Modified REMS. Under the Legacy REMS, Assessment Reports were due every 12 months from initial approval of the REMS. Due to some limitations of the Legacy REMS and further, with FDA exercising the enforcement discretion following the launch of the Modified REMS, a complete assessment of the effectiveness of the REMS in meeting its goal of

mitigating the risk of severe neutropenia associated with clozapine could not be made based on the Assessment Reports alone. Key metrics were analyzed to assess the effectiveness of the Clozapine REMS cumulatively (i.e., both the Legacy REMS from 2015 to 2021 and the Modified REMS from 2021 to 2024) in meeting its goal. These metrics include: 1) adherence to monitoring; 2) evaluation of knowledge surveys; and 3) use of Treatment Rationale. Key findings are presented below.

Description of Metric	Results
1. Adherence to Monitoring	
Due to the difficulty in measuring adherence to monitoring in the Legacy REMS, the number of dispense authorizations that were rejected due to a missing ANC value was selected as a surrogate metric.	Data for Legacy REMS were significantly lower than those for the Modified REMS. This could be attributed to the fact that the Legacy REMS only required one ANC value on file, whereas the Modified REMS required current ANC values submitted monthly via the PSF.
2. Evaluation of Knowledge Surveys	
The Clozapine REMS measures prescriber, pharmacist, and patient/caregiver knowledge about the REMS requirements through surveys. These surveys (known as KAB surveys) are conducted to test REMS stakeholder knowledge on 3 key risk messages: • *Key Risk Message 1:* Understand the risk of severe neutropenia associated with clozapine • *Key Risk Message 2:* Understand the need for appropriate patient monitoring with clozapine • *Key Risk Message 3:* Understand the requirements of the Clozapine REMS	• Prescribers: Survey results over all years demonstrated low scores for questions related to patients with BEN and use of a Treatment Rationale • Pharmacists: Survey results for all years demonstrated low scores related to when the greatest risk for neutropenia appears (i.e., in the first 18 weeks), what a pharmacist can do if a PDA is denied due to a prescriber not being certified (note: this was not applicable to the Modified REMS and 2024 KAB scores), and ANC monitoring for patients with BEN • Patients/caregivers: There was a lower mean knowledge rate in earlier years, which can be attributed to multiple changes in the clozapine risk management programs. Following the 2021 Major Modification and implementation of all REMS requirements, the KAB results showed that patients and caregivers have a good understanding of their requirements under the REMS
3. Use of Treatment Rationale	
The Treatment Rationale allows treatment despite abnormal ANC values when a prescriber determines that the benefits of continuing care outweigh the risk of disrupting treatment.	Reviewing the use of the Treatment Rationale may help to better elucidate the frequency at which the risk-benefit assessments are being completed.

ANC = absolute neutrophil count; BEN = benign ethnic neutropenia; KAB = Knowledge, Attitude, and Behavior; PDA = Predispense Authorization; PSF = Patient Status Form; REMS = Risk Evaluation and Mitigation Strategy.

Under enforcement discretion, certain elements of the REMS (such as noncompliance monitoring of prescribers and pharmacies, verification of pharmacy certification by wholesalers-distributors, and obtaining an RDA for all dispenses of clozapine) have not been implemented. Without full implementation of all REMS required processes, the CPMG is unable to complete longitudinal analysis of the REMS elements. Delayed implementation of these REMS elements limits data collection that supports evaluation of the effectiveness of the REMS. In summary, the data presented indicate that the Clozapine REMS is functioning as intended by providing a centralized point of access for prescribers and pharmacies to certify before prescribing or

dispensing clozapine, to enroll and manage patients on clozapine, as well as being a system to detect clozapine-induced neutropenia.

1.4 Potential Areas for Improvement of Clozapine REMS

Potential areas for improvement of the Clozapine REMS and the benefit it would provide to stakeholders are summarized below.

Potential Area for Improvement	Benefit to Stakeholders
Drive greater awareness and education	Address misconceptions and common questions
Manage transitions in care more effectively	Ensure continued access to treatment during transitions between prescribers and pharmacies and from inpatient to outpatient care
Improve communication across institutional reporting systems	Reduce burden on physicians and pharmacies
Improve AE collection	Obtain more meaningful data on incidence and outcomes of AEs related to clozapine-induced neutropenia.

AE = adverse event.

1.5 Overall Conclusion

The risk management requirements for clozapine have existed in various forms since 1989 to ensure that patients and clinicians are aware of the risks of adverse events (AEs) related to clozapine-induced neutropenia. Without the REMS in place, physicians or patients may not adhere to the strict monitoring regimen specified in product labeling, which could result in undetected neutropenia and increased morbidity and mortality. Notwithstanding, patient safety, continuity of care, and patient access to clozapine are the highest priorities. Through stakeholder input, evaluation of assessment data, and ongoing FDA consultation, the CPMG has identified and clarified misconceptions that may be addressed through awareness and education. It has implemented improvements to address challenges and streamline use of the REMS and, as part of good governance, is committed to continue implementation of improvements as necessary. In addition, the CPMG has identified opportunities to potentially improve data collection and reduce stakeholder burden while continuing to help ensure patient safety. The CPMG is committed to collaborating with stakeholders and FDA to make further improvements.

2.0 BACKGROUND

2.1 Overview of Treatment-Resistant Schizophrenia

Schizophrenia is a serious, disabling psychiatric disorder, affecting approximately 1% of people worldwide and ranking among the top 10 global disability causes.[4,5] Schizophrenia is characterized by hallucinations, delusions, disorganized speech and behavior, and negative signs and symptoms such as reduced emotional expression, avolition, and cognitive impairment.[5] Symptom onset generally occurs in late adolescence or early adulthood,[6] and the disorder may be more common in men (incidence rate ratio approximately 1.7).[7,8] The etiology includes genetic, environmental, and neurobiological causes. No specific gene is responsible for the disease as multiple genetic factors are involved. Environmental factors include prenatal/obstetrical risks and psychosocial stressors. Neurobiologically, schizophrenia is associated with neurotransmitter abnormalities in dopamine and glutamate systems and structural changes in the brain.[5]

Despite the availability of more than 60 antipsychotic therapies worldwide, up to one-third of patients with schizophrenia are resistant to treatment.[9-12] TRS has broadly been defined as the persistence of positive symptoms despite at least 2 trials of adequate dose and duration of antipsychotic medication with documented adherence.[9,13] Patients with TRS have poorer outcomes compared with other patients with severe mental illnesses. They also have worse achievement of functional milestones of everyday living, including lower marriage rates, and higher rates of residence in facilities.[14] Furthermore, persistent positive, negative, and cognitive symptoms result in worsened social functioning and long-term disability.[14-19] Finally, TRS costs 3- to 11-fold more in patients with schizophrenia in remission, adding an estimated $34 billion to the US medical system.[20] For these patients with TRS with significant disease burden, clozapine is the only approved treatment option, with approximately half of patients with TRS responding.[21,22]

2.2 Overview of Clozapine

Clozapine, a serotonin-dopamine antagonist belonging to the atypical antipsychotic drug class, is indicated for TRS and reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder. Clozapine was approved in the US in 1989 under the brand name Clozaril®. A number of formulations, including Fazaclo® orally disintegrating tablet (ODT; currently discontinued) and Versacloz® suspension, and a number of generic oral tablets and ODTs are also marketed in the US in various strengths (12.5, 25, 50, 100, and 200 mg).

2.2.1 Benefits and Utilization of Clozapine

Since its approval in 1989, clozapine has demonstrated added benefits. Clozapine not only provides a tremendous treatment benefit for patients with TRS, but patients on clozapine also appear to live longer than those receiving other antipsychotic drugs. Clozapine is also associated with reduced persistence of psychosis, reduced risk of relapse, hospitalization, suicide, and mortality, reduced violence and aggression, improved functioning, reduced family burden, and considerable direct and indirect economic benefits. Thirty years post-approval, clozapine remains the only approved drug for TRS.

Despite the proven efficacy and advantages of clozapine and guidelines recommending the start of clozapine after 2 antipsychotic treatment failures, many patients never receive a trial of

clozapine. For those patients who do receive clozapine, however, the trial is often delayed by years after having failed multiple antipsychotic drugs with ensuing consequences.

Lengthy delays in the implementation of clozapine are associated with a poorer response to the drug once it is prescribed.[23-26] Therefore, earlier consideration and integration of clozapine into treatment strategies are warranted.[5]

Clozapine is grossly underutilized in clinical practice.[27] In one retrospective study using Medicaid claims data, clozapine accounted for only 5.5% of antipsychotics prescribed for TRS between 2002 and 2005.[28] It is estimated that only approximately 30% of patients who would benefit from clozapine receive it.[29,30] Approximately 30% to 60% of patients with TRS respond to clozapine treatment.[22,31,32] Each hospital admission reduces the likelihood of response by 4% to 8%.[33] In women, for each year's delay in clozapine initiation, the probability of substantial improvement is reduced by 15%.[34] Identifying variables associated with better response to clozapine could help select patients, which would lead to earlier use of clozapine, and better long-term outcomes.[35]

2.2.2 Risk of Neutropenia Associated With Clozapine

The use of clozapine has been associated with various risks, including severe neutropenia (agranulocytosis), orthostatic hypotension, bradycardia/syncope, seizures, myocarditis, pneumonia, constipation, paralytic ileus, cardiomyopathy and mitral valve incompetence, and increased mortality in elderly patients with dementia-related psychosis. Severe neutropenia, defined as an ANC <500 cells/μL, is associated with an increased risk of serious and potentially fatal infections; hence, early detection is important.

Clozapine treatment increases the risk of neutropenia, but epidemiologic findings are inconsistent. The prevalence of clozapine-associated neutropenia is low, and neutropenia-related death is rare. A meta-analysis of 36 studies involving more than 250,000 clozapine-treated patients evaluated the prevalence of neutropenia and related death.[36] Neutropenia caused by clozapine was estimated to be 0.4% and related death was 0.05%.

The risk of clozapine-induced neutropenia decreases steeply over time.[37,38] A recent observational study of 26,630 individuals with schizophrenia treated with clozapine showed that most cases of serious neutropenia occurred within the first 18 weeks of treatment and that the risk was negligible after 2 years.[37]

The mechanism by which clozapine causes neutropenia is unknown and is not dose-dependent. Because of the risk of severe neutropenia, clozapine is available only through the Clozapine REMS.

2.2.3 Clozapine Monitoring

The stringency of clozapine monitoring can affect utilization rates as frequent monitoring can lead to patients and clinicians discontinuing clozapine.[39] Previous studies suggested that flexible neutrophil monitoring may contribute to longer-term clozapine maintenance.[40]

Globally, there are wide variations in the guidelines for clozapine monitoring. A single evidence-based and standardized international guideline could help address the underutilization of clozapine in the management of patients with schizophrenia while simultaneously addressing safety concerns.

Taken together, it is important to recognize the potential role of clozapine to improve the lives of patients with TRS. People on clozapine live longer, and for some it can be life-changing. However, the overemphasis of risks and the burden of lifelong reporting requirements can discourage patients from trying clozapine.

2.3 History of Clozapine Risk Management Program

The risk management strategies for clozapine have evolved since its approval in 1989 (Table 1). The Clozaril Patient Monitoring System (CPMS) was created in 1989, which evolved into the Clozaril National Registry (CNR) in 1991 to ensure weekly monitoring of white blood cell (WBC) counts for patients on clozapine. The introduction of generic versions of clozapine from other manufacturers starting in 1997 resulted in additional, independent systems implemented by each of the individual manufacturers of clozapine products to mitigate the risk of agranulocytosis (severe neutropenia). To mitigate the risk of severe neutropenia associated with the use of clozapine, each manufacturer was responsible for maintaining its own patient registry, in addition to the CNR. From 1989 to 2005, only WBC counts were required, and the maximum interval between blood tests was 2 weeks. In 2005, ANC values and criteria for monitoring every 4 weeks were added to the label.

The National Non-Rechallenge Master File (NNRMF), a key component of the CNR, was created to ensure that patients who had developed severe leukopenia or severe granulocytopenia while on clozapine, regardless of the manufacturer, could not be put back onto the drug. The NNRMF was developed by the reference listed drug holder to record all patients who developed severe leukopenia or severe granulocytopenia while on clozapine, regardless of the manufacturer of the clozapine product, and prevent patients from being rechallenged with clozapine. Unless covered under a waiver program, patients in hospice, with chemotherapy-induced neutropenia or who had benign ethnic neutropenia (BEN), were often excluded from clozapine therapy under historical labeling recommendations and individual clozapine registry requirements.

In 2012, the US FDA notified manufacturers that held applications for clozapine products of the requirement to submit a proposal for a single, shared REMS for all products containing clozapine to ensure that the benefits of the drug outweigh the risk of developing severe neutropenia. The single, shared Clozapine REMS was approved on 15 September 2015 and replaced the 6 individual clozapine patient registries (maintained by individual clozapine manufacturers) and the NNRMF. The NNRMF was discontinued with the launch of the Clozapine REMS, and prescribers were allowed greater flexibility in resuming clozapine treatment. The evolution of the Clozapine REMS is summarized below.

Table 1 Timeline of Key Clozapine Regulatory Events

Date	Type of Event	Regulatory Event
1989	FDA approval	US approval of Clozaril
1989	Created CPMS	Created the CPMS at the time of Clozaril approval
1991	Established CNR	The CPMS evolved into the CNR to ensure weekly monitoring of WBC counts for patients on clozapine.
1997	Implemented additional independent systems	• Introduction of generic versions of clozapine from other manufacturers starting in 1997 resulted in additional, independent systems put in place by each of the individual manufacturers of

Date	Type of Event	Regulatory Event
		clozapine products to mitigate the risk of agranulocytosis (severe neutropenia). • To mitigate the risk of severe neutropenia associated with the use of clozapine, each manufacturer was responsible for maintaining its own patient registry, in addition to the CNR.
1989-2005	Label	Only WBC counts were required, and the maximum interval between blood tests was 2 weeks.
2005	Label	ANC values and criteria for monitoring every 4 weeks were added to the label.
27 Mar 2008	Issued Federal Register notice	The FDA issued a Federal Register notice identifying clozapine as one of the drugs deemed to have an approved REMS in effect.
Aug 2012	Notification of REMS	The FDA notified manufacturers that held applications for clozapine products of the requirement to submit a proposal for a single, shared REMS for all products containing clozapine to ensure that the benefits of the drug outweigh the risk of developing severe neutropenia.
15 Sep 2015	Approval of shared REMS	The FDA approved the shared Clozapine REMS.
12 Oct 2015	Initial launch of REMS	• REMS website and Contact Center went live/became publicly available. • Following this initial launch and to minimize the burden of the implementation of the Clozapine REMS, the FDA and the CPMG agreed to implement the program in multiple phases with multiple launches (as described below).
May 2016	Initial PDA launch of REMS	• The initial PDA launch evaluated whether the patient was enrolled and if there was a patient lab on file within the acceptable range or a valid Treatment Rationale on file documenting the prescriber's decision that the benefits outweigh the risks of dispensing clozapine. • The initial PDA launch did not evaluate if the lab result was current based on the patient's monitoring frequency or prevent a dispense if a prescriber or pharmacy was not certified.
Feb 2019	Launch/major modification of REMS	• This launch incorporated the functionality of the initial launch and included the addition of the evaluation of prescriber and outpatient pharmacy certification. • The 2019 modification provided certified outpatient pharmacies with an opportunity to apply clinical judgment and continue to dispense clozapine to enrolled patients when a patient's prescriber is not certified in the Clozapine REMS via a Dispense Rationale. • The 2019 modification did not evaluate whether the lab result on file was current based on the patient's monitoring frequency.
Q4 2019 - 2021	Preparation of major REMS modification	• The FDA offered tentative agreement to CPMG that the full implementation of the Clozapine REMS requirements could be accomplished following a REMS modification to remove the requirements associated with the centralized communication requirement (i.e., the "switch"). • Sponsors and their vendors collaborated across 2020 and 2021 to prepare and submit a major REMS modification for the FDA's review and approval.

Date	Type of Event	Regulatory Event
29 Jul 2021	Approval of modified REMS	The FDA approved the Modified Clozapine REMS.
August 2021	Transition Contact Center and Website Launch	• On 2 August 2021, CPMG launched a Transition Contact Center to answer questions about the upcoming REMS modification and support stakeholder reenrollment/recertification. • On 16 August 2021, CPMG launched a transition website to allow for stakeholder reenrollment/recertification online.
15 Nov 2021	Launch/major modification of REMS	• This launch transitioned the program to a new platform and removed the centralized communication requirement (i.e., the "switch"). • The PDA was replaced by an RDA, available via the website and REMS Contact Center. • The modification introduced a monthly PSF as a requirement for patient eligibility to receive the drug.
19 Nov 2021	Temporary period of enforcement discretion	The FDA implemented a temporary period of enforcement discretion for certain REMS requirements (i.e., that wholesalers-distributors only ship clozapine to pharmacies certified in the Clozapine REMS and that pharmacies obtain an RDA).
02 Nov 2022	Additional enforcement discretion	• The FDA announced they were temporarily exercising additional enforcement discretion to ensure continuity of care for patients taking clozapine as well as continuation of the previous enforcement discretion. • Specifically, the FDA noted they do not intend to object if inpatient pharmacies dispense a days' supply of clozapine at discharge that aligns with the patient's monitoring frequency.
21 Sep 2023	Re-evaluation of REMS	The FDA announced that as part of their regular review of all REMS, and in light of the FDA's continued exercise of enforcement discretion, the FDA is conducting a thorough reevaluation of the Clozapine REMS to determine whether the REMS can be modified to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of clozapine.

ANC = absolute neutrophil count; CNR = Clozaril National Registry; CPMG = Clozapine Product Manufacturers Group; CPMS = Clozaril Patient Monitoring System; FDA = Food and Drug Administration; PDA = Predispense Authorization; PSF = Patient Status Form; RDA = REMS Dispense Authorization; REMS = Risk Evaluation and Mitigation Strategy; US = United States; WBC = white blood cell.

2.3.1 REMS Transition and Enforcement Discretion

As shown in Table 1, the Modified REMS was approved on 29 July 2021. To support the transition of the Modified REMS, the CPMG started to operate a Transition Contact Center on 02 August 2021. The intent was to encourage and support recertification and reenrollment activities and to answer stakeholder questions regarding the Clozapine REMS transition, changes in stakeholder requirements, and certification and registration.

On 16 August 2021, the new Clozapine REMS website, with limited functionality, was launched to allow recertification and reenrollment activities to be completed online to assist stakeholders in preparing for the launch of the Modified Clozapine REMS on 15 November 2021. Two outbound call campaigns were conducted to encourage recertification and reenrollment in the Clozapine REMS prior to 15 November 2021. These campaigns were directed at high decile

prescribers (prescribers with ≥10 patients in the Legacy Clozapine REMS) and authorized representatives for chain/corporate pharmacies and wholesalers-distributors. A total of 31,266 calls were received by the Transition Contact Center; the majority (98.8%) of these calls were related to Clozapine REMS general operations. There was extensive outreach via email (initial and secondary—2 waves each) and hardcopy mail (initial and secondary—2 waves each) to prescribers, pharmacies, designees, and wholesalers-distributors prior to the launch of the Modified REMS. The number of emails sent was 46,772 and 38,287 for the initial communication waves 1 and 2, respectively; a similar number of emails was sent for the secondary communication. The number of hardcopy mailings sent was 45,014 and 6,924 for the initial hardcopy mail waves 1 and 2, respectively; a similar number of hardcopy mailings was sent for the secondary communication.

Despite these extensive efforts, the transition from the Legacy REMS to the Modified REMS in November 2021 did not go as planned. As a result of these issues and to ensure continuity of care, the FDA exercised enforcement discretion in November 2021, which included: (1) pharmacists may dispense without obtaining an RDA; and (2) wholesalers may ship to uncertified pharmacies. In November 2022, additional enforcement discretion was exercised to address the concern that inpatient pharmacies are not allowed to dispense 7 days' supply of clozapine to the patient upon discharge. With this additional enforcement discretion, the FDA does not object if pharmacies at inpatient facilities dispensed a quantity of clozapine upon discharge that is consistent with the patient's monitoring frequency (i.e., weekly monitoring = 7 days' supply; twice monthly monitoring = 14 days' supply; monthly monitoring = 30 days' supply).

3.0 SCOPE OF CLOZAPINE REMS

3.1 Clozapine REMS Overview

3.1.1 Clozapine REMS Goals and Objectives

The Clozapine REMS is a set of steps that all patients, prescribers, and pharmacists must follow.

The goal of the Clozapine REMS is to mitigate the risk of severe neutropenia associated with the use of clozapine.

The objectives of the Clozapine REMS are to:

1. Educate prescribers and pharmacists about the risk of severe neutropenia and appropriate monitoring requirements.
2. Inform patients about the risk of severe neutropenia and appropriate monitoring requirements.
3. Ensure prescribers submit documentation that periodic monitoring of patients is performed to identify severe neutropenia.
4. Ensure the prescriber documents a risk-benefit assessment when ANC falls below the acceptable range as described in the prescribing information.
5. Establish long-term safety and safe use of clozapine by enrolling all patients who receive clozapine in the registry.

3.1.2 Elements to Assure Safe Use

ETASU are intended to provide patients safe access to drugs with known serious risks that would otherwise be unavailable.

The Clozapine REMS Sponsors must ensure that HCPs, patients, pharmacies, and wholesalers-distributers comply with the required ETASU and additional requirements. These include:

- HCPs who prescribe clozapine must be certified in the REMS.
- Patients must be enrolled in the REMS by a prescriber or prescriber designee.
- On a monthly basis, prescribers must document and submit the ANC results, monitoring frequency, and appropriateness for continuing treatment for each patient via the PSF. A copy of the PSF is provided in Appendix A.
- Prescribers, prescriber designees, and pharmacists may document and submit individual ANC lab values outside of the PSF process.
- Pharmacies that dispense clozapine must be certified in the REMS.
- Pharmacies are required to obtain an RDA to dispense each clozapine prescription online or by calling the Contact Center.

Additional requirements:

- A certified pharmacy is required to confirm their authorized representative every 2 years.

- Ensure the PSF is received for each patient enrolled in the REMS. If the form is not received within 31 days of the date of the last PSF, the Clozapine REMS must contact the prescriber for the form.
- Wholesalers-distributors must register and ensure clozapine is distributed only to certified pharmacies.

3.1.3 Structure and Organization of Clozapine REMS

Table 2 lists all the current Sponsors in the Clozapine REMS.

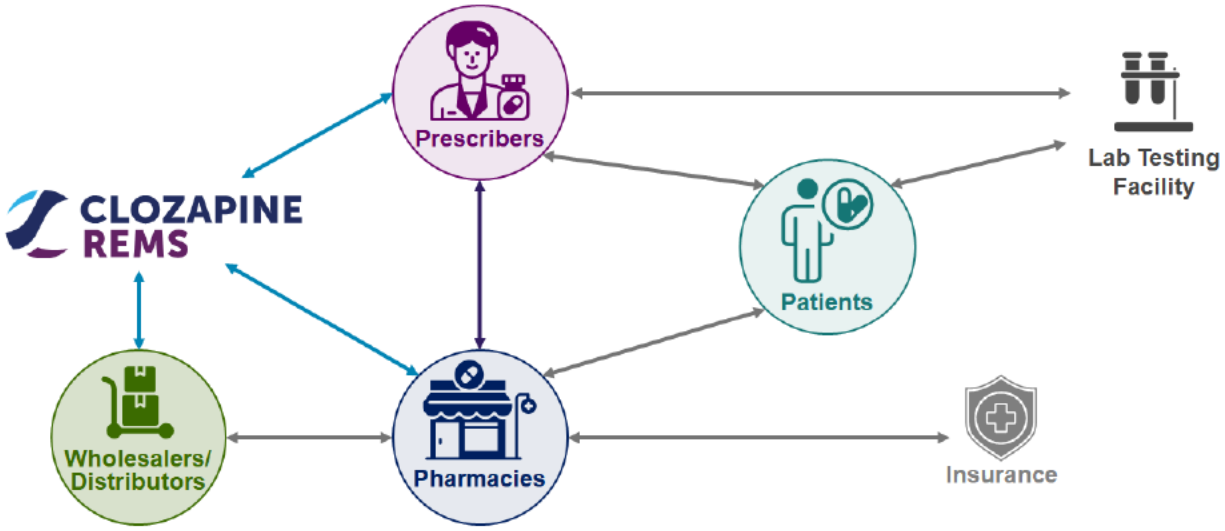
Table 2 Clozapine REMS Sponsors

Product Name	Current Application Holder	Added to REMS
Branded Products		
Clozaril®	HLS Therapeutics (USA), Inc.	15 Sep 2015
Versacloz®	Tasman Pharma, Inc.	15 Sep 2015
Generic Products		
Clozapine Tablets, USP	Accord Healthcare, Inc.	25 Nov 2015
Clozapine Tablets, USP	Aurobindo Pharma USA, Inc.	29 Nov 2016
Clozapine Tablets, USP	Dr. Reddy's Laboratories, Inc.[a]	17 Sep 2015
Clozapine Tablets, USP	Mylan Inc., A Viatris Company	15 Sep 2015
Clozapine ODT	Mylan Inc., A Viatris Company	15 Sep 2015
Clozapine Tablets, USP	Sun Pharmaceutical Industries, Inc.	15 Sep 2015
Clozapine ODT	Teva Pharmaceuticals USA, Inc.	25 Nov 2015

Note: Table reflects Sponsors with active NDA(s)/ANDA(s).
[a] Exiting REMS participant.
ANDA = Abbreviated New Drug Application; NDA = New Drug Application; ODT = orally disintegrating tablet; REMS = Risk Evaluation and Mitigation Strategy; USP = United States Pharmacopeia.

The Clozapine REMS provides a centralized point of access for prescribers/pharmacies to certify before prescribing/dispensing clozapine and through which to enroll and manage patients on clozapine (Figure 1). All key stakeholders interact with the Clozapine REMS. Prescriber interactions include certification, which includes enrollment and completion of a Knowledge Assessment (KA), patient enrollment, and entry of PSFs. Similarly, pharmacy interactions include certification; pharmacies must also obtain authorization to dispense each prescription to verify that the patient is enrolled and authorized to receive drug. Wholesalers-distributors must confirm that a pharmacy is certified in the Clozapine REMS before distributing to the pharmacy. Although patients and their caregivers do not interact directly with the Clozapine REMS, they do interact with their prescriber, lab, and pharmacy in order to be authorized to obtain clozapine.

Figure 1 Stakeholder Interactions With the Clozapine REMS



REMS = Risk Evaluation and Mitigation Strategy.

To minimize the risk of severe neutropenia associated with the use of clozapine, the REMS includes key requirements by stakeholders, as detailed in Table 3.

Table 3 Key Clozapine REMS Requirements by Stakeholder

Clozapine REMS Stakeholder	Requirement
Prescribers	• Must certify in the Clozapine REMS to prescribe clozapine • Must enroll all patients in the Clozapine REMS • Must provide a baseline ANC when enrolling a new patient • Must order ANC testing for each of their clozapine patients according to the clozapine prescribing information • Must verify each clozapine patient's ANCs in the Clozapine REMS monthly, using the PSF (submit an ANC Lab outside of the monthly reporting requirement using the ANC Lab Reporting Form)
Outpatient Pharmacies	• Must certify in the Clozapine REMS to dispense clozapine • Must obtain an RDA prior to dispensing a clozapine prescription – For the first dispensing after enrollment, the RDA will verify that ▪ The pharmacy is certified ▪ The patient is enrolled ▪ The patient's treatment is not interrupted or discontinued – For subsequent dispensing, the RDA will verify that ▪ The pharmacy is certified ▪ The patient is enrolled ▪ A PSF has been completed in the last 37 days • The prescriber has authorized the continuation of treatment if one or more labs are missing • The prescriber has provided a Treatment Rationale if the most current ANC lab value is below the acceptable range

Clozapine REMS Stakeholder	Requirement
	▪ The patient's treatment is not interrupted or discontinued
Inpatient Pharmacies	• Must certify in the Clozapine REMS to dispense clozapine • Must obtain an RDA before the **initial** dispensing of clozapine – For the first dispensing after enrollment, the RDA will verify that ▪ The pharmacy is certified ▪ The patient is enrolled ▪ The patient's treatment is not interrupted or discontinued
Patients	• Must be enrolled in the Clozapine REMS by a certified prescriber or prescriber designee to receive clozapine • Must comply with the ANC testing requirements
Wholesalers-Distributors	• Must enroll in the REMS to be authorized to purchase and distribute clozapine • Must establish processes and procedures to ensure the drug is distributed only to certified pharmacies

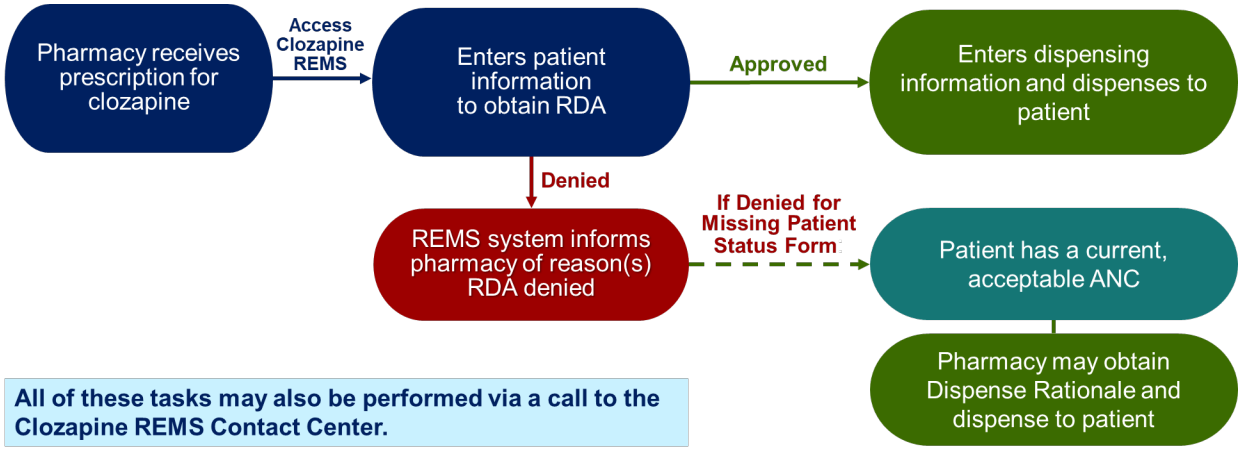
ANC = absolute neutrophil count; PSF = Patient Status Form; RDA = REMS Dispense Authorization; REMS = Risk Evaluation and Mitigation Strategy.

3.1.4 REMS Dispense Authorization Process

The RDA is the last Clozapine REMS system interaction prior to a patient being dispensed clozapine (Figure 2). The RDA is the authorization for a pharmacist to dispense a prescription. Outpatient pharmacies must obtain an RDA before ***each*** dispensing of a clozapine product and inpatient pharmacies must obtain an RDA before the ***first*** dispensing to a patient. Prior to providing an RDA, the system verifies that the patient is enrolled and authorized to receive the drug. To be authorized to receive the drug, the patient must have a current Patient Enrollment Form (PEF; received within the last 30 days) or a current PSF (received within the last 37 days) and not be in an Interrupted or Discontinued status. If the patient is enrolled (not in Interrupted or Discontinued status) but does not have a current PEF or a current PSF, the pharmacist may be able to use a Dispense Rationale to dispense clozapine to the patient. A Dispense Rationale requires a current ANC (obtained in the last 30 calendar days) within the acceptable range. The Dispense Rationale use is limited to 3 per patient per calendar year in the outpatient setting. This Dispense Rationale limit has been suspended with the enforcement discretion, thereby allowing for an unlimited number of Dispense Rationales to be used on an individual patient in the outpatient setting; inpatient use of the Dispense Rationale is unlimited by design and not affected by the enforcement discretion.

If all conditions are met, the RDA is generated; otherwise, it is rejected. When an RDA is rejected, the pharmacist is provided with the specific reason(s) for rejection. The prescriber is notified if the RDA is rejected because the patient is in an Interrupted or Discontinued status. This allows the stakeholder to address the problem preventing the RDA from being issued (e.g., by submitting a Treatment Rationale, by submitting an ANC within acceptable range). Once the problem has been resolved, the pharmacist can resubmit the RDA request. If all conditions are satisfied, the RDA is issued, and the pharmacist is authorized to dispense to the patient.

Figure 2 Pharmacy REMS Dispense Authorization Process

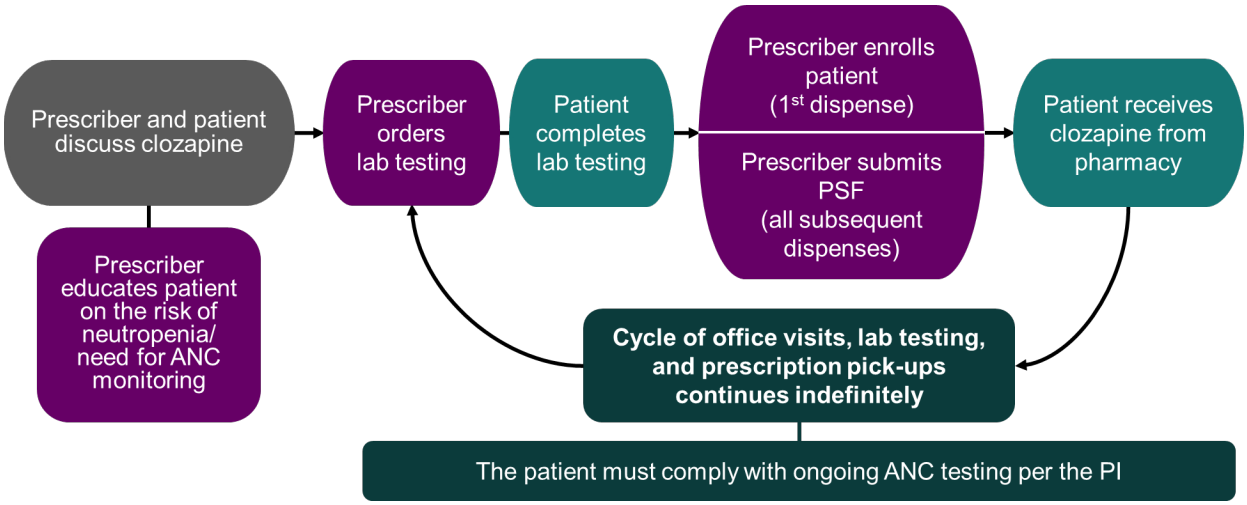


ANC = absolute neutrophil count; RDA = REMS Dispense Authorization.

3.1.5 Clozapine REMS Requirements for Patients and Prescribers

In adherence with REMS requirements, the patient and prescriber journey begins with a discussion of clozapine wherein the prescriber educates the patient on the risk of neutropenia and the need for ANC monitoring (Figure 3). Next, the prescriber orders lab testing for the patient prior to treatment initiation. Once the patient completes the testing, the prescriber enrolls the patient in the REMS. Thereafter, the patient can pick up clozapine from the pharmacy. The patient must comply with ongoing ANC testing, and their prescriber must continue to submit the PSF monthly for all subsequent dispenses. This cycle of office visits, blood draws, and prescription pick-ups continues indefinitely.

Figure 3 Patient and Prescriber Journey



ANC = absolute neutrophil count; PI, prescribing information; PSF = Patient Status Form.

3.2 Clozapine REMS Reporting

The Clozapine REMS Assessment Reports and corresponding reporting periods are listed in Table 4. Note that throughout the document, Assessments 1 through 5 reporting periods are referred to as Legacy REMS and Assessments 6 and 7 reporting periods are referred to as Modified REMS.

- The FDA informed the CPMG on 02 February 2016 and 09 August 2016 that it was waiving the requirement to submit a 6-month Assessment Report and a Year 1 Assessment Report, respectively, for the Clozapine REMS based on the ongoing communications and reporting by the CPMG to the FDA on the operations of the Clozapine REMS.
- On 18 October 2018, the FDA informed CPMG that the timetable for the submission of assessments will be modified to coincide with the implementation of the modification under review at that time.
- Assessment Report 3 was due on 28 February 2020, one year after the launch of the REMS modification. Subsequent Assessment Reports were to be due annually from the date of approval of that REMS modification.
- On 29 July 2021, the FDA approved a major modification to Clozapine REMS. With this modification, assessments are due 18 months from the date of the approval and every 18 months thereafter.
- An abbreviated REMS Assessment Report 5 was submitted to the FDA on 16 February 2022 to cover the period from the end of the previous reporting period (01 January 2021) through the launch of the modified Clozapine REMS (15 November 2021).
- Assessment 6 Report (i.e., also referred to as the "previous" report) was submitted on 13 February 2023. An addendum to Assessment 6 Report was submitted on 19 April 2024.
- Assessment 7 Report (i.e., also referred to as the "most recent" report) was submitted on 29 July 2024 covering the reporting period 01 December 2022 to 29 May 2024.
- The next report (Assessment Report 8) for the period 30 May 2024 to 30 November 2025 is due on 29 January 2026.

Table 4 Clozapine REMS Year and Corresponding Reporting Period

Clozapine REMS Year/ Assessment Report	Reporting Period	Date of Report Submission
Legacy REMS		
1	16 Jul 2016 to 15 Jul 2017	15 Sep 2017 (Resubmission: 22 Feb 2019)
2	16 Jul 2017 to 15 Jul 2018	22 Feb 2019
3	16 Jul 2018 to 31 Dec 2019[a] 16 Jul 2018 – 27 Feb 2019 28 Feb 2019 – 31 Dec 2019	30 Apr 2020
4	01 Jan 2020 to 31 Dec 2020	17 Mar 2021
5	01 Jan 2021 to 15 Nov 2021	16 Feb 2022

Clozapine REMS Year/ Assessment Report	Reporting Period	Date of Report Submission
Modified REMS		
6	29 Jul 2021 to 30 Nov 2022	13 Feb 2023 (Addendum: 19 Apr 2024)
7	01 Dec 2022 to 29 May 2024	29 Jul 2024

[a] The data collection for the reporting period for the Clozapine REMS Program Assessment 3 Report is 16 July 2018 through 31 December 2019. The Assessment 3 reporting period is delineated by two subreporting periods. The first subreporting period starts with the beginning of the Assessment 3 reporting period (16 July 2018) and ends the day before the implementation date of the modification (27 February 2019). The second subreporting period starts with the implementation date of the modification (28 February 2019) and extends to the end of the Assessment 3 reporting period (31 December 2019).
REMS = Risk Evaluation and Mitigation Strategy.

Note that enforcement discretions, implemented by the FDA on 19 November 2021 and 02 November 2022 to ease transition to the Modified REMS, were still in effect during the most recent reporting period (01 December 2022 to 29 May 2024). As a result of the enforcement discretion, monitoring of program compliance and inappropriate patient access was not conducted during the previous and most recent reporting periods. In general, data for these assessment metrics are not available for this reporting period. Therefore, due to the continued enforcement discretions, a complete assessment of the effectiveness of this REMS in meeting its stated goals could not be made.

3.2.1 Differences Between Legacy and Modified REMS Assessments

Table 5 summarizes key differences between Legacy and Modified REMS assessments.

Table 5 Key Differences Between Legacy and Modified REMS Assessments

Assessment	Description of Differences
Demographics	Demographics information was not reported as part of the Legacy REMS but is reported for the Modified REMS.
Treatment Rationale	• Legacy REMS: A patient's neutropenia level is determined from the patient's ANC. When a patient's ANC indicates moderate neutropenia (ANC 500-999 cells/µL, General Population) or severe neutropenia (ANC <500 cells/µL, General Population and Patients With BEN), a documented Treatment Rationale is required from the patient's prescriber to allow the patient to continue treatment in the Clozapine REMS. – Valid Treatment Rationales are ▪ *Patient Has BEN:* The patient has BEN and, therefore, would not require interruption of therapy unless ANC <500 cells/µL. ▪ *Benefits Outweigh Risks:* The prescriber believes that the benefits of clozapine therapy outweigh the risk of severe neutropenia. – Treatment Rationale of "Patient Has BEN" does not expire. A Treatment Rationale of "Benefits Outweigh Risks" will expire at the next reported ANC, or on a date specified by the prescriber, not to exceed 6 months from the provision of the Treatment Rationale. • Modified REMS: A patient's neutropenia level is determined by the patient's ANC. When a patient's ANC indicates moderate neutropenia (ANC 500-999 cells/µL, General Population) or severe neutropenia (ANC <500 cells/µL, General Population and Patients With BEN), a documented Treatment Rationale is required from the patient's prescriber to allow the patient to continue treatment in the Clozapine REMS. A Treatment Rationale is used when the prescriber believes that the benefits of clozapine therapy

Assessment	Description of Differences
	outweigh the risk of severe neutropenia. The prescriber must provide an end date for the Treatment Rationale, which may not exceed 6 months from the current date. – In the Modified REMS, there are patient types of General Population Patients and Patients With BEN. Therefore, if the ANC of a patient with BEN falls below 500 cells/μL, that patient is interrupted unless the prescriber creates a Treatment Rationale, which would expire.
Dispense Rationale	• The Modified Clozapine REMS provides certified pharmacies with an opportunity to apply clinical judgment and continue to dispense clozapine to enrolled patients when a rejection is received because a current PSF is not on file. To dispense to a patient who does not have an associated certified prescriber, the pharmacist must provide a Dispense Rationale to the Clozapine REMS.

ANC = absolute neutrophil count; BEN = benign ethnic neutropenia; PSF = Patient Status Form; REMS = Risk Evaluation and Mitigation Strategy.

4.0 CLOZAPINE REMS ASSESSMENT RESULTS

4.1 Modified REMS Assessment

Data are presented below for the most recent reporting period and cumulatively for the previous and most recent reporting periods. Where available, data from the previous reporting period are also presented.

4.1.1 REMS Implementation and Operation

4.1.1.1 Prescriber Certification

In the Clozapine REMS, prescribers can be in one of the following statuses:

1. **Unknown:** The prescriber has created login credentials on the Clozapine REMS website, has attempted/completed a KA, or both, but has not enrolled in the Clozapine REMS.
2. **Enrolled:** The prescriber has completed an enrollment form but has not successfully completed the KA.
3. **Certified:** The prescriber has completed an enrollment form and has successfully completed the KA.
4. **Deactivated:** The prescriber has been removed from the Clozapine REMS.
5. **Temporary Suspension:** The prescriber is temporarily suspended from participating in the Clozapine REMS due to noncompliance with the Clozapine REMS requirements.
6. **Permanent Suspension:** The prescriber is permanently suspended from participating in the Clozapine REMS due to noncompliance with the Clozapine REMS requirements.

At the end of the most recent reporting period, there were 58,452 prescribers in a certified status, 36 prescribers in a deactivated status, 532 prescribers in an enrolled status, and 3,444 in an unknown status (Table 6). One prescriber, a nurse practitioner, was placed under a status of temporary suspension during the reporting period for noncompliant activity identified in the previous reporting period.

The majority of certified prescribers were physician MDs (51.0%).

Table 6 Status of Prescribers at the End of the Reporting Period, Stratified by Credentials

Status	Credentials	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
		Count	Percent[a]	Count	Percent[a]
Certified	Physician MD	26,378	55.35	31,872	51.02
	Nurse Practitioner	12,923	27.12	19,216	30.76
	Physician DO	3,069	6.44	4,058	6.50
	Physician Assistant	1,690	3.55	2,348	3.76
	Other	651	1.37	958	1.53
Certified Total		**44,711**	**93.82**	**58,452**	**93.57**

Status	Credentials	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
		Count	Percent[a]	Count	Percent[a]
Deactivated	Physician MD	9	0.02	26	0.04
	Nurse Practitioner	4	0.01	5	0.01
	Unknown	2	0.00	2	0.00
	Other	1	0.00	1	0.00
	Physician Assistant	0	0.00	1	0.00
	Physician DO	0	0.00	1	0.00
Deactivated Total		**16**	**0.03**	**36**	**0.00**
Enrolled	Physician MD	246	0.52	283	0.45
	Nurse Practitioner	150	0.31	188	0.30
	Physician DO	24	0.05	37	0.06
	Physician Assistant	12	0.03	19	0.03
	Other	4	0.01	5	0.01
Enrolled Total		**436**	**0.91**	**532**	**0.85**
Temporary Suspension	Nurse Practitioner	0	0.00	1	0.00
Temporary Suspension Total		**0**	**0.00**	**1**	**0.00**
Unknown	Unknown	2,472	5.19	3,410	5.46
	Nurse Practitioner	14	0.03	20	0.03
	Other	2	0.00	10	0.02
	Physician Assistant	2	0.00	4	0.01
	Physician DO	1	0.00	0	0.00
	Physician MD	1	0.00	0	0.00
Unknown Total		**2,492**	**5.23**	**3,444**	**5.52**
TOTAL		**47,655**	**100**	**62,465**	**100**

[a] May not sum due to rounding.

Certified prescribers were evenly distributed in the geographic regions of the US with 26.6% in the South, 25.6% in the Northeast, 20.9% in the West, and 20.2% in the Midwest (Table 7).

Table 7 Status of Prescribers at the End of the Reporting Period, Stratified by Geographic Region

Status	Geographic Region[a]	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
		Count	Percent[b]	Count	Percent[b]
Certified	South	12,411	26.04	16,594	26.57
	Northeast	12,399	26.02	16,017	25.64
	West	10,112	21.22	13,080	20.94

Status	Geographic Region[a]	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
		Count	Percent[b]	Count	Percent[b]
	Midwest	9,658	20.27	12,600	20.17
	US Territory	130	0.27	160	0.26
	Military	1	0.00	1	0.00
Certified Total		**44,711**	**93.82**	**58,452**	**93.58**
Decertified	Northeast	2	0.00	10	0.02
	Midwest	4	0.01	9	0.01
	South	5	0.01	9	0.01
	West	3	0.01	6	0.01
	Unknown	2	0.00	2	0.00
Decertified Total		**16**	**0.03**	**36**	**0.06**
Enrolled	South	129	0.27	177	0.28
	Northeast	126	0.26	149	0.24
	Midwest	97	0.20	109	0.17
	West	81	0.17	94	0.15
	US Territory	3	0.01	3	0.00
Enrolled Total		**436**	**0.91**	**532**	**0.85**
Temporary Suspension	Northeast	0	0.00	1	0.00
Temporary Suspension Total		**0**	**0.00**	**1**	**0.00**
Unknown	Unknown[c]	2,370	4.97	3,299	5.28
	Northeast	46	0.10	51	0.08
	South	34	0.07	39	0.06
	Midwest	23	0.05	31	0.05
	West	19	0.04	24	0.04
Unknown Total		**2,492**	**5.23**	**3,444**	**5.51**
TOTAL		**47,659**	**100**	**62,465**	**100**

[a] As defined by the US Census.
[b] May not sum due to rounding.
[c] Prescribers who have only created login credentials have not provided a state; therefore, the geographic region is unknown.
US = United States.

During the most recent reporting period, 35,195 prescribers prescribed clozapine at least once (Table 8). The majority of these active prescribers were physician MDs (55.4%). Active prescribers were fairly evenly distributed in the geographic regions of the US with 28.1% in the Northeast, 26.7% in the South, 22.9% in the West, and 22.1% in the Midwest (Table 9).

Table 8 Active Prescribers, Stratified by Credential

Credential	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
Physician MD	18,264	59.48	19,510	55.43	23,290	55.97
Nurse Practitioner	8,954	29.16	11,577	32.89	13,429	32.28
Physician DO	1,966	6.40	2,329	6.62	2,790	6.71
Physician Assistant	1,132	3.69	1,344	3.82	1,604	3.86
Other	389	1.27	435	1.24	495	1.19
Total	**30,705**	**100**	**35,195**	**100**	**41,608**	**100**

[a] May not sum due to rounding.

Table 9 Active Prescribers, Stratified by Geographic Region

Geographic Region[a]	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[b]	Count	Percent[b]	Count	Percent[b]
Northeast	8,777	28.58	9,897	28.12	11,826	28.42
South	8,146	26.53	9,393	26.69	11,255	27.05
West	6,993	22.77	8,053	22.88	9,443	22.70
Midwest	6,714	21.87	7,766	22.07	8,987	21.60
US Territory	75	0.24	86	0.24	97	0.23
Total	**30,705**	**100**	**35,195**	**100**	**41,608**	**100**

[a] As defined by US Census.
[b] May not sum due to rounding.
US = United States.

4.1.1.2 Pharmacy Certification

Inpatient and outpatient pharmacies can be in one of the following statuses:

1. **Enrolled:** A completed enrollment form has been submitted for the pharmacy, but the authorized representative has not successfully completed the KA.
2. **Certified:** A completed enrollment form has been submitted for the pharmacy, and the authorized representative has successfully completed the KA.
3. **Deactivated:** The pharmacy has been removed from the Clozapine REMS.
4. **Decertified:** The pharmacy is suspended from participating in the Clozapine REMS due to noncompliance with the Clozapine REMS requirements.

At the end of the most recent reporting period, there were a total of 47,604 pharmacies certified in the Clozapine REMS; of these, 4,317 were certified inpatient pharmacies and 43,287 were certified outpatient pharmacies (Table 10).

Overall, there were 2,710 pharmacies in a decertified status and 125 in an enrolled status.

Table 10 Status of Pharmacies at the End of the Reporting Period, Stratified by Pharmacy Type

Certification Status	Pharmacy Type	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
		Count	Percent[a]	Count	Percent[a]
Certified	Inpatient	4,096	8.58	4,317	8.56
	Outpatient	43,537	91.15	43,287	85.82
Certified Total		**47,633**	**99.73**	**47,604**	**94.38**
Decertified	Inpatient	15	0.03	413	0.82
	Outpatient	9	0.02	2,297	4.55
Decertified Total		**24**	**0.05**	**2,710**	**5.37**
Enrolled	Inpatient	32	0.07	44	0.09
	Outpatient	75	0.16	81	0.16
Enrolled Total		**107**	**0.23**	**125**	**0.25**
Certification Status Total		**47,764**	**100**	**50,439**	**100**

[a] May not sum due to rounding.

Table 11 presents the pharmacies by geographic region. The largest percentage of certified pharmacies were outpatient pharmacies in the South (32.2%) followed by the Midwest (19.5%), the Northeast (17.3%), and the West (16.5%).

Table 11 Status of Pharmacies at the End of the Reporting Period, Stratified by Pharmacy Type and Geographic Region

Certification Status	Pharmacy Type	Geographic Region	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
			Count	Percent[a]	Count	Percent[a]
Certified	Inpatient	Midwest	1,056	2.21	1,149	2.28
		Northeast	867	1.82	901	1.79
		South	1,343	2.81	1,414	2.80
		US Territory	9	0.02	9	0.02
		West	821	1.72	844	1.67
	Certified Inpatient Total		**4,096**	**8.58**	**4,317**	**8.56**
	Outpatient	Midwest	9,965	20.86	9,847	19.52
		Military	1	0.00	1	0.00
		Northeast	8,674	18.16	8,711	17.27

Certification Status	Pharmacy Type	Geographic Region	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
			Count	Percent[a]	Count	Percent[a]
		South	16,438	34.42	16,222	32.16
		US Territory	220	0.46	208	0.41
		West	8,239	17.25	8,298	16.45
	Certified Outpatient Total		**43,537**	**91.15**	**43,287**	**85.81**
Certified Total			**47,633**	**99.73**	**47,604**	**94.37**
Decertified	Inpatient	Midwest	0	0.00	82	0.16
		Northeast	5	0.01	75	0.15
		South	5	0.01	159	0.32
		US Territory	0	0.00	1	0.00
		West	5	0.01	96	0.19
	Decertified Inpatient Total		**15**	**0.03**	**413**	**0.82**
	Outpatient	Midwest	2	0.00	464	0.92
		Northeast	1	0.00	364	0.72
		South	3	0.01	1,109	2.20
		US Territory	0	0.00	17	0.03
		West	3	0.01	343	0.68
	Decertified Outpatient Total		**9**	**0.02**	**2,297**	**4.55**
Decertified Total			**24**	**0.05**	**2,710**	**5.37**
Enrolled	Inpatient	Midwest	7	0.01	8	0.02
		Northeast	4	0.01	8	0.02
		South	12	0.03	16	0.03
		West	9	0.02	12	0.02
	Enrolled Inpatient Total		**32**	**0.07**	**44**	**0.09**
	Outpatient	Midwest	10	0.02	14	0.03
		Northeast	16	0.03	19	0.04
		South	36	0.08	39	0.08
		West	13	0.03	9	0.02
	Enrolled Outpatient Total		**75**	**0.16**	**81**	**0.17**
Enrolled Total			**107**	**0.22**	**125**	**0.26**
Certification Status Total			**47,764**	**100**	**50,439**	**100**

[a] May not sum due to rounding.
US = United States.

During the most recent reporting period, 2,996 inpatient pharmacies and 24,988 outpatient pharmacies dispensed clozapine at least once (Table 12). The largest percentage of active pharmacies were outpatient pharmacies in the South (30.2%), followed by the Midwest (22.3%), the Northeast (20.7%), and the West (15.7%).

Table 12 Active Pharmacies, Stratified by Pharmacy Type and Geographic Region

Pharmacy Type	Geographic Region	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
		Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
Inpatient	Midwest	722	2.87	814	2.91	922	2.90
	Northeast	597	2.37	658	2.35	738	2.32
	South	818	3.25	913	3.26	1,079	3.40
	US Territory	1	0.00	—	0.00	1	0.00
	West	557	2.21	611	2.18	712	2.24
Inpatient Total		**2,695**	**10.71**	**2,996**	**10.70**	**3,452**	**10.86**
Outpatient	Midwest	5,767	22.91	6,239	22.29	7,012	22.07
	Northeast	5,460	21.69	5,792	20.70	6,558	20.64
	South	7,333	29.13	8,446	30.18	9,632	30.31
	US Territory	97	0.39	109	0.39	128	0.40
	West	3,818	15.17	4,402	15.73	4,994	15.72
Outpatient Total		**22,475**	**89.29**	**24,988**	**89.29**	**28,324**	**89.14**
Pharmacy Total		**25,170**	**100**	**27,984**	**100**	**31,776**	**100**

[a] May not sum due to rounding.
US = United States.

4.1.1.3 Prescriber Designee Certification

At the end of the most recent reporting period, there were 23,316 prescriber designees in the Clozapine REMS (Table 13). Of these, 20,576 (88.3%) prescriber designees were authorized to work on behalf of a certified prescriber, 1,822 (7.8%) were enrolled but were not associated with a certified prescriber, and 918 (3.9%) had been associated with a prescriber but are no longer authorized to work on the prescriber's behalf.

Table 13 Status of Prescriber Designees at the End of the Reporting Period

Enrollment Status	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]
Authorized	14,016	88.21	20,576	88.25
Enrolled	1,176	7.4	1,822	7.81
Unauthorized	697	4.39	918	3.94
Enrollment Status Total	**15,889**	**100**	**23,316**	**100**

[a] May not sum due to rounding.

During the most recent reporting period, 20,338 prescriber designees were active, meaning they were associated with a prescriber who prescribed clozapine at least once during the reporting period (Table 14).

Table 14 Active Designees

Active Designees	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022) Count	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024) Count	Cumulative (29 Jul 2021 – 29 May 2024) Count
Active	13,656	20,338	21,106
Active Designees Total	**13,656**	**20,338**	**21,106**

4.1.1.4 Patient Status

Patients enrolled in the Clozapine REMS can be in one of the following treatment statuses:

1. **Active:** Receiving clozapine at regular intervals consistent with their monitoring frequency.
2. **Interrupted:** Clozapine usage has stopped temporarily pending next actions before resuming therapy or being permanently discontinued.
3. **Discontinued:** Clozapine usage has stopped.

The Clozapine REMS ended the reporting period with 154,178 patients. The majority of these patients (149,203; 96.8%) were in an Active treatment status, 3,622 (2.4%) had been discontinued, and 1,353 (0.9%) were in an Interrupted treatment status (Table 15).

Table 15 Total Patient Count by Treatment Status

Treatment Status	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022) Count	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022) Percent[a]	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024) Count	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024) Percent[a]
Active	122,500	97.81	149,203	96.77
Discontinued	1,707	1.36	3,622	2.35
Interrupted	1,033	0.82	1,353	0.88
Treatment Status Total	**125,240**	**100**	**154,178**	**100**

[a] May not sum due to rounding.

The majority of clozapine patients range from 20 to 69 years of age, with the age group 30-39 having the largest percentage (21.2%) of patients (Table 16).

Table 16 Total Patient Count Stratified by Age Group

Age Group	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022) Count	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022) Percent[a]	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024) Count	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024) Percent[a]
0-9	59	0.05	83	0.05
10-19	2,387	1.91	2,427	1.57
20-29	16,200	12.94	19,073	12.37

Age Group	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]
30-39	25,908	20.69	32,602	21.15
40-49	24,241	19.36	30,073	19.51
50-59	25,300	20.20	27,696	17.96
60-69	23,296	18.60	29,228	18.96
70-79	6,802	5.43	11,009	7.14
80-89	972	0.78	1,825	1.18
90-99	74	0.06	159	0.10
100+	1	0.00	3	0.00
Total	**125,240**	**100**	**154,178**	**100**

[a] May not sum due to rounding.

More males (62%) than females (37.7%) are enrolled in the Clozapine REMS (Table 17).

Table 17 Total Patients Stratified by Gender

Gender	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]
Male	77,964	62.25	95,602	62.01
Female	47,054	37.57	58,092	37.68
Other	222	0.18	312	0.20
Unknown	0	0.00	172	0.11
Total	**125,240**	**100**	**154,178**	**100**

[a] May not sum due to rounding.

Patients who are not Hispanic or Latino make up over 89.6% of enrolled patients (Table 18).

Table 18 Total Patients Stratified by Ethnicity

Ethnicity	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]
Not Hispanic or Latino	113,428	90.57	138,074	89.55
Hispanic or Latino	11,812	9.43	15,399	9.99
Unknown	0	0.00	705	0.46
Total	**125,240**	**100**	**154,178**	**100**

[a] May not sum due to rounding.

The 2 most common patient races reported during enrollment are Caucasian (70%) and Black or African American (16.3%) (Table 19).

Table 19 Total Patients Stratified by Race

Race	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]
Caucasian	89,240	71.26	107,943	70.01
Black or African American	19,182	15.32	25,139	16.31
Other	9,527	7.61	11,726	7.61
Asian	4,467	3.57	5,529	3.59
American Indian or Alaska Native	1,581	1.26	2,038	1.32
Native Hawaiian or Other Pacific Islander	464	0.37	602	0.39
More than one race	779	0.62	1,201	0.78
Total	**125,240**	**100**	**154,178**	**100**

[a] May not sum due to rounding.

Due to the transient nature of some clozapine patients, the ZIP code is not a mandatory field on the PEF. Because of this, it is not possible to determine the geographic region for 23.2% of the patients (Table 20). Patients are evenly distributed in the Northeast (21.5%), Midwest (19.4%), South (18.2%), and West (17.5%).

Table 20 Total Patients Stratified by Geographic Region

Geographic Region	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]
Not Provided	27,844	22.23	35,727	23.17
Northeast	27,967	22.33	33,205	21.54
Midwest	24,976	19.94	29,920	19.41
South	22,505	17.97	28,056	18.20
West	21,705	17.33	26,969	17.49
US Territory	243	0.19	301	0.20
Total	**125,240**	**100**	**154,178**	**100**

[a] May not sum due to rounding.
US = United States.

A patient is considered actively on clozapine if the patient received at least one authorization to dispense during the most recent reporting period. During the most recent reporting period, 115,298 patients received at least one authorization to dispense (Table 21). The age groups with the most patients receiving at least one authorization were 30-39 (21%), 40-49 (19.7%), 60-69 (19.2%), 50-59 (18.5%), and 20-29 (12.3%).

Table 21 Active Patients Stratified by Age Group

Age Group	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
0-9	12	0.01	14	0.01	15	0.01
10-19	2,024	1.94	1,908	1.65	2,102	1.57
20-29	13,547	12.99	14,219	12.33	16,400	12.28
30-39	21,414	20.54	24,209	21.00	27,919	20.90
40-49	20,142	19.32	22,671	19.66	26,004	19.47
50-59	21,026	20.17	20,976	18.19	24,106	18.05
60-69	19,461	18.67	22,089	19.16	25,660	19.21
70-79	5,766	5.53	7,943	6.89	9,668	7.24
80-89	807	0.77	1,185	1.03	1,580	1.18
90-99	58	0.06	82	0.07	130	0.10
100+	0	0.00	2	0.00	2	0.00
Total	**104,257**	**100**	**115,298**	**100**	**133,586**	**100**

[a] May not sum due to rounding.

Similar to the gender of all enrolled patients, more males (61.7%) than females (38%) received at least one authorization to dispense (Table 22).

Table 22 Active Patients Stratified by Gender

Gender	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
Male	64,528	61.89	71,088	61.66	82,440	61.71
Female	39,552	37.94	43,855	38.04	50,752	37.99
Other	177	0.17	355	0.31	394	0.29
Total	**104,257**	**100**	**115,298**	**100**	**133,586**	**100**

[a] May not sum due to rounding.

Similar to the ethnicity of all enrolled patients, more patients who are not Hispanic or Latino (90.2%) than those who are Hispanic or Latino (9.4%) received at least one authorization to dispense (Table 23).

Table 23 Active Patients Stratified by Ethnicity

Ethnicity	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
Not Hispanic or Latino	94,840	90.97	103,967	90.17	120,288	90.05
Hispanic or Latino	9,417	9.03	10,804	9.37	12,771	9.56
Unknown	0	0.00	527	0.46	527	0.39
Total	**104,257**	**100**	**115,298**	**100**	**133,586**	**100**

[a] May not sum due to rounding.

Similar to the race of all enrolled patients, Caucasian patients (71.7%) and Black or African American patients (15.1%) received the majority of authorizations to dispense (Table 24).

Table 24 Active Patients Stratified by Race

Race	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
Caucasian	75,448	72.37	82,646	71.68	94,876	71.02
Black or African American	15,321	14.70	17,395	15.09	20,848	15.61
Other	7,558	7.25	8,223	7.13	9,789	7.33
Asian	3,612	3.46	4,140	3.59	4,744	3.55
American Indian or Alaska Native	1,326	1.27	1,514	1.31	1,763	1.32
Native Hawaiian or Other Pacific Islander	339	0.33	409	0.35	482	0.36
More than one race	653	0.63	971	0.84	1,084	0.81
Total	**104,257**	**100**	**115,298**	**100**	**133,586**	**100**

[a] May not sum due to rounding.

Similar to the geographic region of all enrolled patients, active patients are evenly distributed in the geographic regions of the US (Table 25).

Table 25 Active Patients Stratified by Geographic Region

Geographic Region	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
Not Provided	22,881	21.95	25,898	22.46	44,186	33.08
Northeast	23,674	22.71	25,373	22.01	25,373	18.99

Geographic Region	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
Midwest	21,438	20.56	23,470	20.36	23,470	17.57
South	18,241	17.50	20,525	17.80	20,525	15.36
West	17,853	17.12	19,829	17.20	19,829	14.84
US Territory	170	0.16	203	0.18	203	0.15
Total	**104,257**	**100**	**115,298**	**100**	**133,586**	**100**

[a] May not sum due to rounding.

4.1.1.5 Program Compliance

A patient may receive a clozapine dispense for a prescription written by a prescriber that is not certified in the Clozapine REMS. This can be accomplished by either a Transition Dispense Rationale or a Dispense Rationale. During the reporting period, 32,508 clozapine prescriptions were dispensed, which were written by 9,072 uncertified prescribers (Table 26).

Table 26 Number of Clozapine Prescriptions Written by an Uncertified Prescriber

Method	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count of Clozapine Dispenses	Count of Unique Prescribers	Count of Clozapine Dispenses	Count of Unique Prescribers	Count of Clozapine Dispenses	Count of Unique Prescribers
Dispense Rationale	3,925	1,863[a]	26,433	7,960[a]	30,365	9,029[a]
Transition Dispense Rationale	21,985	6,817[b]	6,075	1,550[b]	28,060	7,869[b]
Total	**25,910**	**8,336[c]**	**32,508**	**9,072[c]**	**58,425**	**15,890[c]**

[a] Unique across Dispense Rationales.
[b] Unique across Transition Dispense Rationales.
[c] Unique across both Transition Dispense Rationales and Dispense Rationales.

4.1.2 Evaluation of Safe-Use Behavior

4.1.2.1 Clozapine Utilization Data

During the most recent reporting period, 115,298 patients received at least one RDA, for a total of 2,812,609 RDAs (Table 27). It is important to note that there is not necessarily a 1:1 relationship between an RDA and a dispense of clozapine. While the RDA is the authorization for the pharmacy to dispense clozapine, it does not guarantee that clozapine was actually dispensed to the patient. If clozapine is not dispensed to the patient, the pharmacy is expected to

reverse the authorization, but there is no way to ensure this is done. During the most recent reporting period, 70,929 authorizations were reversed (Table 27).

Table 27 REMS Dispense Authorizations

REMS Dispense Authorizations[a]	Previous Reporting Period (29 Jul 2021 - 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
Authorized	1,195,261	67.09	2,017,864	71.74	3,213,125	69.94
Rejected	543,649	30.52	723,816	25.73	1,267,465	27.59
Reversed	42,622	2.39	70,929	2.52	113,551	2.47
RDA Total	**1,781,532**	**100**	**2,812,609**	**100**	**4,594,141**	**100**

[a] Clozapine REMS database.
RDA = REMS Dispense Authorization; REMS = Risk Evaluation and Mitigation Strategy.

Table 28 is presented in response to an FDA request to estimate the number of patients in the US who received a prescription dispense for clozapine from an outpatient retail pharmacy. These data were obtained by IQVIA™ from a retrospective assessment of the number of patients who received a prescription dispensing for clozapine from a US outpatient retail pharmacy for the reporting period 01 December 2022 through 29 May 2024. Outpatient retail pharmacies were defined as retail drugstores, grocery store pharmacies, ambulatory care pharmacies, and pharmacies dispensing to long-term care (LTC) and rehabilitation facilities. Prescription dispensing to prison systems were not included in the estimate, as the data source (IQVIA Longitudinal Prescriptions [LRx] database) does not contain prescription dispensing information from prison systems.

Pharmacies are certified in the Clozapine REMS as either an outpatient pharmacy or an inpatient pharmacy. No further delineation is available for certified outpatient pharmacies to determine how a pharmacy aligns with the definitions utilized by IQVIA. Without this determination, it is difficult to verify if the data are comparable. Furthermore, the IQVIA LRx database used for the assessment represents approximately 94% of prescriptions dispensed at retail pharmacies, 72% dispensed for combined mail order, and 75% dispensed at LTC facilities.

This retrospective assessment by IQVIA indicated that 106,051 patients had a retail pharmacy dispensing for clozapine in the LRx database between 01 December 2022 and 29 May 2024.

Table 28 Number of Patients With ≥1 Prescription Dispensing for Clozapine at a US Outpatient Retail Pharmacy in the LRx Database Between 01 Dec 2022 Through 29 May 2024

	N
Total Patients[a]	**106,051**

Note: US outpatient retail pharmacy is defined as retail drugstores, grocery pharmacies, ambulatory care pharmacies, and pharmacies dispensing to LTC and rehabilitation facilities. Prescriptions dispensed in prison systems are not included in the LRx database.
[a] N = 6 patients had invalid or missing age; N = 95 patients had missing or unknown sex; and N = 0 patients had missing/unknown age and sex.
LRx = Longitudinal Prescriptions; LTC = long-term care; US = United States.

Dispense authorizations were evenly dispersed throughout the geographic regions of the US, with 22.7% in the Northeast, 21.1% in the Midwest, 18.8% in the West, and 16% in the South (Table 29).

Table 29 Approved REMS Dispense Authorizations Stratified by Geographic Region

Geographic Region	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
Northeast	271,551	22.72	457,763	22.69	729,314	22.70
Not Provided	250,118	20.93	429,511	21.29	679,629	21.15
Midwest	257,007	21.50	425,670	21.10	682,677	21.25
West	233,280	19.52	378,420	18.75	611,700	19.04
South	181,637	15.20	323,455	16.03	505,092	15.72
US Territory	1,668	0.14	3,045	0.15	4,713	0.15
Total	**1,195,261**	**100**	**2,017,864**	**100**	**3,213,125**	**100**

[a] May not sum due to rounding.
REMS = Risk Evaluation and Mitigation Strategy; US = United States.

4.1.2.1.1 Time to Authorize Unique Prescriptions

When an RDA is rejected, the relevant stakeholder is notified of the reason for rejection. This allows the stakeholder to address the problem preventing the RDA from being issued. Once the problem has been resolved, the pharmacist can resubmit the RDA request.

Table 30 presents the minimum, maximum, average, and median days it took to obtain an RDA after a rejection through the REMS Contact Center, Application Programming Interface (API), website, and overall.

In the most recent reporting period, the minimum days to obtain an authorization after a rejection for all methods was 0 days.

The maximum days for obtaining an RDA through the Contact Center was 476 days, the average was 8 days, and the median was 0 days.

The maximum days for obtaining an RDA through the API was 365 days, the average was 26.4 days, and the median was 12 days.

The maximum days for obtaining an RDA through the website was 538 days, the average was 9.7 days, and the median was 1 day.

The maximum days for obtaining an RDA overall was 538 days, the average was 10.6 days, and the median was 1 day.

Table 30 Time to Authorization Between Rejection and RDA

Time to Authorization	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)
Clozapine REMS Contact Center		
Minimum Days	0	0
Maximum Days	332	476
Average Days	11.96	7.98
Median Days	1	0
Clozapine REMS API		
Minimum Days	0	0
Maximum Days	307	365
Average Days	42.86	26.35
Median Days	16	12
Clozapine REMS Website		
Minimum Days	0	0
Maximum Days	364	538
Average Days	14.6	9.72
Median Days	2	1
Overall		
Minimum Days	0	0
Maximum Days	364	538
Average Days	18.05	10.55
Median Days	2	1

API = Application Programming Interface; REMS = Risk Evaluation and Mitigation Strategy; RDA = REMS Dispense Authorization.

Table 31 presents the minimum, maximum, average, and median days it took to obtain an RDA after a rejection through the REMS Contact Center, API, website, and overall stratified by the reason for rejection.

In the most recent reporting period, the minimum days to obtain an authorization after a rejection for all methods was 0 days.

The maximum days to obtain an authorization via the website after a rejection for "PSF is required" was 538 days, with a mean of 9.4 days and a median of 1 day for this reject reason.

The maximum days to obtain an authorization via the Contact Center after a rejection for "PSF is required" was 467 days, with a mean of 8.2 days and a median of 0 days for this reject reason.

The maximum days to obtain an authorization via the API after a rejection for "PSF is required" was 365 days, with a mean of 26.8 days and a median of 12 days for this reject reason.

Table 31 Time to Authorization Between Rejection and RDA Stratified by Reason for Rejection

Reason for Rejection	Method	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)				Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)			
		Minimum	Maximum	Mean	Median	Minimum	Maximum	Mean	Median
Dispense Rationale ANC not current	Contact Center	0	218	15.25	2	0	350	11.71	1
	API	0	84	16.90	13	0	59	9.47	5
	Website	0	327	13.83	3	0	437	12.54	3
Dispense Rationale ANC not current across all methods		**0**	**327**	**13.88**	**3**	**0**	**437**	**12.52**	**3**
Dispense Rationale ANC too low	Contact Center	0	223	25.83	6	0	83	4.61	0
	API	0	212	56.80	22	NA[a]	NA[a]	NA[a]	NA[a]
	Website	0	290	20.24	5	0	422	22.10	3
Dispense Rationale ANC too low across all methods		**0**	**290**	**20.57**	**5**	**0**	**422**	**20.45**	**2**
Dispense Rationale limit has been reached	Website	0	50	2.84	0	NA[a]	NA[a]	NA[a]	NA[a]
Dispense Rationale limit has been reached across all methods		**0**	**50**	**2.84**	**0**	**NA[a]**	**NA[a]**	**NA[a]**	**NA[a]**
Patient is in discontinued treatment status	Contact Center	0	17	4.88	1	0	28	4.10	0
	API	0	30	19.20	21	0	243	18.99	5
	Website	0	155	12.53	2	0	483	23.99	3
Patient is in discontinued treatment status across all methods		**0**	**155**	**12.51**	**2**	**0**	**483**	**22.73**	**4**
Patient is in interrupted treatment status	Contact Center	0	251	29.73	7	0	107	4.96	0
	API	0	307	123.71	175	0	34	4.83	0
	Website	0	364	23.28	5	0	492	21.25	2
Patient is in interrupted treatment status across all methods		**0**	**364**	**58.08**	**14**	**0**	**492**	**19.88**	**2**
PSF is required	Contact Center	0	332	11.24	0	0	467	8.16	0
	API	0	299	30.45	14	0	365	26.77	12

Reason for Rejection	Method	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)				Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)			
		Minimum	Maximum	Mean	Median	Minimum	Maximum	Mean	Median
	Website	0	339	14.28	1	0	538	9.43	1
PSF is required across all methods		**0**	**339**	**16.10**	**2**	**0**	**538**	**10.31**	**1**
Pharmacy is not certified	Contact Center	NA	NA	NA	NA	0	0	0	0
	Website	0	1	0.80	1	0	4	0.70	0
Pharmacy is not certified across all methods		**0**	**1**	**0.80**	**1**	**0**	**4**	**0.54**	**0**
Pharmacy personnel is not certified	Contact Center	0	0	0.00	0	NA[a]	NA[a]	NA[a]	NA[a]
Pharmacy personnel is not certified across all methods		**0**	**0**	**0.00**	**0**	**NA[a]**	**NA[a]**	**NA[a]**	**NA[a]**
The patient was not found	Contact Center	NA[a]	NA[a]	NA[a]	NA[a]	0	0	0.00	0
	API	0	50	25.00	25	0	250	46.83	10
	Website	0	22	1.56	0	0	145	3.03	0
The patient was not found across all methods		**0**	**50**	**3.30**	**0**	**0**	**250**	**4.26**	**0**
The pharmacy personnel was not found	Website	0	28	2.31	0	0	29	2.00	0
The pharmacy personnel was not found across all methods		**0**	**28**	**2.31**	**0**	**0**	**29**	**2.00**	**0**
The entered ANC indicates that the patient has moderate neutropenia and has been moved to an interrupted treatment status	Contact Center	NA[a]	NA[a]	NA[a]	NA[a]	0	2	0.39	0
	Website	NA[a]	NA[a]	NA[a]	NA[a]	0	154	10.03	1
The entered ANC indicates that the patient has moderate neutropenia and has been moved to an interrupted treatment status across all methods		**NA[a]**	**NA[a]**	**NA[a]**	**NA[a]**	**0**	**154**	**8.78**	**0**

Reason for Rejection	Method	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)				Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)			
		Minimum	Maximum	Mean	Median	Minimum	Maximum	Mean	Median
The entered ANC indicates that the patient has severe neutropenia and has been moved to an interrupted treatment status	Contact Center	NA[a]	NA[a]	NA[a]	NA[a]	0	68	3.47	0
	API	NA[a]	NA[a]	NA[a]	NA[a]	0	2	1	1
	Website	NA[a]	NA[a]	NA[a]	NA[a]	0	128	9.22	1
The entered ANC indicates that the patient has severe neutropenia and has been moved to an interrupted treatment status across all methods		**NA[a]**	**NA[a]**	**NA[a]**	**NA[a]**	**0**	**128**	**8.40**	**0**
Across all reasons for rejection and all methods		**0**	**364**	**18.05**	**2**	**0**	**538**	**10.55**	**1**

[a] NA indicates that there are no data for this reason for rejection and method.
ANC = absolute neutrophil count; API = Application Programming Interface; NA = not applicable; PSF = Patient Status Form; RDA = REMS Dispense Authorization.

4.1.2.2 Patient Status Forms

The PSF is the primary communication tool for a prescriber to submit patient data to the REMS. During clozapine treatment, the prescriber is required to document and submit ANC results monthly to the Clozapine REMS using the PSF. This form is also used to document the patient's monitoring frequency and appropriateness of continuing treatment (Treatment Rationale) and to change the patient's treatment status. The next PSF is due within 37 calendar days after the date of the last PSF. A missing PSF will result in a dispense authorization rejection and may disrupt the patient's care if a Dispense Rationale cannot be used.

If a patient's treatment has been interrupted or discontinued, the prescriber must submit a PSF to resume treatment.

For the most recent reporting period, 1,732,050 PSFs were submitted for 120,943 unique patients (Table 32).

Table 32 Number of PSFs Submitted

Description	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)
PSFs submitted	**1,084,430**	**1,732,050**
Count of unique patients	110,651	120,943

PSF = Patient Status Form.

At the end of the most recent reporting period, the majority (56.8%) of patients' PSFs were not yet due (Table 33).

Table 33 PSF Status as of the Cut-off Date

PSF Status	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]
Not yet due	13,340	12.8	75,822	56.76
Past due	89,193	85.55	54,098	40.50
Discontinued – not expected	1,263	1.21	2,880	2.16
Interrupted – requires a PSF to resume	461	0.44	784	0.59
Total	**104,257**	**100**	**133,584**	**100**

[a] May not sum due to rounding.
PSF = Patient Status Form.

During the most recent reporting period, 501,049 PSFs were received past the due date (Table 34). As a result, 68,788 patients experienced 694,062 rejections due to a missing PSF (Table 35).

Table 34 Number of PSFs Not Received Within 37 Calendar Days After the Date of the Last PSF Submission

PSF Status	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022) Count	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024) Count	Cumulative (29 Jul 2021 – 29 May 2024) Count
PSFs Not Received on Time	242,456	501,049	743,505

PSF = Patient Status Form.

Table 35 Number of Unique Patients for Whom Clozapine Treatment Was Interrupted Due to a Missing PSF

Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
Unique Patients	Count of Interruptions	Unique Patients	Count of Interruptions	Unique Patients	Count of Interruptions
57,773	505,960	68,788	694,062	88,662	1,200,777

PSF = Patient Status Form.

When a dispense authorization is rejected due to a missing PSF, the pharmacist may use a Dispense Rationale to dispense clozapine to the patient. When including Dispense Rationales, 75.2% of patients receive a dispense authorization within 7 days of the rejection (Table 36).

Table 36 Days to Any Successful RDA (Includes DRs) After a Late PSF

Days to Successful RDA	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022) Count	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022) Percent[a]	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024) Count	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024) Percent[a]
0-7	298,667	65.15	495,799	75.22
8-14	41,743	9.11	49,079	7.45
15-21	25,976	5.67	23,005	3.49
22-28	26,617	5.81	27,081	4.11
29-56	33,650	7.34	36,765	5.58
57-84	10,023	2.19	10,730	1.63
85-112	6,120	1.34	5,499	0.83
113-140	5,125	1.12	3,314	0.50
141-168	1,909	0.42	2,237	0.34
169-196	1,079	0.24	1,564	0.24
197-224	1,670	0.36	1,007	0.15
225-252	2,551	0.56	718	0.11
253-280	2,906	0.63	660	0.10
281-308	228	0.05	432	0.07

Days to Successful RDA	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]
309-336	153	0.03	385	0.06
337-364	1	0.00	245	0.04
≥365	0	0.00	635	0.10
Total	**458,418**	**100**	**659,155**	**100**

[a] May not sum due to rounding.
DR = Dispense Rationale; PSF = Patient Status Form; RDA = REMS Dispense Authorization.

When excluding Dispense Rationales, 31.8% of patients received a dispense authorization within 7 days of the rejection (Table 37).

Table 37 Days to Any Successful RDA (Excludes DRs) After a Late PSF

Days to Successful RDA	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]
0-7	114,343	31.73	158,844	31.83
8-14	34,820	9.66	47,103	9.44
15-21	24,606	6.83	28,208	5.65
22-28	45,350	12.58	57,380	11.50
29-56	71,127	19.74	89,971	18.03
57-84	26,787	7.43	36,556	7.33
85-112	15,315	4.25	21,850	4.38
113-140	11,330	3.14	14,465	2.90
141-168	6,506	1.81	10,590	2.12
169-196	3,763	1.04	8,021	1.61
197-224	2,355	0.65	6,419	1.29
225-252	1,611	0.45	5,280	1.06
253-280	1,366	0.38	3,887	0.78
281-308	892	0.25	2,805	0.56
309-336	178	0.05	2,250	0.45
337-364	2	0.00	1,669	0.33
≥365	0	0.00	3,675	0.74
Total	**360,351**	**100**	**498,973**	**100**

[a] May not sum due to rounding.
DR = Dispense Rationales; PSF = Patient Status Form; RDA = REMS Dispense Authorization.

When submitting a PSF, the prescriber is required to indicate if the patient is being monitored as recommended in the Prescribing Information. During the reporting period, 6,519 PSFs were submitted by 3,799 prescribers for 5,169 unique patients where the prescriber indicated that the patient was not being monitored as recommended (Table 38). When this occurs, the Clozapine REMS Contact Center conducts an outreach to the prescriber. The goal of this outreach is to

increase compliance by educating stakeholders on the monitoring requirements and utilizing approved resources to address any related questions or concerns.

Table 38 PSFs Where the Prescriber Indicated the Patient Is Not Being Monitored as Recommended

	Previous Reporting Period (29 Jul 2021 – 29 May 2024)			Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)			Cumulative (29 Jul 2021 – 29 May 2024)		
	Count of PSFs	Count of Unique Patients	Count of Unique Prescribers	Count of PSFs	Count of Unique Patients	Count of Unique Prescribers	Count of PSFs	Count of Unique Patients	Count of Unique Prescribers
PSFs where Patient is Not Being Monitored	6,012	4,566	3,123	6,519	5,169	3,799	12,531	9,337	6,091

PSF = Patient Status Form.

When submitting a PSF, the prescriber is required to report the patient's ANC lab values according to the patient's monitoring schedule. For example, the PSF for a patient in a weekly monitoring schedule should have 4 ANC lab values submitted. If a required lab is not obtained, the prescriber must indicate the reason for the missing lab on the PSF. Overall, the majority of PSFs were submitted with the expected number of reported ANC lab values (Table 39).

Table 39 ANCs Reported According to the Monitoring Frequency (Most Recent Reporting Period)

Monitoring Frequency	Number of ANC Labs Reported	Percent of Patients								
		Dec 2022	Jan 2023	Feb 2023	Mar 2023	Apr 2023	May 2023	Jun 2023	Jul 2023	Aug 2023
Weekly	0	0.68	1.06	0.93	0.63	0.47	0.39	0.34	0.41	0.43
	1	1.15	1.54	1.38	1.47	1.78	1.70	1.58	1.26	1.40
	2	1.55	1.72	1.30	1.35	1.52	1.48	1.42	1.19	1.30
	3	2.29	2.25	2.04	1.73	1.99	1.83	1.70	1.93	1.97
	≥4	94.32	93.42	94.34	94.81	94.25	94.61	94.96	95.21	94.90
Every 2 weeks	0	0.45	0.71	1.03	0.88	0.63	0.34	0.31	0.23	0.40
	1	1.70	2.07	1.60	1.66	1.78	1.53	1.80	1.64	1.52
	≥2	97.86	97.22	97.37	97.46	97.59	98.13	97.88	98.13	98.07
Monthly	0	1.95	1.42	1.48	1.18	0.86	0.67	0.73	0.72	0.67
	≥1	98.05	98.58	98.52	98.82	99.14	99.33	99.27	99.28	99.33
Monitoring Frequency	**Number of ANC Labs Reported**	**Percent of Patients**								
		Sep 2023	**Oct 2023**	**Nov 2023**	**Dec 2023**	**Jan 2024**	**Feb 2024**	**Mar 2024**	**Apr 2024**	**May 2024**
Weekly	0	0.27	0.27	0.29	0.26	0.24	0.25	0.28	0.25	0.36
	1	1.37	1.51	1.27	1.28	1.84	1.35	1.25	1.38	1.35
	2	1.55	1.44	1.55	1.51	1.74	1.30	1.46	1.25	1.20
	3	1.89	1.76	1.64	2.19	2.03	1.91	1.96	1.91	1.94
	≥4	94.91	95.01	95.24	94.76	94.15	95.19	95.05	95.21	95.15
Every 2 weeks	0	0.28	0.45	0.42	0.54	0.59	0.39	0.34	0.28	0.37
	1	1.47	1.70	1.73	1.94	1.98	1.50	1.52	1.56	1.47
	≥2	98.25	97.85	97.85	97.51	97.43	98.11	98.15	98.15	98.16
Monthly	0	0.71	0.66	0.65	0.80	0.85	0.67	0.61	0.68	0.81
	≥1	99.29	99.34	99.35	99.0	99.15	99.33	99.39	99.32	99.19

ANC = absolute neutrophil count.

PSFs may be submitted with missing ANC values. When this occurs, the prescriber must provide a reason for the missing ANC values. Valid reasons include: (1) patient refused, (2) clinician discretion, and (3) extrinsic factors (e.g., weather, transportation issues). If ≥1 labs are missing, the prescriber is required to authorize continuation of therapy.

During the reporting period, 3,690 patients received 11,635 RDAs where the PSF had no ANC values submitted. The median number of RDAs per patient where the PSF had no ANC values submitted was 2, ranging from 1 to 80. A majority of these patients (60.2%) had 1 or 2 RDAs where the PSF had no ANC values submitted.

4.1.2.3 Treatment Rationales

A patient's neutropenia level is determined by the patient's ANC. When a patient's ANC indicates moderate neutropenia (ANC 500-999 cells/μL, general population) or severe neutropenia (ANC <500 cells/μL, general population and patients with BEN), a documented Treatment Rationale is required from the patient's prescriber to allow the patient to continue treatment in the Clozapine REMS. A Treatment Rationale is used when the prescriber believes that the benefits of clozapine therapy outweigh the risk of severe neutropenia. The prescriber must provide an end date for the Treatment Rationale, which may not exceed 6 months from the current date.

Of the 4,076 patients having an ANC <1,000 cells/μL submitted, 3.4% had a Treatment Rationale created (Table 40).

Table 40 Patients With a Treatment Rationale After Having an ANC <1,000 cells/μL Submitted

Task	Previous Reporting Period (29 Jul 2021 – 29 May 2024)				Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)			
	Count of Tasks	Count of Patients	Count of TRs	Percent	Count of Tasks	Count of Patients	Count of TRs	Percent
ANC <1,000 cells/μL Submitted	4,267	2,568	216	5.06	6,295	4,076	212	3.37

ANC = absolute neutrophil count; TR = Treatment Rationale.

During the most recent reporting period, 282 Treatment Rationales were submitted, of which 22 were submitted for patients with BEN and 260 were submitted for general population patients. The average number of Treatment Rationales submitted per prescriber was 1.7; the median was 1, ranging from 1 to 59.

4.1.2.4 Dispense Rationales

The Clozapine REMS provides certified pharmacies with an opportunity to apply clinical judgment and continue to dispense clozapine to enrolled patients when a patient's prescriber has not submitted the monthly PSF by using a Dispense Rationale. To use a Dispense Rationale, the pharmacist must possess a current and acceptable ANC lab value for the patient.

During the most recent reporting period, there were 192,552 instances in which clozapine was dispensed using a Dispense Rationale (Table 41). Clozapine was dispensed under a Dispense Rationale to 41,281 patients (Table 42).

Table 41 Number of Dispense Rationales Authorized

	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	Cumulative (29 Jul 2021 – 29 May 2024)
Dispense Rationales Authorized	97,252	192,552	289,804

Table 42 Number of Unique Patients Receiving a Clozapine Prescription Under a Dispense Rationale

	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	Cumulative (29 Jul 2021 – 29 May 2024)
Number of Unique Patients	31,745	41,281	55,792

Within 37 days after a Dispense Rationale was used, 82,659 PSFs were received (Table 43).

Table 43 PSFs Received Within 37 Days After a Dispense Rationale

	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)
	Count	Count
PSFs Received	49,314	82,659

PSF = Patient Status Form.

4.1.2.5 Transition Dispense Rationales

A Transition Dispense Rationale was implemented in the Clozapine REMS to reduce patient access issues during the first 90 days of operations of the Modified Clozapine REMS. Due to the enforcement discretion, the Transition Dispense Rationale remained available via the Clozapine REMS Contact Center and website during the most recent reporting period. In addition, the limit of using 3 Transition Dispense Rationales during the initial 90-day period was not enforced.

During the most recent reporting period, 17,164 Transition Dispense Rationales were requested for 3,796 patients, most of which were authorized (97.3%). Most (2.7%) of the denied Transition Dispense Rationales were denied because of a low ANC value (Table 44).

Table 44 Transition Dispense Rationales Requested and Outcomes

Outcome	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		Cumulative (29 Jul 2021 – 29 May 2024)	
	Count	Percent[a]	Count	Percent[a]	Count	Percent[a]
Authorized	55,004	96.21	16,699	97.29	71,703	96.46
Denied due to a low ANC value	2,110	3.69	464	2.70	2,574	3.46
Denied due to ANC value not current	56	0.10	1	0.01	57	0.08
Denied due to a low ANC value and not current	2	0.00	0	0.00	2	0.00
Denied due to limit reached	1	0.00	0	0.00	1	0.00
Outcome Totals	**57,173**	**100**	**17,164**	**100**	**74,337**	**100**

[a] May not sum due to rounding.
ANC = absolute neutrophil count.

4.1.3 Evaluation of Required Monitoring

4.1.3.1 Neutropenia

Within the most recent reporting period, 1,266 general population patients had 1,391 ANC values <500 cells/µL submitted, 1,236 general population patients had 1,431 ANC values of 500-999 cells/µL submitted, and 7,199 general population patients had 10,889 ANC values of 1,000-1,499 cells/µL submitted (Table 45 and Table 46).

Within the most recent reporting period, 58 patients with BEN had 75 ANC values <500 cells/µL submitted and 122 patients with BEN had 224 ANC values of 500-999 cells/µL submitted (Table 45 and Table 46).

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 cells/µL. For example, an ANC value of 8,000 cells/µL is equivalent to 8×10^3 cells/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 updated on 21 February 2022 to require the stakeholder to confirm that the value is correct when an ANC <100 cells/µL is entered.

Table 45 Number of Unique Patients With Neutropenia Stratified by Patient Type

Neutropenia by Patient Population		Previous Reporting Period (29 Jul 2021 – 30 Nov 2022) Count	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024) Count	Cumulative (29 Jul 2021 – 29 May 2024) Count
BEN patient	BEN neutropenia	117	122	221
	BEN severe neutropenia	171	58	235
General population patient	Mild neutropenia	5,458	7,199	11,392
	Moderate neutropenia	1,917	1,236	2,944
	Severe neutropenia	5,296	1,266	6,166

BEN = benign ethnic neutropenia.

Table 46 Total Instances of Neutropenia Stratified by Patient Type

Neutropenia by Patient Population		Previous Reporting Period (29 Jul 2021 – 30 Nov 2022) Count	Most Recent Reporting Period (01 Dec 2022 – 29 May 2024) Count	Cumulative (29 Jul 2021 – 29 May 2024) Count
BEN patient	BEN neutropenia	180	224	404
	BEN severe neutropenia	219	75	294
BEN Patient Total		**399**	**299**	**698**
General population patient	Mild neutropenia	7,447	10,889	18,336
	Moderate neutropenia	2,167	1,431	3,598
	Severe neutropenia	5,871	1,391	7,262
General Patient Total		**15,485**	**13,711**	**29,196**
Total		**15,884**	**14,010**	**29,894**

BEN = benign ethnic neutropenia.

Eleven patients with BEN and 55 general population patients with an ANC value indicating severe neutropenia had Treatment Rationales created to allow continued clozapine treatment (Table 47).

Table 47 Number of Patients Reported With Severe Neutropenia Who Received a Treatment Rationale

Patient Population	Previous Reporting Period (29 Jul 2021 – 30 Nov 2022)			Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)		
	Count of Unique Patients With Severe Neutropenia	Count of Patients With a Treatment Rationale	Percent[a]	Count of Unique Patients With Severe Neutropenia	Count of Patients With a Treatment Rationale	Percent
BEN patient	171	10	5.85	58	11	18.97
General population patient	5,296	104	1.96	1,266	55	4.34
Total	**5,467**	**114**	**2.09**	**1,324**	**66**	**4.98**

BEN = benign ethnic neutropenia.

The majority of general population and patients with BEN (78.9%) with an ANC value indicating severe neutropenia were in active status at the end of the most recent reporting period (Table 48).

Table 48 Status for Patients With Reported Severe Neutropenia

Status by Patient Population		Previous Reporting Period (29 Jul 2021 – 29 May 2024)		Most Recent Reporting Period (01 Dec 2022 – 29 May 2024)	
		Count	Percent[a]	Count	Percent[a]
BEN patient	Active	146	2.67	48	3.63
	Interrupted	24	0.44	9	0.68
	Discontinued	1	0.02	1	0.08
BEN Patient Total		**171**	**3.13**	**58**	**4.38**
General population patient	Active	4,703	86.03	997	75.30
	Interrupted	525	9.60	229	17.30
	Discontinued	68	1.24	40	3.02
General Patient Total		**5,296**	**96.87**	**1,266**	**95.62**
Total		**5,467**	**100**	**1,324**	**100**

[a] May not sum due to rounding.
BEN = benign ethnic neutropenia.

4.1.3.2 Analysis of Time to Onset and Incidence Rate for Severe Neutropenia

An analysis was performed to calculate time to onset and incidence rate for severe neutropenia. The analysis included 5,151 patients who were enrolled in the Clozapine REMS between 01 June 2022 and 17 September 2022 and who did not match a Legacy REMS patient. These patients had ≥2 years of Clozapine REMS involvement.

Limitations of this analysis were as follows:

- **Time to onset of severe neutropenia:** Calculated as time from clozapine initiation to the date of first ANC lab draw consistent with severe neutropenia. The best surrogate for clozapine initiation is the RDA. However, these data may be missing due to the enforcement discretion allowing a dispense without an RDA.
  - 1,123 (21.8%) of patients had no RDAs recorded in the system. Of these, 1,029 (91.6%) had *no rejections* recorded in the system.
- **ANC values entered in the incorrect unit:** An ANC value entered in an incorrect unit may falsely appear as severe neutropenia, skewing the time to onset.
- **Missed lab reason:** Allows the patient to obtain an RDA without knowing if the patient has severe neutropenia.

Table 49 shows the current status of the patients included in the analysis. More than 62% of the patients are Inactive, which indicates a late PSF. The median days in the Inactive status are 706 days. This may indicate that: 1) these patients have dropped out of the Clozapine REMS and were not discontinued by the prescriber; and 2) a lack of data due to the enforcement discretion.

Table 49 Current Patient Status

Status	N = 5,151	%
Treatment Inactive (Late PSF)[a]	3,195	62.03
Treatment Active	1,629	31.62
Treatment Discontinued	261	5.07
Treatment Interrupted	66	1.28

[a] Days in Inactive Status: Mean = 578, Median = 706, Minimum = 0, Maximum = 811.
PSF = Patient Status Form.

A total of 4,028 (78.2%) patients had at least one RDA (indicating clozapine initiation). From these patients, 32 (0.6%) had at least one ANC submitted that indicated severe neutropenia (Table 50).

Two (6.3%) of the 32 patients were reported (on the PSF) as having experienced an AE due to clozapine-induced neutropenia. Additionally, 11 patients with no indication of severe neutropenia were reported as having experienced an AE due to clozapine-induced neutropenia.

Table 50 Current Status of Patients With Severe Neutropenia

Status	N = 32	%
Treatment Inactive (Late PSF)[a]	7	21.88
Treatment Active	14	43.75
Treatment Discontinued	1	3.13
Treatment Interrupted	10	31.25

[a] Days in Inactive Status: Mean = 172, Median = 79, Minimum = 6, Maximum= 671.
PSF = Patient Status Form.

Based on the available data, the incidence rate for severe neutropenia is 0.0058 per patient-year of exposure (5.8 per 1000 patient-years).

Exposure was determined by calculating the total days' supply for all patients in the analysis. For dispenses when days' supply was provided, the median days' supply was 28 days. Therefore, a days' supply of 28 days was used when the days' supply was not available.

4.1.4 Key Performance Indicator

A Key Performance Indicator (KPI) is used to measure the performance of the Clozapine REMS. The KPI is defined as: By the end of the first reporting period, 75% of Clozapine RDAs will be associated with evidence of a prescriber having done a risk/benefit analysis to continue clozapine therapy, including appropriate monitoring results or why that monitoring was not done, as evidenced by their initial submission of a PEF and ongoing submission of a PSF. The KPI was measured quarterly.

The KPI for each quarter is presented in Table 51. The lowest KPI for the most recent reporting period is 87.24%. While this exceeds the KPI threshold, there are limitations to using this as an accurate KPI. This KPI does not include dispenses that were obtained through the Transition Dispense Rationale. The Transition Dispense Rationale is used for patients who are not enrolled in the Clozapine REMS. As a result, there is no evidence that a risk/benefit analysis was performed by the prescriber before prescribing. Additionally, the enforcement discretion allows pharmacists to dispense clozapine without an RDA. As a result, the total number of dispenses in the KPI is likely to be underrepresented.

Table 51 Key Performance Indicator by Quarter

Quarter	Key Performance Indicator (%)
Dec 2021 – Feb 2022	58.52
Mar 2022 – May 2022	78.23
Jun 2022 – Aug 2022	77.16
Sep 2022 – Nov 2022	79.52
Dec 2022 – Feb 2023	90.98
Mar 2023 – May 2023	91.68
Jun 2023 – Aug 2023	87.24
Sep 2023 – Nov 2023	88.30
Dec 2023 – Feb 2024	90.84
Mar 2024 – May 2024	92.08

4.1.5 Safety Surveillance

AEs may be reported to the Clozapine REMS by any individual such as an HCP, patient, patient advocate, or pharmacist. To ensure Clozapine REMS Contact Center reporting procedures are standardized and universal, all AEs are reported to the responsible Sponsor pharmacovigilance (PV) team(s) for investigation and determination. The Clozapine REMS Contact Center obtains as much detail as possible from the reporter of the AE case; however, each report must include at minimum identified reporter, identified patient, event description, and suspected drug. The Contact Center agent will attempt to warm-transfer the reporter to the responsible REMS Sponsor PV department. If the call is unable to be warm-transferred to the REMS Sponsor, the

Contact Center agent will complete a Potential Adverse Event (PAE)/ Product Complaint (PC)/ Medical Information Request (MIR) Intake Form, which is sent to the responsible REMS Sponsor within 1 business day. Once the AE case is submitted, individual Sponsor PV teams conduct follow up with the reporter to obtain additional information or clarification, as needed.

Each REMS Sponsor's respective PV department is responsible for investigating all AEs. Sponsors are required to submit all AEs to the FDA via the FDA 3500A MedWatch form. The Clozapine REMS Contact Center does not submit AE reports directly to the FDA. Each Clozapine REMS Sponsor has its own policies and procedures for investigating AEs; however, they must follow title 21 of the Code of Federal Regulations subpart 314.80 *Postmarketing Reporting of Adverse Drug Experiences.* AEs submitted to the FDA via the 3500A MedWatch form are included in the FDA Adverse Event Reporting System (FAERS) database. The FAERS database also includes reports submitted directly to the FDA by healthcare professionals and consumers. It is possible that a report accounted for in FAERS annual totals may be counted more than once if a healthcare professional or consumer reports an event directly to the FDA as well as to a manufacturer.

When submitting a PSF, the prescriber can indicate the patient experienced an AE due to clozapine-induced neutropenia. AEs reported via the PSF are sent to the responsible REMS Sponsor for investigation and reporting to the FDA.

During the most recent reporting period, 439 PSFs were submitted for 390 (0.32%) patients with an indication the patient experienced an AE due to clozapine-induced neutropenia (Table 52).

Table 52 Number of PSFs that Indicated an AE

Count of Patients With PSF	Count of PSFs Where an AE is Indicated	Unique Patients with an AE Indicated	Percent of Patients with an AE Indicated
120,943	439	390	0.32

AE = adverse event; PSF = Patient Status Form.

4.1.6 REMS Complaints

A total of 480 REMS complaints were received via the Contact Center between 14 November 2021 and 30 April 2024 (Table 53). The most common types of complaints received were those related to PSF requirement (130, 27.1%), the enrollment process and other (94, 19.6% each), and website functionality (69, 14.4%).

Table 53 REMS Complaints (14 Nov 2021 – 30 Apr 2024)

Type of Complaints Received Via the Contact Center	Description	Total	Percent
Hold Times/Return Calls	Complaints relating to the length of time callers wait to speak with the Contact Center	35	7.3
Website Functionality	Complaints relating to the re-enrollment requirement of the modified REMS	69	14.4

Type of Complaints Received Via the Contact Center	Description	Total	Percent
Enrollment Process	Complaints relating to a stakeholder's ability to perform functions via the website (associate patients, submit for TDR, etc.)	94	19.6
RDA/TDR Process	Complaints relating to processing the RDA/TDR for patients	11	2.3
Website Access	Complaints relating to verification codes, browser issues, overall access	39	8.1
PSF Requirements	Complaints relating to the monthly PSF requirements	130	27.1
ANC Calculation	Complaints relating to the manual calculation of the ANC values	8	1.7
Other	Complaints not categorized into previous buckets	94	19.6
Total Complaints Received		**480**	**100**

ANC = absolute neutrophil count; PSF = Patient Status Form; RDA = REMS Dispense Authorization; REMS = Risk Evaluation and Mitigation Strategy; TDR = Transitional Dispense Rational.

4.2 Legacy REMS Assessment

Data are presented below for the Assessment 5 reporting period and cumulatively for the Assessment 1 through Assessment 5 reporting periods. For some analyses, only data from the Assessment 5 reporting period are available.

4.2.1 REMS Implementation and Operation

4.2.1.1 Prescriber Certification

At the end of the Assessment 5 reporting period, 5,166 new prescribers had been added to the Clozapine REMS (Table 54). Cumulatively, 99,113 prescribers are in the Clozapine REMS. Of these, 65,070 (65.7%) prescribers were certified, 32,398 (32.7%) prescribers were cancelled, 1,274 (1.3%) prescribers were incomplete, and 371 (0.4%) prescribers were deactivated.

Table 54 Number of Prescribers

	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)		Cumulative (15 Sep 2015 – 15 Nov 2021)	
Certification Status	**Count**	**Percent[a]**	**Count**	**Percent[a]**
Canceled	247	4.78	32,398	32.69
Certified	4,434	85.83	65,070	65.65
Deactivated	0	0.00	371	0.37
Incomplete	485	9.39	1,274	1.29
Certification Status Total	**5,166**	**100**	**99,113**	**100**

[a] May not sum due to rounding.

Through the end of the Assessment 5 reporting period, 1,076 prescribers had a changed enrollment status. Of these, 546 (50.8%) prescribers were certified, 519 (48.2%) prescribers were canceled, and 11 (1%) prescribers were deactivated (Table 55).

Table 55 Number of Prescribers That Changed Status During the Reporting Period

Certification Status	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)	
	Count	Percent[a]
Canceled	519	48.23
Certified	546	50.75
Deactivated	11	1.02
Incomplete	0	0.00
Certification Status Total	**1,076**	**100**

[a] May not sum due to rounding.

During the Assessment 5 reporting period, there were 35,330 active prescribers (Table 56). An active status is defined as those prescribers who submitted an ANC lab value for a patient or were associated with a patient who received a Predispense Authorization (PDA). This indicates that only 54.3% of all certified prescribers were active during the reporting period.

Table 56 Active Prescribers

	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)
	Count
Active Prescribers	35,330

4.2.1.2 Pharmacy Certification

At the end of the Assessment 5 reporting period, there were 72,612 pharmacies in the Clozapine REMS; of these, 1,291 new pharmacies were added during the reporting period (Table 57). Out of 1,291 new pharmacies, 1,017 (78.8%) were certified, 172 (13.3%) were incomplete, 89 (6.9%) were canceled, and 13 (1%) pharmacies were deactivated.

Cumulatively, 51,039 (70.3%) pharmacies were certified, 11,250 (15.5%) pharmacies were deactivated, 9,609 (13.2%) pharmacies were canceled, and 714 (1.0%) pharmacies were incomplete.

Table 57 Number of Pharmacies

Certification Status	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)		Cumulative (15 Sep 2015 – 15 Nov 2021)	
	Count	Percent[a]	Count	Percent[a]
Canceled	89	6.89	9,609	13.23

Certification Status	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)		Cumulative (15 Sep 2015 – 15 Nov 2021)	
	Count	Percent[a]	Count	Percent[a]
Certified	1,017	78.78	51,039	70.29
Deactivated	13	1.01	11,250	15.49
Incomplete	172	13.32	714	0.98
Certification Status Total[b]	**1,291**	**100**	**72,612**	**100**

[a] May not sum due to rounding.
[b] Enrollment status total will match for cumulative but may not match for specific pharmacy types because pharmacy types can change year to year.
Source: Assessment Report 5, Table 9.

During the Assessment 5 reporting period, there were 10,238 active pharmacies, where active is defined as those pharmacies that were associated with a PDA (Table 58). This indicates that only 20.1% of all certified pharmacies were active during the reporting period.

Table 58 Active Pharmacies by Type

Pharmacy Type	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)
	Count
Corporate Headquarters	0
Inpatient	2,550
Outpatient-Chain	3,015
Outpatient-Independent	4,669
Veterans Affairs	4
Pharmacy Type Total	**10,238**

4.2.1.3 Prescriber Designee Certification

At the end of the Assessment 5 reporting period, 2,240 new prescriber designees had been added to the Clozapine REMS (Table 59). Of these, 2,075 (92.6%) prescriber designees were certified, 119 (5.3%) were incomplete, and 46 (2%) certifications were canceled.

Cumulatively, 22,418 (90.6%) prescriber designees were certified, 129 (0.5%) certifications were incomplete, 7 (<1%) prescriber designees were deactivated, and 2,187 (8.8%) certifications were canceled. Prescriber designees' certifications that are not completed within 6 months of initiation are canceled.

Table 59 Number of Prescriber Designees

Certification Status	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)		Cumulative (15 Sep 2015 – 15 Nov 2021)	
	Count	Percent[a]	Count	Percent[a]
Canceled	46	2.05	2,187	8.84
Certified	2,075	92.63	22,418	90.61
Deactivated	0	0.00	7	0.03
Incomplete	119	5.31	129	0.52
Certification Status Total	**2,240**	**100**	**24,741**	**100**

[a] May not sum due to rounding.

4.2.1.4 Patient Status

Patients enrolled in the Clozapine REMS can be in one of the treatment statuses defined in Section 4.1.1.4. In addition, patients can also be in the Pretreatment status defined as patients who had been enrolled in the Clozapine REMS prior to beginning clozapine usage.

Cumulatively, there were 220,571 patients in the Clozapine REMS at the end of the Assessment 5 reporting period (Table 60). Majority of these patients (208,912; 94.7%) were active, 8,936 (4%) had been discontinued, 2,157 (1%) were in the pretreatment status, and 566 (0.3%) were interrupted.

The program added 15,104 new patients during the Assessment 5 reporting period, with 14,443 (95.6%) active patients, 369 (2.4%) discontinued patients, 291 (1.9%) pretreated patients, and one (< 1%) interrupted patient (Table 60).

Table 60 Total Patient Count by Treatment Status

Treatment Status	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)		Cumulative (15 Sep 2015 – 15 Nov 2021)	
	Count	Percent[a]	Count	Percent[a]
Active	14,443	95.62	208,912	94.71
Discontinued	369	2.44	8,936	4.05
Interrupted	1	0.01	566	0.26
Pretreatment	291	1.93	2,157	0.98
Treatment Status Total	**15,104**	**100**	**220,571**	**100**

[a] May not sum due to rounding.

4.2.2 Evaluation of Safe-Use Behavior

4.2.2.1 Predispense Authorization

If all requirements were satisfied, a unique prescription submitted for a PDA would experience no rejection and be authorized on the first attempt. During the reporting period, 1,992,327 unique

prescriptions were submitted for authorization (Table 61). Most of these prescriptions (1,966,905) encountered no rejection prior to authorization (Table 62).

If all requirements were not satisfied, the unique prescription may have been submitted more than once before finally receiving a PDA. During the Assessment 5 reporting period, 25,422 unique prescriptions encountered at least one rejection (Table 62).

Cumulatively in the Legacy REMS, there were 12,524,326 unique prescriptions submitted for authorization, with 12,386,934 (98.9%) experiencing no rejection prior to authorization and 137,392 (1.1%) unique prescriptions experiencing at least one rejection prior to authorization (Table 62).

Table 61 Number of Unique Prescriptions Submitted for Authorization

	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)	Cumulative (15 Sep 2015 – 15 Nov 2021)
Prescriptions Submitted for Authorization	**Count**	**Count**
Unique Prescriptions Submitted for Authorization	1,992,327	12,524,326
Unique Prescriptions Submitted for Authorization Total	**1,992,327**	**12,524,326**

Table 62 Unique Prescriptions With Rejections Prior to Authorization

	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)	Cumulative (15 Sep 2015 – 15 Nov 2021)
Rejections Prior to Authorization	**Count**	**Count**
No Rejections Prior to Authorization	1,966,905	12,386,934
Rejected Prior to Authorization	25,422	137,392
Unique Prescriptions Submitted for Authorization Total	**1,992,327**	**12,524,326**

Table 63 presents the minimum, maximum, average, and median days it took to obtain a PDA through the website, Pharmacy Claims Network (PCN; switch), and REMS Contact Center if the initial authorization was rejected.

In the Assessment 5 reporting period, for PDAs obtained through the Clozapine REMS website, the median days for issuance of a PDA after the initial rejection was 10 days, with a minimum of 1 day, a maximum of 1,835 days, and an average of 60.7 days (Table 63). For PDAs obtained through the PCN, the median days for issuance of a PDA was 4 days, with a minimum of 1 day, a maximum of 685 days, and an average of 11.9 days. For PDAs obtained through the Contact Center, the median days for issuance of a PDA was 55 days, with a minimum of 1 day, a maximum of 1,716 days, and an average of 174.6 days. Across all authorization channels, the median days for issuance of a PDA was 4 days, with a minimum of 1 day, a maximum of 1,835 days, and an average of 21.9 days.

Cumulatively, for PDAs obtained through the Clozapine REMS website, the median days for issuance of a PDA after the initial rejection was 9 days, with a minimum of 1 day, a maximum of 1,835 days, and an average of 43.7 days (Table 63). For PDAs obtained through the PCN, the median days for issuance of a PDA was 4 days, with a minimum of 1 day, a maximum of 1,436 days, and an average of 11.6 days. For PDAs obtained through the Contact Center, the median days for issuance of a PDA was 30 days, with a minimum of 1 day, a maximum of 1,716 days, and an average of 101.5 days. Across all authorization channels, the median days for issuance of a PDA was 4 days, with a minimum of 1 day, a maximum of 1,835 days, and an average of 15.1 days.

Table 63 Time to Authorization for PDAs if Initially Rejected

Time to Authorization	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)	Cumulative (15 Sep 2015 – 15 Nov 2021)
Clozapine REMS Website PDA		
Minimum Days	1	1
Maximum Days	1,835	1,835
Average Days	60.720	43.660
Median Days	10	9
Pharmacy Claims Network PDA		
Minimum Days	1	1
Maximum Days	685	1,436
Average Days	11.880	11.570
Median Days	4	4
Contact Center PDA		
Minimum Days	1	1
Maximum Days	1,716	1,716
Average Days	174.560	101.480
Median Days	55	30
Overall		
Minimum Days	1	1
Maximum Days	1,835	1,835
Average Days	21.860	15.090
Median Days	4	4

PDA = Predispense Authorization; REMS = Risk Evaluation and Mitigation Strategy.

4.2.2.2 Treatment Rationales

When a patient's ANC indicated moderate neutropenia (ANC 500-999 cells/µL, general population) or severe neutropenia (ANC <500 cells/µL, general population and patients with BEN), a documented Treatment Rationale was required from the patient's prescriber to allow the patient to continue treatment in the Clozapine REMS. Valid Treatment Rationales included:

1. **Patient Has BEN:** The patient has BEN and, therefore, would not require interruption of therapy unless ANC <500 cells/µL.
2. **Benefits Outweigh Risks:** The prescriber believes that the benefits of clozapine therapy outweigh the risk of severe neutropenia.

A Treatment Rationale of "Patient Has BEN" did not expire. A Treatment Rationale of "Benefits Outweigh Risks" would expire at the next reported ANC or on a date specified by the prescriber, not exceeding 6 months from the provision of the Treatment Rationale.

Within the Assessment 5 reporting period, 221 Treatment Rationales were submitted with 200 rationales of "Benefits Outweigh Risks" and 21 rationales of "Patient Has BEN" (Table 64). Cumulatively, there were 1,297 Treatment Rationales submitted, with 1,185 rationales of "Benefits Outweigh Risks" and 112 rationales from "Patient Has BEN."

Table 64 Treatment Rationales Submitted

Treatment Rationales	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)	Cumulative (15 Sep 2015 – 15 Nov 2021)
Patient Has BEN	21	112
Benefit Outweighs Risk	200	1,185
Treatment Rationales Total	**221**	**1,297**

BEN = benign ethnic neutropenia.

4.2.2.3 Dispense Rationales

The Clozapine REMS provided certified outpatient pharmacies with an opportunity to apply clinical judgment and continue to dispense clozapine to enrolled patients when a patient's prescriber was not certified in the Program by using a Dispense Rationale. To dispense to a patient who did not have an associated certified prescriber, the pharmacist must provide a Dispense Rationale to the Clozapine REMS.

A Dispense Rationale was valid for 72 hours (3 calendar days). If the dispense did not occur within this timeframe, a new Dispense Rationale must be provided for the dispense to occur.

During the Assessment 5 reporting period, there were 3,559 instances in which clozapine was dispensed using a Dispense Rationale. Cumulatively, there have been 16,399 instances of clozapine dispensed using a Dispense Rationale (Table 65).

Table 65 Count of Instances Where a Clozapine Prescription Was Dispensed During a 3-Day Dispense Rationale

	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)	Cumulative (15 Sep 2015 – 15 Nov 2021)
Total Number of Instances	**3,559**	**16,399**

The majority of patients in the reporting period and cumulatively who received clozapine through a Dispense Rationale received 1 prescription (Table 66).

Table 66 Count of Patients Receiving a Clozapine Prescription Under a Dispense Rationale Window Stratified by the Number of Prescriptions Authorized by a Dispense Rationale

Number of Prescriptions	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)	Cumulative (15 Sep 2015 – 15 Nov 2021)
1	1,637	6,008
2	459	1,893
3	296	1,364
4	18	246
5	4	112
6	4	87
7	0	20
8	0	22
9	0	11
10	0	1
11	0	2
Total of All Prescriptions	**2,418**	**9,766**

4.2.3 Evaluation of Required Monitoring

4.2.3.1 Neutropenia

Within the Assessment 5 reporting period, 176 unique patients reported an ANC <500 cells/µL, 447 unique patients with ANC 500-999 cells/µL, 4,168 unique patients with ANC 500-1,499 cells/µL, and 3,721 unique patients with ANC 1,000-1,499 cells/µL (Table 67). Cumulatively, 1,053 unique patients with ANC <500 cells/µL, 2,384 with ANC 500-999 cells/µL, 22,276 patients with ANC 500-1,499 cells/µL, and 19,892 patients with ANC 1,000-1,499 cells/µL.

Table 67 Number of Unique Patients With Severe Neutropenia

ANC	Assessment 5 Reporting Period (01 Jan 2021 – 15 Nov 2021)	Cumulative (15 Sep 2015 – 15 Nov 2021)
	Count	Count
ANC below 500 cells/µL	176	1,053
ANC between 500 cells/µL and 999 cells/µL	447	2,384
ANC between 500 cells/µL and 1499 cells/µL	4,168	22,276
ANC between 1000 cells/µL and 1499 cells/µL	3,721	19,892

ANC = absolute neutrophil count.

4.3 Cumulative Assessment of Clozapine REMS Effectiveness Based on Key Metrics

This section focuses on key metrics used to assess the effectiveness of the Clozapine REMS cumulatively (i.e., both the Legacy REMS from 2015 to 2021 and the Modified REMS from 2021 to 2024) in meeting its goal of mitigating the risk of severe neutropenia associated with clozapine. Data are presented on 1) adherence to monitoring; 2) prescriber, pharmacist, and patient knowledge of neutropenia risk and safe-use conditions; and 3) use of the Treatment Rationale to prescribe clozapine without a current ANC in the acceptable range.

4.3.1 Adherence to Monitoring

When quantifying adherence to monitoring under the Legacy and Modified REMS, it is important to note some limitations in the ability to collect pertinent data. These limitations are 1) Legacy REMS did not include a metric to measure adherence to monitoring; 2) Legacy REMS was never fully implemented and only required patients to have 1 ANC value on file; and 3) the current enforcement discretion allows dispensing without obtaining authorization. It is difficult to measure adherence to monitoring in the Legacy REMS system. A surrogate for this metric is the number of dispense authorizations that were rejected due to a missing ANC value.

As shown in Table 68, data for Legacy REMS were significantly lower than that for the Modified REMS. This could be attributed to the fact that the Legacy REMS only required 1 ANC value on file, whereas the Modified REMS required current ANC values submitted monthly via the PSF.

Table 68 Adherence to Clozapine REMS: Rejections Due to Missing ANC Values

Reporting Period	Rejection Related to Missing ANC Values, n (%)[a,b]	Total Number of Rejections
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	23,504 (30.18)	77,876
16 Jul 2017 – 15 Jul 2018	29,008 (16.18)	179,336
16 Jul 2018 – 31 Dec 2019		
16 Jul 2018 – 27 Feb 2019	4,884 (4.85)	100,785
28 Feb 2019 – 31 Dec 2019	6,103 (1.06)	575,859
01 Jan 2020 – 31 Dec 2020	43,220 (10.67)	405,047
01 Jan 2021 – 15 Nov 2021	43,820 (13.24)	330,979
Modified REMS		
29 Jul 2021 – 30 Nov 2022	504,086 (92.72)	543,649
01 Dec 2022 – 29 May 2024	694,062 (95.89)	723,816

[a] For the Legacy REMS, reasons included: acceptable patient lab is not on file, lab data not saved, patient is not enrolled in REMS, lab not in timeframe, and lab not on file.
[b] For the Modified REMS, reasons included: current PSF is not on file.
ANC = absolute neutrophil count; PSF = Patient Status Form; REMS = Risk Evaluation and Mitigation Strategy.

Another metric to measure adherence to the Clozapine REMS is whether the PSFs are submitted on time. For the Modified REMS, PSFs submitted after the due date doubled from the first to the second reporting period (Table 69). These data explained the large number of dispense authorization rejections due to a missing PSF.

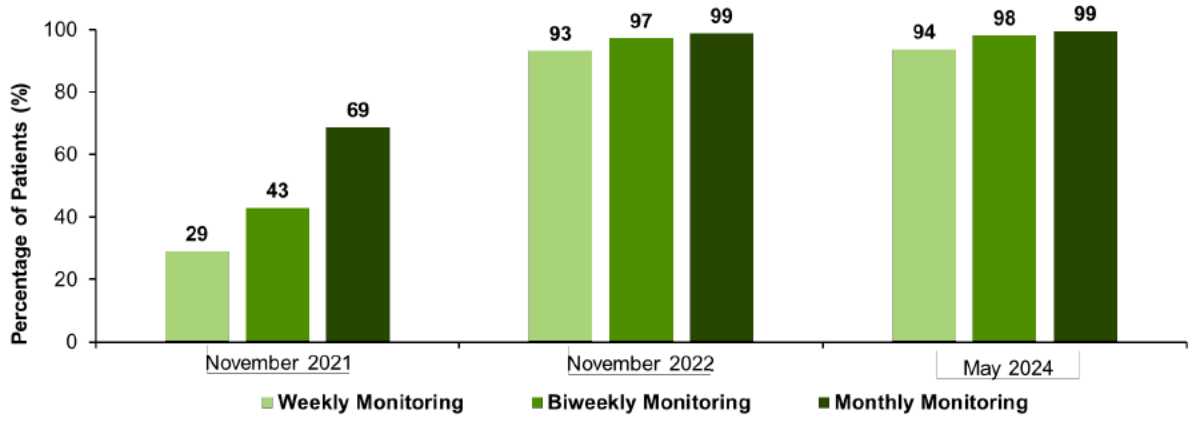
Table 69 Adherence to Clozapine REMS: PSFs Not Submitted On Time

Reporting Period	Number of PSFs Not Received Within 37 Calendar Days After Date of Last PSF Submission	Total Number of PSFs Submitted
Modified REMS		
29 Jul 2021 – 30 Nov 2022	242,456	1,089,386
01 Dec 2022 – 29 May 2024	501,049	1,732,050

PSF = Patient Status Form; REMS = Risk Evaluation and Mitigation Strategy.

When measuring adherence to the monitoring schedule, the percentage of patients who had all the required ANC labs submitted on the PSF was assessed. In the first month of the Modified REMS, the percentage was low across all 3 monitoring frequencies (Figure 4), which is expected when prescribers are getting accustomed to the new PSF requirements. However, at the end of the 2 Modified REMS reporting periods, most patients had their ANC labs submitted according to their monitoring frequency.

Figure 4 Unique Patients Who Had ANCs Reported on Their PSF in Accordance With Their Monitoring Schedule



ANC = absolute neutrophil count; PSF = Patient Status Form.

4.3.2 Evaluation of Knowledge Surveys

Knowledge, Attitude, and Behavior (KAB) surveys are an annual Assessment Report requirement of the Clozapine REMS. Surveys are conducted with Clozapine REMS prescribers, pharmacists, and patients or their caregivers, who have prescribed, dispensed, or been prescribed clozapine in the past 12 months. The objective of KAB surveys is to measure stakeholder knowledge of the risk of severe neutropenia associated with clozapine, appropriate monitoring of clozapine, and the REMS requirements. With the exception of Assessment Reports 5 and 6, KAB surveys have been conducted with each Assessment Report beginning in 2017. The 2018 Assessment Report and survey year did not include prescriber and pharmacist surveys at the direction of the FDA; however, subsequent survey years resumed fielding surveys with prescribers and pharmacists.

The Clozapine REMS Sponsors contract with a third-party vendor to develop the survey protocols and administer the surveys. Prescriber and Pharmacist survey participants are randomly identified through the Clozapine REMS registry and invited to participate in the survey. Patients invited to participate were identified using either a group of pharmacy claims, electronic health record databases, or via a pharmacy partner for the most recent survey year. Inclusion and exclusion criteria must be met to participate, and participation is voluntary. The surveys may be completed either online or by phone with trained Contact Center staff. Survey participants across all 3 stakeholder groups are anonymous and responses are aggregated with other respondents. The annual survey protocol and methodology follow the guidelines provided in the 2019 *FDA Draft Guidance for Industry: Survey Methodologies to Assess REMS Goals That Relate to Knowledge*. The KAB survey protocol is submitted to the FDA annually for review and approval prior to the survey going live.

Each survey is conducted to test REMS stakeholder knowledge on 3 key risk messages:

- **Key Risk Message 1:** Understand of the risk of severe neutropenia associated with clozapine.
- **Key Risk Message 2:** Understand the need for appropriate patient monitoring with clozapine.
- **Key Risk Message 3:** Understand the requirements of the Clozapine REMS.

4.3.2.1 Prescriber Survey Results

Prescribers were identified via the Clozapine REMS database, with a large majority practicing psychiatric medicine year over year. In addition to surveying respondents on their knowledge of the REMS requirements and to assist in performing subanalyses, respondents are asked questions related to demographic information and awareness/receipt of key informational/educational materials (e.g., Prescribing Information, *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*). For each year surveys were conducted, prescriber respondents reported low rates of (1) awareness of *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, (2) receipt of the *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, and (3) review of the *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*. The number of respondents reporting they were aware of and/or received the guide increased in 2024 (i.e., following the 2021 REMS Modification). In 2017, a subanalysis was performed indicating that prescribers who were aware of the Prescribing Information and Healthcare Provider Guide and/or who treated more than 5 patients had higher mean scores.

In 2020, the surveys introduced a knowledge rate performance threshold using a risk-based methodology, and the targeted knowledge rate threshold changed for each key risk message (i.e., to 90% or higher for Key Risk Message 1, and to 85% or higher for Key Risk Messages 2 and 3, from 80% for all Key Risk Messages previously).

For Key Risk Message 1 (i.e., understand the risk of severe neutropenia associated with clozapine), prescriber respondents scored above the target threshold across all survey years with no specific questions lowering the mean score. In 2017, scores were decreased due to low scores associated with whether clozapine treatment should be interrupted as a precautionary measure in any patient who develops a fever of 38.5°C (101.3°F) or greater and an ANC should be obtained (56% correct) (Table 70).

Table 70 Key Risk Message 1 – Understand the Risk of Severe Neutropenia Associated With Clozapine: Prescriber Survey

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	86.0%	True/False: Clozapine treatment should be interrupted as a precautionary measure in any patient who develops a fever of 38.5°C (101.3°F) or greater, and an ANC should be obtained (56% answered correctly)
16 Jul 2018 – 31 Dec 2019	92.0%	No low-scoring question
01 Jan 2020 – 31 Dec 2020	84.0%	No low-scoring question
Modified REMS		
01 Dec 2022 – 29 May 2024	93.0%	No low-scoring question

ANC = absolute neutrophil count; REMS = Risk Evaluation and Mitigation Strategy.

For Key Risk Message 2 (i.e., understand the need for appropriate patient monitoring with clozapine), prescriber respondents scored above the target threshold across all survey years. In 2017, the mean knowledge rate for Key Risk Message 2 was decreased by low scores associated with the following questions: (1) prescribers may choose to continue clozapine treatment in patients with ANCs <1,000 cells/µL if they confirm that the benefits of treatment outweigh the risks of developing severe neutropenia (58.0%), and (2) when patients qualify for a change in ANC monitoring frequency, prescribers will be notified by the Clozapine REMS (44.5% correct) (Table 71). For surveys conducted in 2018, 2019, and 2024, the lowest-scoring question related to the appropriate baseline ANC for patients with BEN, with overall scores of 67%, 62%, and 79%, respectively.

Table 71 Key Risk Message 2 – Understand the Need for Appropriate Patient Monitoring With Clozapine: Prescriber Survey

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	79.1%	True/False: Prescribers may choose to continue clozapine treatment in patients with ANCs <1,000 cells/µL if they confirm that the benefits of treatment outweigh risks of developing severe neutropenia (58% answered correctly) True/False: When patients qualify for a change in ANC monitoring frequency, prescribers will be notified by the Clozapine REMS (44.5% answered correctly)
16 Jul 2018 – 31 Dec 2019	86.0%	According to the USPI, in which of the following patients are the ANC levels acceptable prior to treatment with clozapine? Patient D [with documented BEN]: Before starting treatment with clozapine, the baseline ANC is >1,000 cells/µL (67% answered correctly)

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
01 Jan 2020 – 31 Dec 2020	82.0%	According to the USPI, in which of the following patients are the ANC levels acceptable prior to treatment with clozapine? Patient D [with documented BEN]: Before starting treatment with clozapine, the baseline ANC is >1,000 cells/µL (62% answered correctly)
Modified REMS		
01 Dec 2022 – 29 May 2024	93.0%	No low-scoring question

ANC = absolute neutrophil count; BEN = benign ethnic neutropenia; REMS = Risk Evaluation and Mitigation Strategy; USPI = United States Prescribing Information.

For Key Risk Message 3 (i.e., understand the requirements of the Clozapine REMS), respondents met the target threshold in 2017, 2019, and 2020. In 2017, the overall mean score was lowered by only 59% of respondents correctly answering whether, according to the US Prescribing Information, prescribers should enroll patients in the Clozapine REMS if they have never treated the patient with clozapine before, regardless of the patient's clozapine history (Table 72). In 2019, the overall mean score was lowered by only 68% of prescribers correctly answering whether prescribers must submit a Treatment Rationale to confirm the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia (for patients with moderate or severe neutropenia). This question also scored low in the 2020 survey (i.e., with only 71%) of respondents answering correctly. In 2020, the overall mean score was also lowered by only 69% of respondents correctly answering whether, according to the Clozapine REMS materials, prescribers should enroll patients who have never been treated with clozapine in the REMS. The 2024 results showed that only 44% of prescribers achieved the targeted knowledge rate threshold (i.e., 85% or higher) for Key Risk Message 3; however, as there were only 6 questions for this message, a prescriber had to achieve a 100% on associated questions to achieve the target. Similar to 2019 and 2020, only 68% of respondents correctly answered whether prescribers must submit a Treatment Rationale to confirm the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia (for patients with moderate or severe neutropenia).

Table 72 Key Risk Message 3 – Understand the Requirements of the Clozapine REMS: Prescriber Survey

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	82.4%	True/False: Enroll patients in the Clozapine REMS if you have never treated the patient with clozapine, regardless of the patient's history of clozapine treatment (59% answered correctly)
16 Jul 2018 – 31 Dec 2019	86.0%	True/False: Prescribers must provide a Treatment Rationale to confirm that the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia (for patients with moderate or severe neutropenia.) (68% answered correctly)

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
01 Jan 2020 – 31 Dec 2020	84.0%	True/False: Enroll patients that have never been treated with clozapine in the Clozapine REMS (69% answered correctly). True/False: Prescribers must provide a Treatment Rationale to confirm that the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia (for patients with moderate or severe neutropenia) (71% answered correctly)
Modified REMS		
01 Dec 2022 – 29 May 2024	87.0%	True/False: Prescribers must provide a Treatment Rationale to confirm that the benefits of continuing clozapine treatment outweigh the risks of developing severe neutropenia (for patients with moderate or severe neutropenia.) (68% answered correctly)

REMS = Risk Evaluation and Mitigation Strategy.

4.3.2.2 Pharmacist Survey Results

Pharmacists and/or pharmacy staff were identified via the Clozapine REMS database; from 2019 onward, ≥85% of respondents were pharmacists.

In addition to surveying respondents on their knowledge of the REMS requirements and to assist in performing subanalyses, respondents are asked questions related to demographic information and awareness/receipt of key informational/educational materials (e.g., Prescribing Information, *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*). Pharmacist respondents reported low rates of (1) awareness of the *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, (2) receipt of the *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, and (3) review of the *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*. In 2017, respondents' awareness/receipt of Clozapine REMS tools correlated to higher scores.

In 2020, the surveys introduced a knowledge rate performance threshold using a risk-based methodology, and the targeted knowledge rate threshold changed for each key risk message (i.e., to 85% or higher for Key Risk Message 1, 80% or higher for Key Risk Message 2, and 90% or higher for Key Risk Message 3, from 80% for all Key Risk Messages previously).

Key Risk Message 1 (i.e., understand the risk of severe neutropenia associated with clozapine) was well understood across all survey years. In 2017, the overall mean knowledge score was lowered due to (1) only 61% of pharmacy respondents accurately answering whether the risk of neutropenia is highest in the first 18 weeks of treatment, and (2) only 53.0% of pharmacy respondents correctly answering that treatment should be interrupted inpatient who develop a fever of 38.5°C (101.3°F) or greater and an ANC should be obtained (Table 73). In 2019, 2020, and 2024, only 61%, 68%, and 68%, respectively, correctly responded to the question relating to whether the risk of neutropenia is higher in the first 18 weeks of treatment.

Table 73 Key Risk Message 1 – Understand the Risk of Severe Neutropenia Associated With Clozapine: Pharmacist Survey

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	81.6%	True/False: Risk of neutropenia appears greater in the first 18 weeks of treatment with clozapine (61% answered correctly) True/False: Clozapine treatment should be interrupted as a precautionary measure in any patient who develops a fever of 38.5°C (101.3°F) or greater, and an ANC should be obtained (53% answered correctly)
16 Jul 2018 – 31 Dec 2019	85.0%	True/False: Risk of neutropenia appears greater in the first 18 weeks of treatment with clozapine (61% answered correctly)
01 Jan 2020 – 31 Dec 2020	87.0%	True/False: Risk of neutropenia appears greater in the first 18 weeks of treatment with clozapine (68% answered correctly)
Modified REMS		
01 Dec 2022 – 29 May 2024	88.0%	True/False: Risk of neutropenia appears greater in the first 18 weeks of treatment with clozapine (68% answered correctly)

ANC = absolute neutrophil count; REMS = Risk Evaluation and Mitigation Strategy.

For Key Risk Message 2 (i.e., understand the need for appropriate patient monitoring with clozapine), 2017 results demonstrated that the key risk message was not fully understood. Low scoring questions related to (1) that prescribers may choose to continue clozapine treatment in patient with ANCs less than 1,000 cells/µL if they confirm that the benefits of treatment outweigh the risks of developing severe neutropenia (67.0% correct), (2) baseline ANC for patients with BEN (66.0% correct), (3) when patients qualify for a change in ANC monitoring frequency, prescribers will be notified by the Clozapine REMS (48.5% correct), and (4) questions related to patients with BEN (67.0% correct) (Table 74). For all other years, the lowest scoring question related to whether patients with BEN have a separate ANC monitoring requirement (70%, 74%, and 70% for 2019, 2020, and 2024, respectively).

Table 74 Key Risk Message 2 – Understand the Need for Appropriate Patient Monitoring With Clozapine: Pharmacist Survey

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	76.8%	1. True/False: Prescribers may choose to continue clozapine treatment in patients with ANCs <1,000 cells/µL if they confirm that the benefits of treatment outweigh the risks of developing severe neutropenia (67% answered correctly)

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
		2. True/False: Baseline ANC must be at least 1,000 cells/µL for patients diagnosed with BEN (66% answered correctly) 3. True/False: When patients qualify for a change in ANC monitoring frequency, prescribers will be notified by the Clozapine REMS (48.5% answered correctly) 4. According to the USPI, in which of the following patients are the ANC levels acceptable prior to treatment with clozapine? Patient D [with documented BEN]: Before starting treatment with clozapine, the baseline ANC is >1,100 cells/µL (67% answered correctly).
16 Jul 2018 – 31 Dec 2019	85.0%	True/False: Patients with BEN have a separate ANC monitoring algorithm when treated with clozapine (70% answered correctly)
01 Jan 2020 – 31 Dec 2020	86.0%	No low-scoring question
Modified REMS		
01 Dec 2022 – 29 May 2024	86.0%	True/False: Patients with BEN have a separate ANC monitoring algorithm when treated with clozapine (70% answered correctly)

ANC = absolute neutrophil count; BEN = benign ethnic neutropenia; REMS = Risk Evaluation and Mitigation Strategy; USPI = United States Prescribing Information.

Key Risk Message 3 (i.e., understand the requirements of the Clozapine REMS) fell short of the target threshold in 2020 and 2024; however, the target threshold was 90% correct for these years versus 80% for 2017 and 2018. In 2017, the lowest scoring question related to whether a PDA was required before dispensing clozapine (66% correct). In 2019 and 2020, there was little understanding related to whether a pharmacy can exercise clinical judgement and continue to dispense clozapine by providing a Dispense Rationale (26% correct for both years) (Table 75). In 2024, there was no overall question that can be viewed as lowering overall scores (i.e., the percent correct for each question was 76% or greater). Additionally, because there were only 8 questions, pharmacy respondents needed to answer all 8 questions correctly to achieve the target.

Table 75 Key Risk Message 3 – Understand the Requirements of the Clozapine REMS: Pharmacist Survey

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	85.4%	According to the Clozapine REMS materials, if a PDA is denied for an enrolled patient with the warning message "Prescriber not certified in the Clozapine REMS" an outpatient pharmacy may do which of the following? Exercise clinical judgment and continue to dispense clozapine by providing a Dispense Rationale (26% answered correctly)

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
16 Jul 2018 – 31 Dec 2019	77.0%	For inpatient pharmacies; according to the Clozapine REMS an Eligibility Check evaluates which of the following: Patient ANC is on file (70% answered correctly) Last ANC value for patient on file is acceptable (68% answered correctly)
01 Jan 2020 – 31 Dec 2020	87.0%	According to the Clozapine REMS materials, if a PDA is denied for an enrolled patient with the warning message "Prescriber not certified in the Clozapine REMS" an outpatient pharmacy may do which of the following? Exercise clinical judgment and continue to dispense clozapine by providing a Dispense Rationale (26% answered correctly)
Modified REMS		
01 Dec 2022 – 29 May 2024	87.0%	No low-scoring question

ANC = absolute neutrophil count; PDA = Predispense Authorization; REMS = Risk Evaluation and Mitigation Strategy.

A subanalysis was performed in 2020 and demonstrated that inpatient pharmacists had a significantly higher knowledge score than outpatient pharmacists for Key Risk Message 3. A similar subanalysis was performed in 2024 and demonstrated that authorized representatives had significantly greater mean scores as it related to Key Risk Messages 2 and 3.

4.3.2.3 Patient/Caregiver Survey Results

For all survey years, >75% of patient (or caregiver) respondents had been taking clozapine or caring for a patient taking clozapine for more than 24 months. However, <30% of respondents recall receiving *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia.* Each year, the majority (approximately 75%) of survey participants received information about clozapine from their provider or their provider's staff, and slightly less (approximately 68%) received information about clozapine from a pharmacist or pharmacy staff. Across all survey years, subanalyses demonstrated that patients recalling receipt of the guide had significantly higher mean scores than those who did not.

In 2020, the surveys introduced a knowledge rate performance threshold using a risk-based methodology, and the targeted knowledge rate threshold changed for each key risk message (i.e., to 50% or higher for Key Risk Message 1, to 60% or higher for Key Risk Message 2, and to 30% or higher for Key Risk Message 3, from 80% for all Key Risk Messages previously).

After a review of the survey results for each year, the results showed that patients have a good understanding of the risk of neutropenia when taking clozapine. However, identifying the signs and symptoms of neutropenia often scored low, thus lowering the mean knowledge rate of Key Risk Message 1 (i.e., understand the risk of severe neutropenia associated with clozapine) (Table 76). Patients identified "feeling extremely weak or tired" as a symptom but failed to correctly identify additional symptoms, such as "sores or pain in or around rectal area" and "pain or burning while urinating." In the most recent survey year, only 10% of respondents identified sores or pain in or around rectal area, 14% identified pain or burning while urinating, 57% identified feeling weak or tired, and 43% identified infections, including skin and throat. In

comparison, 75% of respondents were aware that clozapine can cause white blood cells to drop in number (neutropenia).

Table 76 Key Risk Message 1 – Understand the Risk of Severe Neutropenia Associated With Clozapine: Patient Survey

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	32.5%	All
16 Jul 2017 – 15 Jul 2018	28.9%	All
16 Jul 2018 – 31 Dec 2019	47.0%	All
01 Jan 2020 – 31 Dec 2020	55.0%	All
Modified REMS		
01 Dec 2022 – 29 May 2024	37.0%	All

REMS = Risk Evaluation and Mitigation Strategy.

Key Risk Message 2 (i.e., understand the need for appropriate patient monitoring with clozapine) has historically had a high mean knowledge rate for patients and caregivers (Table 77). Between 2019 and 2024, 97% of survey respondents correctly answered that they must have regular blood tests while taking clozapine, and >86% correctly answered that they must have a blood test prior to beginning clozapine. The mean was lower for Key Risk Message 2 with only around 65% of respondents correctly answering, "If your neutrophils are too low, your doctor may schedule blood tests more frequently."

Table 77 Key Risk Message 2 – Understand the Need for Appropriate Patient Monitoring With Clozapine: Patient Survey

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	88.5%	No low-scoring question
16 Jul 2017 – 15 Jul 2018	73.5%	No low-scoring question
16 Jul 2018 – 31 Dec 2019	72.0%	What are the requirements that you [the patient that you care for] must complete to receive Clozapine? If your neutrophils are too low, your doctor may ask you to have blood tests more frequently (65% answered correctly)
01 Jan 2020 – 31 Dec 2020	83.0%	What are the requirements that you [the patient that you care for] must complete to receive Clozapine? If your neutrophils are too low, your doctor may ask you to have blood tests more frequently (65% answered correctly)
Modified REMS		
01 Dec 2022 – 29 May 2024	84.0%	What are the requirements that you [the patient that you care for] must complete to receive Clozapine? If your neutrophils are too low, your doctor may ask you to have blood tests more frequently (66% answered correctly)

REMS = Risk Evaluation and Mitigation Strategy.

Between 2017 and 2019, while the mean knowledge rate for Key Risk Message 3 (i.e., understand the requirements of the Clozapine REMS) did not meet the 80% knowledge rate threshold, the mean knowledge rate was consistent following a period of stability (2015 through 2018) in REMS changes (Table 78). For 2020 (prior to the major modification) and 2024 (following the 2021 major modification), the knowledge rates were 46% and 63%, respectively. The 2017 and 2018 survey years showed >65% mean knowledge score for Key Risk Message 3. However, the mean knowledge rate was lower as <40% of respondents correctly answered, "Clozapine is only available through a special program called the Clozapine REMS." In comparison, 66% of participants in 2024 were correct in responding "Clozapine is only available through a special program called the Clozapine REMS," 70% correctly answered that they must be enrolled in the REMS to receive clozapine, and 74% correctly answered that they can only get their clozapine prescription from a pharmacy that is a part of the REMS.

Table 78 Key Risk Message 3 – Understand the Requirements of the Clozapine REMS: Patient Survey

Reporting Period	Mean Score of Linked Questions	Lowest-Scoring Questions
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	65.1%	Almost all questions
16 Jul 2017 – 15 Jul 2018	66.1%	Almost all questions
16 Jul 2018 – 31 Dec 2019	46.0%	All questions
01 Jan 2020 – 31 Dec 2020	46.0%	All questions
Modified REMS		
01 Dec 2022 – 29 May 2024	63.0%	Correctly identify the REMS requirement "A patient must review the patient guide What You Need to Know About Clozapine and Neutropenia" (44% answered correctly)

REMS = Risk Evaluation and Mitigation Strategy.

It is believed the lower mean knowledge rate in prior years can be attributed to multiple changes in the risk management programs and requirements for clozapine. Following the 2021 Major Modification and implementation of all REMS requirements, the KAB results showed that patients and caregivers have a good understanding of their REMS requirements. In the most recent survey year, patients of clozapine or their caregivers as a group scored below the target performance threshold of 50% for Key Measure 1, and above the target performance thresholds of 60% and 30%, respectively, for Key Measures 2 and 3.

The 2020 and 2024 survey periods also showed there is a significant difference between the mean knowledge scores of caregiver respondents compared with patient respondents for each key risk message. More than double the number of patients than caregivers have completed the survey each year. The condition for which patients are being treated with clozapine cannot be ruled out as a contributing factor to the survey results (2020 Survey Assessment Report). It is important to note there are more than double the number of respondents for the 2024 survey year (729 completers). However, the results did not differ significantly from prior survey years.

4.3.3 Use of Treatment Rationale

The Treatment Rationale allows treatment despite abnormal ANC values when a prescriber determines that the benefits of continuing care outweigh the risk of disrupting treatment. The number of Treatment Rationales submitted are presented by reporting period in Table 79. Reviewing the use of the Treatment Rationale may help to better elucidate the frequency at which the risk-benefit assessments are being completed.

Table 79 Use of Treatment Rationale

Reporting Period	Treatment Rationales Submitted	Number of Patients With Neutropenia (ANC <999 cells/µL)
Legacy REMS		
16 Jul 2016 – 15 Jul 2017	150	751
16 Jul 2017 – 15 Jul 2018	191	545
16 Jul 2018 – 31 Dec 2019		
16 Jul 2018 – 27 Feb 2019	119	360
28 Feb 2019 – 31 Dec 2019	177	580
01 Jan 2020 – 31 Dec 2020	188	796
01 Jan 2021 – 15 Nov 2021	221	623
Modified REMS		
29 Jul 2021 – 30 Nov 2022	285	7,384
01 Dec 2022 – 29 May 2024	282	2,560

ANC = absolute neutrophil count; REMS = Risk Evaluation and Mitigation Strategy.

4.3.4 Summary

Under enforcement discretion, certain elements of the REMS (such as noncompliance monitoring of prescribers and pharmacies, verification of pharmacy certification by wholesalers-distributors, and obtaining an RDA for all dispenses of clozapine) have not been implemented. Without full implementation of all REMS required processes, the CPMG is unable to complete longitudinal analysis of the REMS elements. Delayed implementation of these REMS elements limits data collection that supports evaluation of the effectiveness of the REMS. In summary, the data presented indicate that the Clozapine REMS is functioning as intended by providing a centralized point of access for prescribers and pharmacies to certify before prescribing or dispensing clozapine, to enroll and manage patients on clozapine, as well as being a system to detect clozapine-induced neutropenia.

5.0 STAKEHOLDER FEEDBACK AND OPPORTUNITIES FOR IMPROVEMENT OF CLOZAPINE REMS

The Clozapine REMS serves as an important gatekeeper in ensuring that severe neutropenia is identified during clozapine treatment. Specifically, the REMS provides a centralized point of access for HCPs to certify that a patient's ANC value is in the acceptable range prior to dispensing clozapine. The REMS alerts providers when lab values require further assessment as part of the treatment paradigm and provides mandatory education to the REMS stakeholders. The REMS and its predecessors have served this purpose since 1989, but stakeholders have expressed concerns about the burdens to access. Patient safety, continuity of care, and patient access to clozapine are the highest priorities, and the goal of reviewing the REMS is ultimately to balance these priorities.

5.1 Summary of Approved Clozapine REMS Modifications

Table 80 details the previously approved Clozapine REMS modifications. Overall, the ETASU and requirements of the Clozapine REMS have not changed since its approval in 2015. Ongoing analysis of the REMS and consideration of stakeholder feedback have led to the implementation of modifications to enhance the ease of use for stakeholders without affecting patient safety.

Table 80 Summary of Approved Clozapine REMS Modifications

Date	Summary of Change
15 Sep 2015	Approval of the Clozapine REMS
28 Feb 2019	Major REMS Modification • Changes from original 2015 approval – Turned on requirement for prescriber and outpatient pharmacy certification to obtain PDA – Created DR for outpatient pharmacies to apply clinical judgment and continue to dispense clozapine to enrolled patients when a patient's prescriber was not certified in the Clozapine REMS ▪ Given that the REMS still did not evaluate whether the patient had a current ANC based on the patient's monitoring frequency, the DR was simply a way to circumvent the need for prescriber certification, not missing ANC results (i.e., as is the case in the current iteration of the Clozapine REMS) – Separated enrollment forms for inpatient and outpatient pharmacies (note chain pharmacies previously enrolled separately from non-chain pharmacies, and this approach was maintained) – Introduced new stakeholder education/resource documents and communications regarding REMS modification and resulting process changes/requirements • Summary of new, revised, and removed REMS materials – New ▪ Inpatient Pharmacy Enrollment Form (replaced previous nonspecific "Pharmacy Enrollment Form") ▪ Outpatient Pharmacy Enrollment Form (replaced previous nonspecific "Pharmacy Enrollment Form") ▪ FAQs ▪ How to Start Clozapine and Monitor Patients (Fact Sheet) ▪ Eligibility Check Fact Sheet

Date	Summary of Change
	▪ FDA Fact Sheet ▪ Dear Inpatient Pharmacy Letter ▪ Dear Outpatient Pharmacy using Web PDA Letter ▪ Dear Outpatient Pharmacy Using Switch Letter ▪ Dear Prescriber Letter ▪ Dear Professional Society Cover Letter – Prescriber ▪ Dear Professional Society Cover Letter – Pharmacy ▪ Dear Pharmacy Certification Reminder Letter ▪ Dear Prescriber No Patients Certification Reminder Letter ▪ Dear Prescriber Enrolled Patients Certification Reminder Letter ▪ Dear Migrated Stakeholder Deactivation Letter – Revised ▪ PEF ▪ Prescriber Enrollment Form ▪ Chain Headquarters Pharmacy Enrollment Form ▪ Prescriber Designee Enrollment Form ▪ Distributor Enrollment Form ▪ A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia ▪ Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers ▪ Knowledge Assessment for Healthcare Providers ▪ Acknowledgement Form for Prescriber Designee KA ▪ ANC Lab Reporting Form ▪ Prescriber Designee Education ▪ Pharmacy Staff Enrollment Attestation Language (Web Only) ▪ Website Screen Captures – Removed (these were obsolete with the REMS modifications) ▪ Clozapine_REMS_Dear_Pharmacy_Letter_Wave1_FINAL_2015_09 ▪ Clozapine_REMS_Dear_Pharmacy_Letter_Wave2_FINAL_2015_09 ▪ Clozapine_REMS_Dear_Pharmacy_Letter_Wave3_FINAL_2015_09 ▪ Clozapine_REMS_Dear_Prescriber_Letter_Wave1_FINAL_2015_09 ▪ Clozapine_REMS_Dear_Prescriber_Letter_Wave2_FINAL_2015_09 ▪ Clozapine_REMS_Dear_Prescriber_Letter_Wave3_FINAL_2015_09 ▪ Clozapine_REMS_Pharmacy_Enrollment_Form_FINAL_2015_09 ▪ List of Clozapine Applicants_09_08_2015 ▪ Whats_NEW_with_Clozapine_Document_2015_09 ▪ Clozapine_REMS_Dear_Prof_Soc_Prescr_LtrWve1_FINAL_2015_09 ▪ Clozapine_REMS_Dear_Prof_Soc_Pharm_LtrWve1_FINAL_2015_09
15 Nov 2021	Major REMS Modification • Changes from 28 Feb 2019 Major Modification – Introduced PSF – Replaced PDA with RDA – While original web URL (clozapinerems.com) was maintained, added newclozapinerems.com, which launched in Aug 2021 and allowed stakeholders to reenroll/recertify ahead of 15 Nov 2021 modification launch while original URL continues to support (now legacy) REMS business

Date	Summary of Change
	– Removed "switch" as means of communication with the REMS to obtain an RDA – Required reenrollment/recertification of all REMS stakeholders – Replaced all former REMS materials with new versions; most educational materials were recreated for the modified program ▪ Created Non-Compliance Action Plan, though this has never been enforced o Note that in the Legacy REMS, noncompliance monitoring also did not occur, and no formal noncompliance plan was ever approved by the FDA (though it was drafted and reviewed) – Changed cadence for assessment reporting

ANC = absolute neutrophil count; DR = Dispense Rationale; FAQs = Frequently Asked Questions; FDA = US Food and Drug Administration; KA = Knowledge Assessment; PDA = Predispense Authorization; PEF = Patient Enrollment Form; PSF = Patient Status Form; RDA = REMS Dispense Authorization; REMS = Risk Evaluation and Mitigation Strategy.

5.2 Stakeholder Feedback and Key System Updates

5.2.1 Stakeholder Feedback: Listening Sessions

Between December 2021 and August 2022, the CPMG invited members of organizations representing medical and advocacy groups to share their feedback with the Sponsors and the FDA regarding the Modified REMS.

In 5 listening sessions, stakeholders shared concerns in several areas, including the following:

- Efficacy of the REMS requirements in mitigating patient risk and the increased burden on medical professionals in caring for patients
- Several elements of the REMS requirements, such as RDAs, PSF, and PSF reminders, were cumbersome, and in some circumstances, could prevent patients from receiving the drug.
- In LTC facilities, including psychiatric hospitals and prisons, their classification as an outpatient rather than an inpatient facility may delay patient care.
- Risk of neutropenia may be reduced after the first year of treatment, which could allow reduced restrictions for long-term patients.
- Challenges with navigating the REMS website

The CPMG has taken these concerns and suggestions into consideration, both in updates already made to the REMS and in identifying other potential areas for improvement.

5.2.2 Educational Opportunities

Based on stakeholder feedback and review of the knowledge assessment data, several misconceptions and knowledge gaps that led to perceived barriers and burdens have been identified. Some of the common misconceptions are listed in Table 81.

Table 81 Common Misconceptions About Clozapine REMS

Common Misconception	Fact
Only a limited supply of drug can be dispensed (e.g., 7, 14, or 28 days)	In an outpatient setting, the REMS does not limit the amount of medication that can be dispensed – only that a PSF or Dispense Rationale must be on file at the time of dispense[a]
Cannot dispense without PSF	Pharmacists can dispense using a Dispense Rationale if current ANC is available in the acceptable range
Patients who cannot participate in regular blood/ANC monitoring are denied access	Prescriber may authorize dispensing of medication if patient has missing labs
Lost or missing medications are not allowed to be dispensed per the REMS	Authorization to dispense lost or missing medication is at the discretion of the pharmacy and insurance company

[a] Inpatient dispensing is limited to 7 days at discharge (not currently enforced under enforcement discretion).
ANC = absolute neutrophil count; PSF = Patient Status Form; REMS = Risk Evaluation and Mitigation Strategy.

5.2.3 Key System Updates Based on Stakeholder Feedback

Based on stakeholder feedback, several changes have been implemented. Key changes are listed in Table 82.

Table 82 Key System Updates Based on Stakeholder Feedback

Clozapine REMS Enhancement	Reduction in Stakeholder Burden
Provided ability to remove incorrect ANC entries	Ensures data accuracy and mitigates potential treatment interruptions
Added ANC and monitoring histories	Provides information pharmacist needs to use Dispense Rationale Allows prescribers to review all patient data stored within the REMS, prevents duplicative work, and enhances clinical decision-making
Changed system to prepopulate current ANC values when submitting the PSF online	Eliminates manual reentry of historical data
Added pop-up warning when ANC <100 cells/µL entered	Confirms proper unit of measurement, mitigates therapy disruptions, and decreases erroneous AE reports
Changed the default sort order of RDAs to make the most recent RDA at the top	Facilitates stakeholder review of most recent authorizations
Streamlined prescriber and designee association process	Alleviates the burden on prescribers to fulfill REMS requirements
Added a checkbox to the portal for authorized representative verification	Allows electronic self-service for verification
Enhanced pharmacy lookup tool	Allows users to find pharmacies by ZIP code

AE = adverse event; ANC = absolute neutrophil count; PSF = Patient Status Form; RDA = REMS Dispense Authorization; REMS = Risk Evaluation and Mitigation Strategy.

5.3 Potential Areas for Improvement of Clozapine REMS

Table 83 summarizes potential areas for improvement of the Clozapine REMS and the benefit it would provide to stakeholders.

Table 83 Potential Areas for Improvement

Potential Area for Improvement	Benefit to Stakeholders
Drive greater awareness and education	Address misconceptions and common questions
Manage transitions in care more effectively	Ensure continued access to treatment during transitions between prescribers and pharmacies and from inpatient to outpatient care
Improve communication across institutional reporting systems	Reduce burden on physicians and pharmacies
Improve AE collection	Obtain more meaningful data on incidence and outcomes of AEs related to clozapine-induced neutropenia

AE = adverse event.

6.0 OVERALL CONCLUSION

The risk management requirements for clozapine have existed in various forms since 1989 to ensure that patients and clinicians are aware of the risks of AEs related to clozapine-induced neutropenia. Without the REMS in place, physicians or patients may not adhere to the strict monitoring regimen specified in product labeling, which could result in undetected neutropenia and increased morbidity and mortality. Notwithstanding, patient safety, continuity of care, and patient access to clozapine are the highest priorities. Through stakeholder input, evaluation of assessment data, and ongoing FDA consultation, the CPMG has identified and clarified misconceptions that may be addressed through awareness and education. It has implemented improvements to address challenges and streamline use of the REMS and, as part of good governance, is committed to continue implementation of improvements as necessary. In addition, the CPMG has identified opportunities to potentially improve data collection and reduce stakeholder burden while continuing to help ensure patient safety. The CPMG is committed to collaborating with stakeholders and FDA to make further improvements.

7.0 REFERENCES

1. Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br J Psychiatry*. Dec 2012;201(6):481-5. doi:10.1192/bjp.bp.111.105833

2. National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. Clinical Guideline 178; 2014. Updated 01 Mar 2014. Available from: https://www.nice.org.uk/guidance/cg178. Accessed 24 Aug 2024.

3. Parkes S, Mantell B, Oloyede E, Blackman G. Patients' experiences of clozapine for treatment-resistant schizophrenia: a systematic review. *Schizophr Bull Open*. Jan 2022;3(1):sgac042. doi:10.1093/schizbullopen/sgac042

4. Marder SR, Cannon TD. Schizophrenia. *N Engl J Med*. Oct 31 2019;381(18):1753-1761. doi:10.1056/NEJMra1808803

5. Hany M, Rehman B, Rizvi A, Chapman J. Schizophrenia. [Updated 23 Feb 2024]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539864/.

6. Schmitt A, Falkai P, Papiol S. Neurodevelopmental disturbances in schizophrenia: evidence from genetic and environmental factors. *J Neural Transm (Vienna)*. Mar 2023;130(3):195-205. doi:10.1007/s00702-022-02567-5

7. Jauhar S, Johnstone M, McKenna PJ. Schizophrenia. *Lancet*. Jan 29 2022;399(10323):473-486. doi:10.1016/S0140-6736(21)01730-X

8. Jongsma HE, Turner C, Kirkbride JB, Jones PB. International incidence of psychotic disorders, 2002-17: a systematic review and meta-analysis. *Lancet Public Health*. May 2019;4(5):e229-e244. doi:10.1016/S2468-2667(19)30056-8

9. Demjaha A, Lappin JM, Stahl D, et al. Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors. *Psychol Med*. Aug 2017;47(11):1981-1989. doi:10.1017/S0033291717000435

10. Lally J, Ajnakina O, Di Forti M, et al. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychol Med*. Nov 2016;46(15):3231-3240. doi:10.1017/S0033291716002014

11. Meltzer HY, Rabinowitz J, Lee MA, et al. Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. *Am J Psychiatry*. Apr 1997;154(4):475-82. doi:10.1176/ajp.154.4.475

12. Correll CU, Howes OD. Treatment-resistant schizophrenia: definition, predictors, and therapy options. *J Clin Psychiatry*. Sep 7 2021;82(5)doi:10.4088/JCP.MY20096AH1C

13. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*. Feb 2004;161(2 suppl):1-56.

14. Iasevoli F, Giordano S, Balletta R, et al. Treatment resistant schizophrenia is associated with the worst community functioning among severely-ill highly-disabling psychiatric conditions and is the most relevant predictor of poorer achievements in functional milestones. *Prog Neuropsychopharmacol Biol Psychiatry*. Feb 4 2016;65:34-48. doi:10.1016/j.pnpbp.2015.08.010

15. Burton CZ, Vella L, Harvey PD, Patterson TL, Heaton RK, Twamley EW. Factor structure of the MATRICS Consensus Cognitive Battery (MCCB) in schizophrenia. *Schizophr Res*. May 2013;146(1-3):244-8. doi:10.1016/j.schres.2013.02.026

16. Dickinson D, Bellack AS, Gold JM. Social/communication skills, cognition, and vocational functioning in schizophrenia. *Schizophr Bull*. Sep 2007;33(5):1213-20. doi:10.1093/schbul/sbl067

17. Rocca P, Montemagni C, Zappia S, Pitera R, Sigaudo M, Bogetto F. Negative symptoms and everyday functioning in schizophrenia: a cross-sectional study in a real world-setting. *Psychiatry Res*. Aug 30 2014;218(3):284-9. doi:10.1016/j.psychres.2014.04.018

18. Rosenheck R, Leslie D, Keefe R, et al. Barriers to employment for people with schizophrenia. *Am J Psychiatry*. Mar 2006;163(3):411-7. doi:10.1176/appi.ajp.163.3.411

19. Twamley EW, Doshi RR, Nayak GV, et al. Generalized cognitive impairments, ability to perform everyday tasks, and level of independence in community living situations of older patients with psychosis. *Am J Psychiatry*. Dec 2002;159(12):2013-20. doi:10.1176/appi.ajp.159.12.2013

20. Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol*. Mar 2014;29(2):63-76. doi:10.1097/YIC.0b013e32836508e6

21. Potkin SG, Kane JM, Correll CU, et al. The neurobiology of treatment-resistant schizophrenia: paths to antipsychotic resistance and a roadmap for future research. *NPJ Schizophr*. Jan 7 2020;6(1):1. doi:10.1038/s41537-019-0090-z

22. Siskind D, Siskind V, Kisely S. Clozapine response rates among people with treatment-resistant schizophrenia: data from a systematic review and meta-analysis. *Can J Psychiatry*. Nov 2017;62(11):772-777. doi:10.1177/0706743717718167

23. Ucok A, Cikrikcili U, Karabulut S, et al. Delayed initiation of clozapine may be related to poor response in treatment-resistant schizophrenia. *Int Clin Psychopharmacol*. Sep 2015;30(5):290-295. doi:10.1097/YIC.0000000000000086

24. Yoshimura B, Yada Y, So R, Takaki M, Yamada N. The critical treatment window of clozapine in treatment-resistant schizophrenia: Secondary analysis of an observational study. *Psychiatry Res*. Apr 2017;250:65-70. doi:10.1016/j.psychres.2017.01.064

25. John AP, Ko EKF, Dominic A. Delayed initiation of clozapine continues to be a substantial clinical concern. *Can J Psychiatry*. Aug 2018;63(8):526-531. doi:10.1177/0706743718772522

26. Law C, See YM, Yee JY, Ng BT, Tang C, Lee J. The impact of clozapine delay on clinical outcomes in schizophrenia. *J Clin Psychiatry*. Aug 23 2023;84(5)doi:10.4088/JCP.22m14588

27. Bogers JP, Schulte PF, Van Dijk D, Bakker B, Cohen D. Clozapine underutilization in the treatment of schizophrenia: How can clozapine prescription rates be improved? *J Clin Psychopharmacol*. Apr 2016;36(2):109-111. doi:10.1097/JCP.0000000000000478

28. Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Geographic and clinical variation in clozapine use in the United States. *Psychiatr Serv*. Feb 1 2014;65(2):186-92. doi:10.1176/appi.ps.201300180

29. Bachmann CJ, Aagaard L, Bernardo M, et al. International trends in clozapine use: a study in 17 countries. *Acta Psychiatr Scand*. Jul 2017;136(1):37-51. doi:10.1111/acps.12742

30. Melville NA. Clozapine underutilized in treatment-resistant schizophrenia. MDedge. November 8, 2022, https://www.mdedge.com/psychiatry/article/259297/schizophrenia-other-psychotic-disorders/clozapine-underutilized-treatment

31. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. Sep 1988;45(9):789-96. doi:10.1001/archpsyc.1988.01800330013001

32. Meltzer HY, Bastani B, Kwon KY, Ramirez LF, Burnett S, Sharpe J. A prospective study of clozapine in treatment-resistant schizophrenic patients. I. Preliminary report. *Psychopharmacology (Berl)*. 1989;99(suppl):S68-S72. doi:10.1007/BF00442563

33. Nielsen J, Nielsen RE, Correll CU. Predictors of clozapine response in patients with treatment-refractory schizophrenia: results from a Danish Register Study. *J Clin Psychopharmacol*. Oct 2012;32(5):678-83. doi:10.1097/JCP.0b013e318267b3cd

34. Kohler-Forsberg O, Horsdal HT, Legge SE, MacCabe JH, Gasse C. Predictors of Nonhospitalization and Functional Response in Clozapine Treatment: A Nationwide, Population-Based Cohort Study. *J Clin Psychopharmacol*. Apr 2017;37(2):148-154. doi:10.1097/JCP.0000000000000649

35. Lally J, MacCabe JH. Personalised approaches to pharmacotherapy for schizophrenia. *BJPsych Adv*. 2016;22(2):78-86.

36. Li XH, Zhong XM, Lu L, et al. The prevalence of agranulocytosis and related death in clozapine-treated patients: a comprehensive meta-analysis of observational studies. *Psychol Med*. Mar 2020;50(4):583-594. doi:10.1017/S0033291719000369

37. Northwood K, Myles N, Clark SR, et al. Evaluating the epidemiology of clozapine-associated neutropenia among people on clozapine across Australia and Aotearoa New Zealand: a retrospective cohort study. *Lancet Psychiatry*. Jan 2024;11(1):27-35. doi:10.1016/S2215-0366(23)00343-7

38. Rubio JM, Kane JM, Tanskanen A, Tiihonen J, Taipale H. Long-term persistence of the risk of agranulocytosis with clozapine compared with other antipsychotics: a nationwide cohort and case-control study in Finland. *Lancet Psychiatry*. Jun 2024;11(6):443-450. doi:10.1016/S2215-0366(24)00097-X

39. Legge SE, Hamshere M, Hayes RD, et al. Reasons for discontinuing clozapine: a cohort study of patients commencing treatment. *Schizophr Res*. Jul 2016;174(1-3):113-119. doi:10.1016/j.schres.2016.05.002

40. Ingimarsson O, MacCabe JH, Haraldsson M, Jonsdottir H, Sigurdsson E. Neutropenia and agranulocytosis during treatment of schizophrenia with clozapine versus other antipsychotics: an observational study in Iceland. *BMC Psychiatry*. Dec 12 2016;16(1):441. doi:10.1186/s12888-016-1167-0

8.0 APPENDIX

8.1 Appendix A: Patient Status Form

CLOZAPINE REMS

Patient Status Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Instructions

Assess the patient by obtaining complete blood counts, including the absolute neutrophil count (ANC), as described in the Prescribing Information. Record the ANC data on this form.

You can complete this form online at www.clozapinerems.com or fax it to the Clozapine REMS Contact Center at 1-800-878-5927.

This form must be completed monthly for each patient continuing treatment with clozapine. Please submit page 1 and any pages that apply to your patient's monitoring frequency.

This form may also be used to:

- Interrupt, Discontinue, or Resume Treatment
- Designate the patient as a Benign Ethnic Neutropenia patient
- Create a Treatment Rationale when the patient's ANC level is < 1000/µL for a general population patient or < 500/µL for a BEN patient
- Designate the patient as a Hospice patient

This form can be used by both a prescriber and prescriber designee. The following activities require the signature of a certified prescriber:

- Designating a patient as a Hospice Care patient
- Designating a patient as a Benign Ethnic Neutropenia patient
- Authorizing the continuation of therapy if one or more required labs are missing
- Creating a Treatment Rationale for a patient

By submitting this form, you are authorizing this patient to continue treatment on clozapine, unless Interrupt Treatment or Discontinue Treatment is selected.

Prescriber Information (* Indicates a Required Field)

First Name*: | Last Name*: | Individual NPI #*:

Phone*: | Email Address*: | Fax:

Prescriber Designee Information (* Indicates a Required Field if form is completed by a Prescriber Designee)

First Name*: | Last Name*:

Phone*: | Email Address*: | Fax*:

Patient Information (* Indicates a Required Field)

First Name*: | Last Name*: | REMS Patient ID:

Date of Birth*: MM / DD / YYYY | Zip Code: | Gender: ☐ Male ☐ Female ☐ Other

Patient Status (* Indicates a Required Field)

1. Are you monitoring the patient as recommended in the Prescribing Information?* ☐ Yes ☐ No

2. What is the patient's current monitoring frequency?* ☐ 3 times a week ☐ Every 2 weeks ☐ Weekly ☐ Monthly

3. Change the patient's monitoring frequency to*: ☐ 3 times a week ☐ Every 2 weeks ☐ No Change to the Monitoring Frequency ☐ Weekly ☐ Monthly

4. Did the patient experience any adverse event(s) due to clozapine-induced neutropenia (e.g. infection)?*
   ☐ No
   ☐ Yes → If yes, please provide a phone number where you may be reached by the Clozapine REMS Contact Center for additional information related to this event: (____) ____-____.

Hospice Care patient designation. This section must be completed by the prescriber. The prescriber must sign below.

For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), the prescriber may reduce the frequency of submitting a Patient Status Form to once every 6 months after a discussion with the patient and his/her caregiver. To change the frequency of submitting a Patient Status Form to once every 6 months for a hospice patient, **the prescriber must sign below.**

By signing below, I attest that the above is a hospice care patient.

Prescriber Signature: | Date (MM/DD/YYYY):

Benign Ethnic Neutropenia (BEN) patient designation. This section must be completed by the prescriber. The prescriber must sign below.

A BEN patient designation provides a separate ANC monitoring algorithm for the patient. The BEN designation is a permanent status.

By signing below, I attest that the above is a patient with documented benign ethnic neutropenia.

Prescriber Signature: | Date (MM/DD/YYYY):

Continue to the next pages to provide ANC Lab Data

Page 1 of 5

CLOZAPINE REMS

Patient Status Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Reporting ANC Lab Data

Instructions for entering ANC lab data on the following pages:

1. **Locate the section below that aligns with the patient's current monitoring frequency**
2. **Enter the blood draw date and the ANC range in the appropriate patient population (general or BEN) column or enter the ANC value.**
3. **If a lab is missing, select the reason for missing the lab. Note: If one or more labs are missing, the prescriber is required to authorize the continuation of therapy by providing a signature and date.**
4. **Report of an ANC lab value indicating moderate (general population) or severe neutropenia (general or BEN population) requires treatment to be interrupted or discontinued or the creation of a Treatment Rationale by the prescriber unless a more recent ANC lab value is provided that is ≥ 1000/µL for a general population patient or ≥ 500/µL for a BEN population patient.**

Weekly Monitoring Frequency (Enter data for the last four weekly blood draws for this patient)

Blood Draw Date:	General Patient Population	BEN Patient Population		ANC (per µL):
MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors (e.g., weather, transportation issues)	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	**General Patient Population** ☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	**BEN Patient Population** ☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	**General Patient Population** ☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	**BEN Patient Population** ☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	**General Patient Population** ☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	**BEN Patient Population** ☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	ANC (per µL):

[1] Prescriber signature is required to authorize the continuation of therapy if one or more labs are missing.
[2] Interrupt / Discontinue treatment or create a Treatment Rationale.

Prescriber Signature: ____________________ Date (MM/DD/YYYY): __________

Patient Treatment Status

Complete this section to interrupt, discontinue, or resume treatment for this patient. No selection indicates the patient may continue treatment.

☐ **Interrupt Treatment** ☐ **Discontinue Treatment** ☐ **Resume Treatment**

Treatment Rationale (If Required) (Prescriber Signature required below)

Complete this section to continue treatment if the patient has moderate neutropenia (ANC 500-999/µL for the general population) or severe neutropenia (ANC<500/µL for general population and patients with benign ethnic neutropenia). check and sign below:

☐ Benefits of continuing clozapine treatment outweigh the risk of neutropenia.

Until (MM/DD/YYYY) __________ (not to exceed 6 months)

Prescriber Signature: ____________________ Date (MM/DD/YYYY): __________

Continue to the next page for additional monitoring frequencies

Page 2 of 5

CLOZAPINE REMS

Patient Status Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Every 2 Weeks Monitoring Frequency (Enter data for the last two every two weeks blood draws for this patient)

Blood Draw Date: MM / DD / YYYY	General Patient Population	BEN Patient Population	or	ANC (per µL):
Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors (e.g., weather, transportation issues)	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]		
Blood Draw Date: MM / DD / YYYY	**General Patient Population**	**BEN Patient Population**	or	ANC (per µL):
Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]		

[1] Prescriber signature is required to authorize the continuation of therapy if one or more labs are missing.
[2] Interrupt / Discontinue treatment or create a Treatment Rationale.

Prescriber Signature: [SIGN HERE] **Date (MM/DD/YYYY):**

Patient Treatment Status

Complete this section to interrupt, discontinue, or resume treatment for this patient. No selection indicates the patient may continue treatment.

☐ **Interrupt Treatment** ☐ **Discontinue Treatment** ☐ **Resume Treatment**

Treatment Rationale (If Required) (Prescriber Signature required below)

Complete this section to continue treatment if the patient has moderate neutropenia (ANC 500-999/µL for the general population) or severe neutropenia (ANC<500/µL for general population and patients with benign ethnic neutropenia). **check and sign below:**

☐ Benefits of continuing clozapine treatment outweigh the risk of neutropenia.
Until (MM/DD/YYYY) _____ (not to exceed 6 months)

Prescriber Signature: [SIGN HERE] **Date (MM/DD/YYYY):**

Monthly Monitoring Frequency (Enter data for the last monthly blood draw for this patient)

Blood Draw Date: MM / DD / YYYY	General Patient Population	BEN Patient Population	or	ANC (per µL):
Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors (e.g., weather, transportation issues)	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]		

[1] Prescriber signature is required to authorize the continuation of therapy if one or more labs are missing.
[2] Interrupt / Discontinue treatment or create a Treatment Rationale.

Prescriber Signature: [SIGN HERE] **Date (MM/DD/YYYY):**

Patient Treatment Status

Complete this section to interrupt, discontinue, or resume treatment for this patient. No selection indicates the patient may continue treatment.

☐ **Interrupt Treatment** ☐ **Discontinue Treatment** ☐ **Resume Treatment**

Treatment Rationale (If Required) (Prescriber Signature required below)

Complete this section to continue treatment if the patient has moderate neutropenia (ANC 500-999/µL for the general population) or severe neutropenia (ANC<500/µL for general population and patients with benign ethnic neutropenia). **check and sign below:**

☐ Benefits of continuing clozapine treatment outweigh the risk of neutropenia.
Until (MM/DD/YYYY) _____ (not to exceed 6 months)

Prescriber Signature: [SIGN HERE] **Date (MM/DD/YYYY):**

Continue to the next page for additional monitoring frequencies

CLOZAPINE REMS

Patient Status Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

3 Times Weekly Monitoring Frequency (Enter all ANC lab data collected in the last four weeks).
This section may also be used to record ANCs for patients requiring daily monitoring.

	General Patient Population	BEN Patient Population		ANC (per µL):
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors (e.g., weather, transportation issues)	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY **Reason for missing lab[1]:** ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	

Continued on next page

CLOZAPINE REMS

Patient Status Form

Phone: 888-586-0758
Fax: 800-878-5927
www.clozapinerems.com

Blood Draw Date / Reason for missing lab[1]	General Patient Population	BEN Patient Population		ANC (per µL):
Blood Draw Date: MM / DD / YYYY Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	
Blood Draw Date: MM / DD / YYYY Reason for missing lab[1]: ☐ Patient Refused ☐ Clinician discretion ☐ Extrinsic factors	☐ Normal Range (≥ 1500/µL) ☐ Mild Neutropenia (1000 to 1499/µL) ☐ Moderate Neutropenia (500 to 999/µL)[2] ☐ Severe Neutropenia (< 500/µL)[2]	☐ Normal BEN Range (≥ 1000/µL) ☐ BEN Neutropenia (500 to 999/µL) ☐ BEN Severe Neutropenia (< 500/µL)[2]	or	

[1] **Prescriber signature is required to authorize the continuation of therapy if one or more labs are missing.**

[2] Interrupt / Discontinue treatment or create a Treatment Rationale.

Prescriber Signature: ____________ Date (MM/DD/YYYY): ____________

Patient Treatment Status

Complete this section to interrupt, discontinue, or resume treatment for this patient. No selection indicates the patient may continue treatment.

☐ **Interrupt Treatment** ☐ **Discontinue Treatment** ☐ **Resume Treatment**

Treatment Rationale (If Required) (Prescriber Signature required below)

Complete this section to continue treatment if the patient has moderate neutropenia (ANC 500-999/µL for the general population) or severe neutropenia (ANC<500/µL for general population and patients with benign ethnic neutropenia). **check and sign below:**

☐ Benefits of continuing clozapine treatment outweigh the risk of neutropenia.

Until (MM/DD/YYYY) ____________ (not to exceed 6 months)

Prescriber Signature: ____________ **Date (MM/DD/YYYY):** ____________

Page 5 of 5