

# ***Alameda County Behavioral Health Care Services***

## **Clozapine Monitoring**

### **I. Background**

#### **A. General Information**

Clozapine is an antipsychotic that is FDA approved for treatment-refractory schizophrenia and reduction of recurrent suicidal behavior in schizophrenia or schizoaffective disorder. Numerous studies have demonstrated the effectiveness of this medication for treatment-resistant patients unresponsive to standard antipsychotics with fewer incidences of troubling extrapyramidal reactions, neuroleptic malignant syndrome, and tardive dyskinesia.

#### **B. Clozapine REMS Program**

The requirements to prescribe, dispense, and receive clozapine have changed and are now incorporated into a single, shared program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS). Clozapine REMS is used to manage the potential risk of fatal agranulocytosis that occurs in 1% to 2% of patients prescribed clozapine. As a precautionary measure, the Office of the Medical Director will need to be notified of every patient prescribed clozapine.

#### **C. Clozapine Notification Form for the Office of the Medical Director**

Please complete a clozapine notification form for any patient who is already receiving clozapine admitted to any Alameda County outpatient clinic or anyone newly started on clozapine and fax to the Office of the Medical Director.

### **II. Clozapine Patient Criteria**

Historically, psychiatric guidelines recommended two failed antipsychotic trials prior to initiation of clozapine. A more recent guideline allows for an earlier trial of clozapine in patients with a history of recurrent suicidality, violence, or comorbid substance abuse<sup>1</sup>. The following are recommended monitoring parameters prior to initiation of clozapine:

- A. Documented history of one of the following treatment-resistant diagnoses:
  - 1. Schizophrenia
  - 2. Schizoaffective disorder
  - 3. Bipolar disorder
- B. Be over the age of 16.
- C. A documented history of at least one failed antipsychotic trial of adequate dose and duration. For example, a patient previously on olanzapine 20mg for 6 weeks exhibiting either partial or nonresponse.
- D. Please ensure that none of the following complications or contraindications are present:
  - 1. History of clozapine-induced neutropenia or agranulocytosis
  - 2. Medical condition or drug associated with myeloproliferative disease or immunosuppression
  - 3. Severe medical condition, or other illnesses causing central nervous system depression or concurrent organic state
  - 4. Poor medical compliance and/or poor compliance with lab testing.
  - 5. Initial ANC < 1500/mm<sup>3</sup>
  - 6. History of hypersensitivity to a clozapine related drug (amoxapine, loxapine)
  - 7. History of significant physical illness in the prior month
  - 8. History of blood disorders

<sup>1</sup>Moore TA, et al. The TMAP algorithm for schizophrenia. J Clin Psychiatry 2007; 68(11):1751-62

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- E. The following potential concerns and complications have been addressed, if applicable:
1. History of seizure disorder, or neurological illness, not currently on an anticonvulsant.
  2. Finnish or Jewish background, especially Ashkenazi Jew (may be more susceptible to agranulocytosis).
  3. Laboratory or clinical evidence of significant hepatic, renal, or cardiopulmonary disease that may increase the concentration of clozapine metabolite to a toxic level.
  4. Prostatic enlargement or narrow angle glaucoma that may worsen due to clozapine's anticholinergic properties.
  5. The use of concomitant medications that have potentially additive adverse outcomes including those with the following effects (*Table 2*):
    - a. Bone marrow suppression
    - b. CNS depression
    - c. Seizure provoking or threshold lowering
    - d. Blood pressure lowering agents (anti-hypertensives)
    - e. Substrates/inhibitors/inducers of CYP1A2, 2D6, and 3A4
    - f. Highly protein bound drugs

### **III. Initiation of Clozapine Treatment**

The following must be completed per FDA regulations for prescribing and administering clozapine to clients:

1. Physician must enroll and become certified in the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program
2. Physician (or designee) must enroll clients into the REMS program and review the risk and benefits of clozapine with the client and any caregivers
3. Baseline ANC must be reported prior to initiation of clozapine

#### **IIIa. Clozapine REMS contact information**

1. Website: [www.clozapinerems.com](http://www.clozapinerems.com)
2. Contact number: 844-267-8678
3. Fax number: 844-404-8876

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### IV. Blood Monitoring Requirements (see Table 1):

- A. **All prescribers** of clozapine must enroll and become certified in the REMS program.
  - 1. Become certified at [www.clozapinerems.com](http://www.clozapinerems.com)
    - a. Review the package insert for clozapine
    - b. Review Clozapine and the Risk of Neutropenia: A guide for Healthcare Providers
    - c. Submit and pass the Knowledge Assessment for Healthcare Providers
    - d. Submit the one-time Clozapine REMS Prescriber Enrollment Form
- B. Enroll client and determine if client meets criteria for benign ethnic neutropenia (BEN).
- C. Baseline ANC > 1500/mm<sup>3</sup> obtained within 7 days of starting clozapine.
- D. Ongoing CBC with differential obtained per the appropriate monitoring guidelines and within 1 week prior to the next prescription for clozapine. Results must be reported to the REMS program prior to dispensing clozapine. Fax results to the client's pharmacy.
- E. Interruptions in therapy may be needed when ANC falls below 1000/mm<sup>3</sup>. Any desire to continue therapy when ANC counts are < 1000/mm<sup>3</sup> will require submission of a treatment rationale to the REMS program and the benefits vs risk documented in the medical chart.
- F. If the ANC < 500/mm<sup>3</sup>, interrupt clozapine therapy, continue blood draws per monitoring guidelines, obtain hematology consultation and do not restart clozapine unless the prescriber determines and documents that the benefits outweigh the risk.
- G. Patients with normal ANC - Draw routine ANC once a week for the first 6 months of therapy, then every other week for the next 6 months. If no blood dyscrasias develop, may reduce to once monthly monitoring thereafter.
- H. Obtain an EKG if cardiovascular sequelae are observed.
- I. Obtaining a clozapine blood level may be warranted if:
  - 1. Noncompliance is suspected
  - 2. There is an unexpected outcome (inadequate efficacy or clinical evidence of toxicity)
  - 3. Target blood levels associated with clozapine's effectiveness is 350-450 ng/mL

### V. Lab Reporting Requirements

- A. The REMS program has eliminated the need to report the WBC. Only ANC results need to be submitted. However, in order to obtain an ANC lab result, a CBC with differential should be ordered.
- B. ANC results can be reported to the REMS program by submitting online, faxing the completed ANC reporting form or by calling the REMS program. See contact information in Section IIIa. The ANC reporting form can be accessed online and is attached at the end of this document.

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## Clozapine Monitoring

### VI. Monitoring Parameters for Clozapine:

#### A. Serious Side effects

1. **Agranulocytosis** – Occurs in ~1-2% of clozapine treated patients. The FDA requires participation in the clozapine REMS program to monitor for this serious condition in clozapine treated clients. Risk is highest during the first 6 months of clozapine therapy. In addition to the routine laboratory monitoring of the ANC, obtain additional ANCs if the patient exhibits clinical signs and symptoms of infection such as fever/chills, mucosal necrosis in throat and perianal or genital areas, urinary frequency or burning.
2. **Seizure** – Seizures of all types have been reported in the literature with the most common being tonic-clonic seizures. Incidence of seizures varies widely, up to 22% depending on the duration of use, and the risk is known to be dose proportional.<sup>2,4</sup> The risk also increases with elevated clozapine plasma levels (>1000mcg/ml).<sup>5</sup> It is generally accepted that doses ≥600 mg/day represent the highest risk. Use caution for patients with a history of seizures or other predisposing factors for seizures. If a seizure occurs while a patient is on clozapine, one recommendation is to decrease clozapine dose by ½, initiate an anticonvulsant, and may gradually titrate clozapine upward until clinical response.<sup>2,4</sup>
3. **Respiratory depression** – Reports of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines, caution is advised when clozapine is initiated in patients taking medications such as opioids and benzodiazepines that may cause additive respiratory depression.
4. **Myocarditis**—Evidence suggests that clozapine is associated with fatal myocarditis. Risk is highest during the first month of initiation and re-initiation secondary to a delayed hypersensitivity reaction (IgE). It is estimated that clozapine induced myocarditis occurs in 1.1-5% of cases.<sup>6</sup> Signs and symptoms of myocarditis may include: unexplained fatigue, dyspnea, tachypnea, fever, chest pain, and palpitations, other signs/symptoms of heart failure, tachycardia, ST-T wave abnormalities on EKG, elevated troponins and CRP. A published monitoring algorithm is available for early detection of clozapine induced myocarditis (*Figure 1*).<sup>7</sup> If myocarditis is highly suspected, clozapine treatment should be promptly discontinued.

2. Miller DD. Review and Management of Clozapine's side effects. J. Clin Psychiatry 2000; 61(suppl 8): 14-17

3. Grover S, Hazari N, Chakrabarti S, et al. Association of Clozapine with Seizures: A brief Report Involving 222 Patients Prescribed Clozapine. East Asian Arch Psychiatry. 2015; 25(2):73-8.

4. Williams A, Park SH. Seizure Associated with Clozapine: Incidence, Etiology, and Management. CNS Drugs. 2015;29(2):101-11.

5. Varma S, Bishara D, Besag FM, et al. Clozapine-related EEG changes and seizures:dose and plasma-level relationships. Ther Adv Psychopharmacol. 2011;1(2):47-66.

6. Ronaldson KJ, Fitzgerald PB, McNeil JJ. Clozapine-induced myocarditis, a widely overlooked adverse reaction. Acta Psychiatr Scand. 2015;132(4):231-40.

7. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. Aust N Z J Psychiatry. 2011;45(6):458-65.

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## Clozapine Monitoring

- B. Common side effects
1. **Sedation** – Sedation is secondary to clozapine’s anti-histamine effects and appears to positively correlate with higher serum levels. Targeting serum levels between 350-400ng/mL and consolidating to bedtime dosing may help improve daytime sedation.
  2. **Constipation and urinary incontinence** – Anticholinergic effects of clozapine may result in constipation and urinary incontinence while reduced bladder tone as a result of adrenergic antagonism also contributes to urinary incontinence. Eliminate unnecessary anticholinergic agents the medication regimen and/or add a stool softener such as docusate sodium and encourage reduced fluid intake near bedtime if bed wetting and clinically appropriate.
  3. **Marked hypotension** – Orthostatic hypotension with or without syncope can occur with clozapine treatment. Patients are more likely to experience this side effect in conjunction with dizziness during initiation and rapid dose escalation. Monitor blood pressure (supine and standing) during initiation and when clinically indicated.
  4. **Increased glucose, lipids, and/or weight** – Hyperglycemia, hyperlipidemia, and weight gain have been reported in patients treated with atypical antipsychotics including clozapine. Patients with established diagnoses of diabetes mellitus, hyperlipidemia, or obesity who are started on clozapine should be monitored regularly for worsening of glucose or lipid control, or for further weight gain. Patients prescribed clozapine should undergo fasting blood glucose and lipid testing, along with weight monitoring, at baseline and periodically during treatment (*see Alameda County BHCS Psychotropic Medication Practice Guidelines*).
  5. **Fever or other possible clozapine-induced side effects** – During clozapine therapy, patients may experience transient temperature elevations above 100.4° F, with the peak incidence within the first 3 weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis or myocarditis. In the presence of high fever, the possibility of Neuroleptic Malignant Syndrome must be considered.
  6. **Hypersalivation** – Clozapine induced hypersalivation affects approximately 30-80% of patients on clozapine and may resolve over time, but may also persist and worsen at night. Clozapine’s complex pharmacology: its agonistic activity on the M4 receptor as well as its antagonistic activity on the  $\alpha$ 2 receptor are often attributed for the paradoxical hypersalivation side effect. Consider glycopyrrolate, 1% atropine sulfate ophthalmic drops administered sublingually or ipratropium bromide HFA inhaler administered sublingually. Caution should be used with clonidine given the potential for additive orthostasis and for agents with increased risk of additive systemic anticholinergic effects such as glycopyrrolate and benztropine.<sup>8</sup>
  7. Consider using the Glasgow Antipsychotic Side-effects Scale-Clozapine (GASS-C) for patients to subjectively report and monitor clozapine side effect burden and severity (*Figure 2*).<sup>9</sup>

<sup>8</sup>Bird AM, Smith TL, Walton AE. Current treatment strategies for clozapine-induced sialorrhea. *Ann Pharmacother.* 2011;45(5):667-75.

<sup>9</sup>Hynes C, Keating D, McWilliams S, et al. Glasgow Antipsychotic Side effects Scale for Clozapine-Development and validation of a clozapine-specific side-effects scale. *Schizophr Res.* 2015;168(1-2):505-13.

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## **Clozapine Monitoring**

### **VII. Discontinuation of Clozapine:**

- A. Generally, clozapine may be tapered and discontinued for patients who have not experienced substantial benefit from it after a trial period of no longer than 24 weeks. At least 12 of those 24 weeks should be at a therapeutic dose.
- B. The pharmacy will be notified of a patient's discontinuation of clozapine.
- C. The case manager will be informed of the clozapine discontinuation and the need for subsequent blood tests in the event that the patient needs assistance.
- D. If discontinuation is unrelated to development of a neutropenia, continue existing ANC monitoring until the ANC is  $\geq 1500/\text{mm}^3$  for the general population and  $\geq 1000$  for BEN population.
- E. If discontinuation is due to a neutropenia, obtain ANC daily until  $\geq 1000/\text{mm}^3$  for the general population ( $500/\text{mm}^3$  for BEN population) and then thrice weekly until ANC  $\geq 1500/\text{mm}^3$  ( $\geq$  patient's baseline for BEN population).
- F. Once clozapine is no longer prescribed for the patient, change their treatment status to inactive in the clozapine REMS program.
- G. Monitor patient for symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea.



**Fax to: Office of the Medical Director  
at 510-567-6850**

## **Clozapine Notification Form**

- Currently on clozapine**
- Initiation of clozapine**

**Date:** \_\_\_\_\_

**Client's Name:** \_\_\_\_\_

**Insyst #:** \_\_\_\_\_ **Date of Birth:** \_\_\_\_\_

**Name of prescribing physician:** \_\_\_\_\_

**BHCS Program:** \_\_\_\_\_

# Alameda County Behavioral Health Care Services

## Clozapine Monitoring

Table 1 – Frequency of ANC Monitoring and Treatment Recommendations

### Recommended Monitoring Frequency and Clinical Decisions by ANC Level

ANC Level	Treatment Recommendation	ANC Monitoring
<b>Normal Range for a New Patient</b> <ul style="list-style-type: none"> <li>General Population (ANC <math>\geq</math> 1500/<math>\mu</math>L)</li> </ul>	<ul style="list-style-type: none"> <li>Initiate treatment</li> <li>If treatment interrupted:                             <ul style="list-style-type: none"> <li>&lt; 30 days, continue monitoring as before</li> <li><math>\geq</math> 30 days, monitor as if new patient</li> </ul> </li> <li>Discontinuation for reasons other than neutropenia</li> </ul>	<ul style="list-style-type: none"> <li>Weekly from initiation to 6 months</li> <li>Every 2 weeks from 6 to 12 months</li> <li>Monthly after 12 months</li> <li>See Section 2.4 of the full Prescribing Information</li> </ul>
<b>BEN POPULATION</b> <ul style="list-style-type: none"> <li>BEN Population (ANC <math>\geq</math> 1,000/<math>\mu</math>L)</li> <li>Obtain at least two baseline ANC levels before initiating treatment</li> </ul>	<ul style="list-style-type: none"> <li>Discontinuation for reasons other than neutropenia</li> </ul>	<ul style="list-style-type: none"> <li>See Section 2.4 of the full Prescribing Information</li> </ul>
<b>Mild Neutropenia (1000 to 1499/<math>\mu</math>L)*</b>	<b>GENERAL POPULATION</b> <ul style="list-style-type: none"> <li>Continue treatment</li> </ul>	<b>GENERAL POPULATION</b> <ul style="list-style-type: none"> <li>Three times weekly until ANC <math>\geq</math> 1500/<math>\mu</math>L</li> <li>Once ANC <math>\geq</math> 1500/<math>\mu</math>L, return to patient's last "Normal Range" ANC monitoring interval**</li> </ul>
	<b>BEN POPULATION</b> <ul style="list-style-type: none"> <li>Mild Neutropenia is normal range for BEN population, continue treatment</li> <li>Obtain at least two baseline ANC levels before initiating treatment</li> <li>If treatment interrupted                             <ul style="list-style-type: none"> <li>&lt; 30 days, continue monitoring as before</li> <li><math>\geq</math> 30 days, monitor as if new patient</li> </ul> </li> <li>Discontinuation for reasons other than neutropenia</li> </ul>	<b>BEN POPULATION</b> <ul style="list-style-type: none"> <li>Weekly from initiation to 6 months</li> <li>Every 2 weeks from 6 to 12 months</li> <li>Monthly after 12 months</li> <li>See Section 2.4 of the full Prescribing Information</li> </ul>
<b>Moderate Neutropenia (500 to 999/<math>\mu</math>L)*</b>	<b>GENERAL POPULATION</b> <ul style="list-style-type: none"> <li>Recommend hematology consultation</li> <li>Interrupt treatment for suspected clozapine induced neutropenia</li> <li>Resume treatment once ANC normalizes to <math>\geq</math> 1000/<math>\mu</math>L</li> </ul>	<b>GENERAL POPULATION</b> <ul style="list-style-type: none"> <li>Daily until ANC <math>\geq</math> 1000/<math>\mu</math>L, then</li> <li>Three times weekly until ANC <math>\geq</math> 1500/<math>\mu</math>L</li> <li>Once ANC <math>\geq</math> 1500/<math>\mu</math>L, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval**</li> </ul>
	<b>BEN POPULATION</b> <ul style="list-style-type: none"> <li>Recommend hematology consultation</li> <li>Continue treatment</li> </ul>	<b>BEN POPULATION</b> <ul style="list-style-type: none"> <li>Three times weekly until ANC <math>\geq</math> 1000/<math>\mu</math>L or <math>\geq</math> patient's known baseline.</li> <li>Once ANC <math>\geq</math> 1000/<math>\mu</math>L or patient's known baseline, then check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval**</li> </ul>
<b>Severe Neutropenia (less than 500/<math>\mu</math>L)*</b>	<b>GENERAL POPULATION</b> <ul style="list-style-type: none"> <li>Recommend hematology consultation</li> <li>Interrupt treatment for suspected clozapine induced neutropenia</li> <li>Do not rechallenge unless prescriber determines benefits outweigh risks</li> </ul>	<b>GENERAL POPULATION</b> <ul style="list-style-type: none"> <li>Daily until ANC <math>\geq</math> 1000/<math>\mu</math>L</li> <li>Three times weekly until ANC <math>\geq</math> 1500/<math>\mu</math>L</li> <li>If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC <math>\geq</math> 1500/<math>\mu</math>L</li> </ul>
	<b>BEN POPULATION</b> <ul style="list-style-type: none"> <li>Recommend hematology consultation</li> <li>Interrupt treatment for suspected clozapine induced neutropenia</li> <li>Do not rechallenge unless prescriber determines benefits outweigh risks</li> </ul>	<b>BEN POPULATION</b> <ul style="list-style-type: none"> <li>Daily until ANC <math>\geq</math> 500/<math>\mu</math>L</li> <li>Three times weekly until ANC <math>\geq</math> patients established baseline</li> <li>If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC <math>\geq</math> 1000/<math>\mu</math>L or at patient's baseline</li> </ul>

\* Confirm all initial reports of ANC less than 1500/ $\mu$ L (ANC < 1000/ $\mu$ L for BEN patients) with a repeat ANC measurement within 24 hours

\*\* If clinically appropriate

# Alameda County Behavioral Health Care Services

**Table 2 – Drug Interactions (see Section II.E.5.)**

Class	Examples	Interaction
Bone marrow suppressants	Carbamazepine, sulfonamides, propylthiouracil, zidovudine, chemotherapeutic agents	Additive risk of myelosuppression
Antihypertensive agents	Hydrochlorothiazide, atenolol, metoprolol, verapamil, diltiazem, lisinopril, enalapril, prazosin, terazosin, clonidine	Additive risk of orthostasis, hypotension
CNS depressants and active agents	Benzodiazepines, lithium, opioids, and other very sedating agents	Additive risks of sedation, respiratory depression, loss of consciousness
Highly protein bound drugs	Warfarin, divalproex Na, phenytoin, digoxin	Clozapine may displace or be displaced from protein binding sites by these agents. Monitor closely for adverse effects.
Substrates/inhibitors/inducers of CYP 1A2, 2D6, and 3A4	Erythromycin, ketoconazole, SSRIs can increase clozapine levels Cigarette smoking, carbamazepine may decrease clozapine levels	Potential for drug-drug interactions. Monitor for loss/reduction of drug efficacy or for increased toxicity.

**Figure 1: Monitoring for Clozapine Induced Myocarditis<sup>7</sup>**

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MONITORING FOR CLOZAPINE-INDUCED MYOCARDITIS

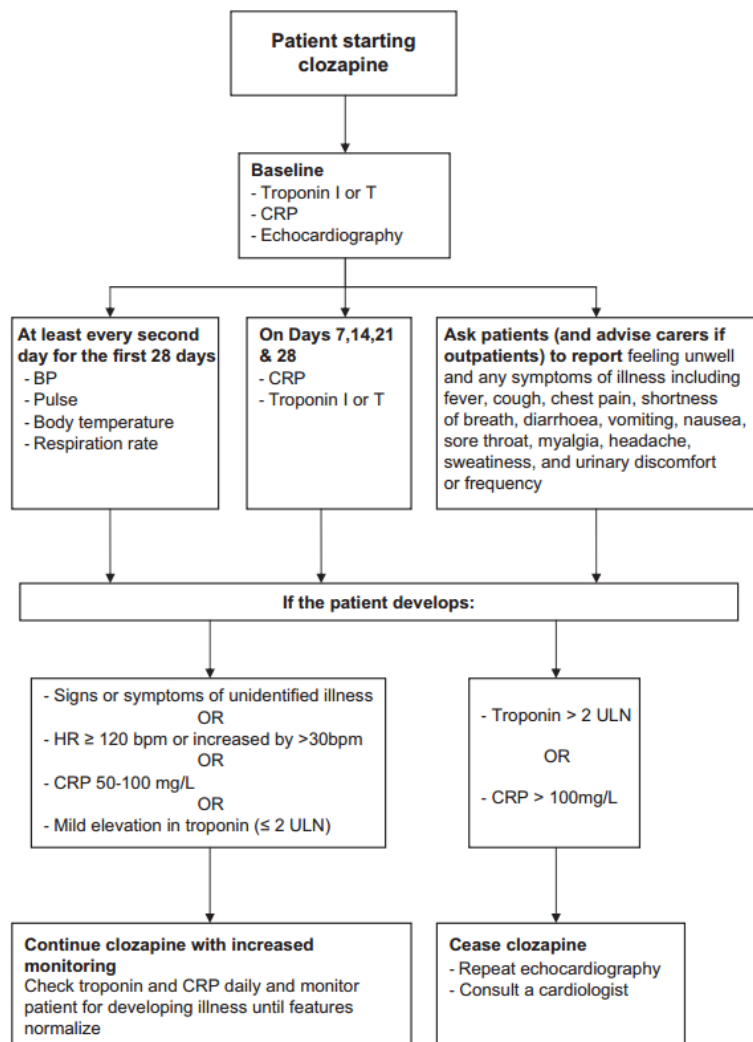


Figure 5. Proposed protocol for monitoring patients commenced on clozapine for clozapine-induced myocarditis. BP, blood pressure; bpm, beats per minute; CRP, C-reactive protein; HR, heart rate; ULN, upper limit of normal.

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**Figure 2: Glasgow Antipsychotic Side effects Scale for Clozapine (GASS-C)**

**GASS for Clozapine**

**Name:** \_\_\_\_\_ **Current Medications:** \_\_\_\_\_  
**Date:** \_\_\_\_\_ \_\_\_\_\_  
**Caffeine intake:** .....cups/day \_\_\_\_\_  
**Smoker: Y / N** .....cigarettes/day \_\_\_\_\_

**Has there been a recent change in your smoking habit?: Increase/Decrease by.....cigarettes/day**

This questionnaire is being used to determine if you are suffering from excessive side effects from your medication. Please put a tick in the column which best indicates how often or how severely you have experienced the following side effects.

Over the <b>past week</b> :	Never	Once	A few times	Everyday	Tick if severe or distressing
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					

I have also experienced:  
 (please write down any other side effects **OR PHYSICAL PROBLEMS OR COMPLAINTS** that you may have experienced over the **past week**)

17	
18	
19	
20	

**Staff Information**

1. Allow the service user to fill in the side-effects scale themselves. All questions relate to the previous week.

**2. Scoring**

0 Points	"Never"
1 point	"Once"
2 points	"A few times"
3 points	"Everyday"

**3. Results**

0-16	absent/mild side-effects
17-32	moderate side-effects
33-48	severe side-effects

**4. Side-effects covered include:**

1-2	Drowsiness and sedation
3	Postural hypotension
4	Tachycardia
5	Myoclonus
6	Hypersalivation
7-8	Anticholinergic side-effects
9-10	Gastrointestinal side-effects
11	Constipation
12	Nocturnal enuresis
13-14	Screening for diabetes mellitus
15	Weight gain
16	Sexual dysfunction

5. The column relating to the severity/distress experienced with a particular side effect is not scored, but is intended to inform the clinician of the service user's views and condition.

6. Questions 17 to 20 invite the service user to report any other side-effects or problems not already mentioned. These questions should not be scored but may instigate a discussion with the service user if clinically appropriate.

# Alameda County Behavioral Health Care Services

## CLOZAPINE REMS

The Single Shared System for Clozapine  
No Blood, No Drug™

## ANC Lab Reporting Form

Phone: 844-267-8678  
Fax: 844-404-8876  
www.clozapinerems.com

### Instructions for Prescribers

For immediate online Absolute Neutrophil Count (ANC) reporting please go to [www.clozapinerems.com](http://www.clozapinerems.com).  
Use this form to submit ANC monitoring information or update patient information.

**For INPATIENTS:** The prescriber and in-patient pharmacist must review the ANC before clozapine can be dispensed. Submit ANC to the Clozapine REMS Program within 7 days of the blood draw date.

**For OUTPATIENTS:** The out-patient pharmacist must obtain a pre-dispense authorization (PDA) from the Clozapine REMS Program before clozapine can be dispensed.

To obtain a PDA, a current and acceptable ANC must be reported to the Clozapine REMS Program or the prescriber must provide a treatment rationale (see Section 3) to authorize treatment if a patient's ANC indicates moderate to severe neutropenia (General Population) or severe neutropenia (Patients with BEN).

### Section 1: ANC Lab Reporting

#### Prescriber Information (All Fields Required)

Name:		NPI or DEA:	
Phone:	Email:	Fax:	
Submitter:	<input type="checkbox"/> Prescriber	<input type="checkbox"/> Prescriber Designee	<input type="checkbox"/> Pharmacy

#### Patient Information (All Fields Required)

Name		
Date of Birth (MM/DD/YYYY):	Zip Code:	Gender:

#### ANC Monitoring (All Fields Required)

Blood Draw Date (MM/DD/YYYY):	ANC (per $\mu$ L):
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### Section 2: Patient Updates (if applicable)

#### Change Treatment Status

Complete this section if you want to change this patient's treatment status. If this section is left blank, no changes will be made.

I want to change this patient's treatment status to: **(check one)**

- Active (restarting or continuing clozapine requires a treatment rationale for patients with moderate or severe neutropenia. Please refer to the "Treatment Rationale" section)
- Interrupted
- Discontinued

#### Change Monitoring Frequency

Complete this section if you want to change this patient's monitoring frequency. If this section is left blank, no changes will be made.

Based on the clozapine prescribing information, my patient is eligible for a change in ANC monitoring frequency. I want to change the ANC monitoring frequency to: **(check one)**

- Weekly
- Every 2 weeks
- Every 4 weeks

### Section 3: Prescriber Authorization

#### Treatment Rationale\*

Complete this section if the patient has moderate neutropenia (ANC 500-999/ $\mu$ L for the General Population) or severe neutropenia (ANC < 500/ $\mu$ L for General Population and Patients with BEN) and you want to continue treatment.

The treatment rationale is (check one and sign below):

- Benefits of continuing clozapine treatment outweigh risk of neutropenia
- Until next ANC Lab
- Until (MM/DD/YYYY) \_\_\_\_\_  
*No more than 6 months from today*
- Patient has Benign Ethnic Neutropenia (BEN) (No Expiration)

#### Hospice Care\*

For hospice patients (i.e., terminally ill patients with an estimated life expectancy of six months or less), the prescriber may reduce the ANC monitoring frequency to once every 6 months, after a discussion with the patient and his/her caregiver.

If you want to change the monitoring frequency to once every 6 months for a hospice patient, **check the box and sign below:**

- This is a hospice patient.

#### Authorizing Prescriber Information (All Fields Required)

Name:		NPI or DEA:	
Authorizing Prescriber Signature:		Date (MM/DD/YYYY):	

\*Authorizing Prescriber Signature is required for a change in treatment rationale, and/or for a hospice care patient.

# Alameda County Behavioral Health Care Services

**CLOZAPINE REMS**  
The Single Shared System for Clozapine  
No Blood, No Drug™

## Prescriber Enrollment Form

Phone: 844-267-8678  
Fax: 844-404-8876  
www.clozapinerems.com

### Instructions

For immediate certification, please go to [www.clozapinerems.com](http://www.clozapinerems.com).

To submit this form via fax, please complete all required fields below and fax to 844-404-8876. You will receive a confirmation via the contact preference you list below.

Clozapine is only available through the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. In order to become certified and prescribe clozapine, you must:

1. Review *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*
  2. Successfully complete the *Knowledge Assessment for Healthcare Providers*
  3. Complete and submit this one-time *Prescriber Enrollment Form* along with the completed *Knowledge Assessment for Healthcare Providers*
- If you have any questions, require additional information, or need further copies of Clozapine REMS Program documents, please visit the program website at [www.clozapinerems.com](http://www.clozapinerems.com), or call the Clozapine REMS Program at 844-267-8678.

### Prescriber Responsibilities

By signing this form, I attest that:

1. I understand that clozapine is only available through the Clozapine REMS Program and that I must comply with the program requirements to prescribe clozapine
2. I have reviewed *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, reviewed the clozapine Prescribing Information, and successfully completed the *Knowledge Assessment for Healthcare Providers*
3. I understand the risk of severe neutropenia associated with clozapine
4. Prior to initiating treatment, I agree to provide *What You Need To Know About Clozapine: A Guide for Patients and Caregivers* to each patient and/or his/her caregiver. I will review it with him/her to inform them about the risks associated with clozapine, including severe neutropenia and the Clozapine REMS Program requirements – unless I determine that the patient's adherence to the treatment regimen will be negatively impacted by providing *What You Need To Know About Clozapine: A Guide for Patients and Caregivers*
5. I will enroll all patients I treat with a clozapine product in the Clozapine REMS Program
6. I understand the ANC testing and monitoring requirements as described in the clozapine Prescribing Information
7. I understand there is a different ANC monitoring algorithm for patients with Benign Ethnic Neutropenia (BEN)
8. I will order ANC testing for each patient according to the clozapine Prescribing Information
9. I will report the ANC for each patient to the Clozapine REMS Program and I understand the ANC must be provided before clozapine can be dispensed
10. I understand that, as described in *Clozapine and the Risk of Neutropenia: A Guide for Healthcare Providers*, I must authorize the continuation of clozapine treatment if the patient has moderate or severe neutropenia before clozapine can be dispensed
11. I agree that personnel from the Clozapine REMS Program may contact me to gather information or resolve discrepancies or to provide other information related to the Clozapine REMS Program
12. I understand that clozapine manufacturers or their agents and contractors may contact me via phone, mail, or email to survey me on the effectiveness of the program requirements for the Clozapine REMS Program
13. I will not share my credentials for the Clozapine REMS Program website or allow others to sign into the website using my credentials

### Prescriber Information (All Fields Required Unless Otherwise Indicated)

First Name:	MI (opt):	Last Name:
NPI:	DEA:	
Email:	Credentials (MD, DO, NP, PA):	
Clinic / Practice Name:		
Address:		
City:	State:	Zip Code:
Phone:	Ext (opt):	Fax:
Contact Preference (please select one):	<input type="checkbox"/> Email	<input type="checkbox"/> Fax
Prescriber's Signature:		Date (MM/DD/YYYY):

# Alameda County Behavioral Health Care Services

## CLOZAPINE REMS

The Single Shared System for Clozapine  
No Blood, No Drug™

## Patient Enrollment Form

Phone: 844-267-8678

Fax: 844-404-8876

[www.clozapinerems.com](http://www.clozapinerems.com)

### Instructions for Prescribers

For immediate enrollment, please go to [www.clozapinerems.com](http://www.clozapinerems.com).

For enrollment via fax, please complete all required fields below and fax to 844-404-8876. For enrollment via the contact center, please call 844-267-8678. Enrollment confirmation will be sent via the contact preference specified on the prescriber's *Clozapine REMS Prescriber Enrollment Form*.

#### Complete this form for a patient if:

- This patient has never been treated with clozapine previously, OR
- If you have never treated this patient with clozapine (regardless of the patient's history of clozapine treatment)

Clozapine is only available through the shared Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program. In order to treat a patient with clozapine, the patient **MUST** be enrolled in the shared Clozapine REMS Program. To enroll a patient you must:

1. Provide the patient or caregiver with *What You Need To Know About Clozapine: A Guide for Patients and Caregivers*
2. Inform the patient or caregiver about the risk of severe neutropenia with clozapine and the Clozapine REMS Program requirements unless you determine that the patient's adherence to the treatment regimen will be negatively impacted by providing the *What You Need To Know About Clozapine: A Guide for Patients and Caregivers* and informing them about this risk.
3. Complete and submit this *Clozapine REMS Patient Enrollment Form*

If you have any questions, require additional information, or need further copies of Clozapine REMS Program documents, please visit the program website at [www.clozapinerems.com](http://www.clozapinerems.com), or call the Clozapine REMS Program at 844-267-8678.

### PATIENT INFORMATION (All fields required for Enrollment)

First Name:	Last Name:
Gender: <input type="checkbox"/> Male <input type="checkbox"/> Female	
Race: <input type="checkbox"/> Caucasian <input type="checkbox"/> African American <input type="checkbox"/> Asian <input type="checkbox"/> Hispanic <input type="checkbox"/> Other:	
Date of Birth (MM/DD/YYYY):	Zip Code:
Is this patient actively on clozapine therapy? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	

### LAB INFORMATION (ANC must be provided before clozapine is dispensed, but is not required for patient enrollment)

Blood Draw Date (MM/DD/YYYY):	ANC (per $\mu$ L):
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### PRESCRIBER INFORMATION (All Fields Required)

Name:		
NPI or DEA:		
Phone:	Email:	Fax:
Submitter: <input type="checkbox"/> Prescriber <input type="checkbox"/> Prescriber Designee		

### BENIGN ETHNIC NEUTROPENIA (BEN) PATIENT ATTESTATION\* (Signature required only for attestation of BEN diagnosis)

By signing below, I attest that the above patient has Benign Ethnic Neutropenia (BEN).

Prescriber Signature:	Date (MM/DD/YYYY):
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\*Enrollment for patients with BEN must be completed by faxing this signed document to 844-404-8876 or by accessing the Clozapine REMS Program website at [www.clozapinerems.com](http://www.clozapinerems.com).