

CLOZAPINE PATIENT MANAGEMENT

1. REASON FOR ISSUE: This Veterans Health Administration (VHA) directive provides policy for the safe and effective use of the atypical antipsychotic drug clozapine consistent with requirements by the Food and Drug Administration (FDA).

2. SUMMARY OF MAJOR CHANGES: Major changes include:

a. Updated definition of a clozapine prescriber to include Advanced Practice Nurses, Physician Assistants, Clinical Pharmacist Practitioners (CPP), and physicians with expertise in managing and prescribing clozapine and registered with the FDA Clozapine Risk Evaluation and Mitigation Strategy (REMS).

b. Updated description of Clozapine Treatment Manager (CTM) to include a psychiatrist or CPP. **NOTE:** *This may be a shared role when appropriate.*

c. Defined responsibilities for Pharmacy Benefits Management (PBM) service to provide oversight of the National Clozapine Coordinating Center (NCCC). NCCC develops and deploys processes to ensure the safe and effective use of clozapine.

d. Updated responsibilities of the NCCC to identify VA medical facilities, pharmacies and clozapine prescribers not in compliance with Clozapine REMS requirements and advise on corrective action plans as required.

e. Defined responsibilities of VISN Network Directors and VA medical facility Directors to ensure their respective VA medical facilities and clozapine prescribers comply with Clozapine REMS requirements for prescribers and patients as outlined in this directive.

f. Removed appendices and defined all VA medical facility, pharmacy and clozapine prescriber requirements to be outlined in procedures and guidance documents located at:

https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/NCCC/SitePages/NCCC.aspx. **NOTE:** *This is an internal VA website that is not available to the public.*

g. Updated training and registration requirements for clozapine prescribers consistent with Clozapine REMS changes.

3. RELATED ISSUES: VHA Handbook 1160.01, Uniform Mental Health Services in VA Medical Centers and Clinics, dated September 11, 2008; VHA Directive 1108.08, VHA Formulary Management Process, November 2, 2016.

4. RESPONSIBLE OFFICE: The Pharmacy Benefits Management Services (12PBM) in the Office of the Assistant Under Secretary for Health for Patient Care Services (12) is

responsible for the content of this directive. Questions may be addressed to the Chief Consultant, Pharmacy Benefits Management at 202-461-7326.

5. RESCISSIONS: VHA Handbook 1160.02, Clozapine Patient Management Protocol (CPMP), dated December 23, 2008, is rescinded. The following VA Forms are rescinded: 10-0363; 10-0363A; 10-0363B; 10-0363C; 10-0363D; 10-0363E; 10-0363F.

6. RECERTIFICATION: This VHA directive is scheduled for recertification on or before the last working day of May 2027. This VHA directive will continue to serve as national VHA policy until it is recertified or rescinded.

**BY DIRECTION OF THE OFFICE OF THE
UNDER SECRETARY FOR HEALTH:**

/s/ Beth Taylor, DHA, RN, FAAN, NEA-BC
Assistant Under Secretary for Health
for Patient Care Services/CNO

DISTRIBUTION: Emailed to the VHA Publications Distribution List on May 17, 2022.

NOTE: *All references herein to VA and VHA documents incorporate by reference subsequent VA and VHA documents on the same or similar subject matter.*

TABLE OF CONTENTS
CLOZAPINE PATIENT MANAGEMENT

1. PURPOSE 1

2. BACKGROUND 1

3. DEFINITIONS 2

4. POLICY 2

5. RESPONSIBILITIES 2

6. TRAINING 8

7. RECORDS MANAGEMENT 8

8. REFERENCES 8

CLOZAPINE PATIENT MANAGEMENT

1. PURPOSE

This Veterans Health Administration (VHA) directive establishes policy concerning the safe and effective use of clozapine consistent with requirements by the Food and Drug Administration (FDA). Clozapine must be an available treatment option to any Veteran who may benefit. **AUTHORITY:** 21 U.S.C. § 355-1; 38 U.S.C. § 7301(b).

2. BACKGROUND

a. The United States Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) specifies guidelines and procedures that minimize the risk of clozapine-related adverse effects, in particular serious reduction in the number of neutrophils (i.e., neutropenia). The FDA maintains a registry system, Clozapine REMS, that tracks pharmacies, prescribers, patients, prescriptions, and blood test results on a national basis.

b. The Clozapine REMS is mandated by FDA and operated by the Clozapine Product Manufacturers' Group (CPMG) to ensure compliance with the FDA REMS for clozapine. Clozapine REMS requires adherence to Elements to Assure Safe Use (ETASU) including registration of pharmacies, prescribers and patients to control the prescribing and dispensing of this medication. The Clozapine REMS regulations and procedures apply to all clozapine patients, providers and pharmacies, including those in VHA. The Department of Veterans Affairs (VA) Central Office Pharmacy Benefits Management (PBM) service provides oversight of the National Clozapine Coordinating Center (NCCC), working collaboratively with the Office of Mental Health and Suicide Prevention (OMHSP), to provide guidance and policy for the VA medical facilities, pharmacies and clozapine prescribers to ensure the safe and effective use of clozapine within VHA. PBM ensures compliance with Clozapine REMS and advises the FDA Clozapine REMS administrators, while reducing burdens of compliance for VA staff.

c. The Clozapine Management System was developed to modernize "VA National Data System, System of Records (SOR) 121VA10A7, National Patient Databases-VA, VA National Clozapine Coordinating Center (NCCC) Registry" and the related software that supports the safe and effective use of clozapine in VHA. It monitors use of clozapine by providing automated prescribing and dispensing safety checks through interfaces with the electronic medical record and pharmacy systems. It serves as a database with VA information on pharmacies, prescribers, patients, prescriptions, dispensing, laboratory test results, and includes functionality for report generation. Within the current VA electronic health record (EHR) (i.e., VistA), the NCCC registry requires all clozapine prescribers to possess an individual Drug Enforcement Administration (DEA) registration to prescribe the medication. **NOTE:** *Clozapine is not a controlled substance medication. Prescribers must be certified to prescribe clozapine by enrolling in the Clozapine REMS program but prescribing does not require a DEA registration. Software changes to the VistA EHR would be required to allow prescribing of clozapine by all clozapine prescribers outlined in this directive. VA medical facilities*

utilizing the Cerner EHR do not require an individual clozapine prescriber to possess a DEA registration to prescribe clozapine, consistent with the Clozapine REMS program. Therefore, Cerner EHR expands prescribing ability to all clozapine prescribers. Many Clinical Pharmacist Practitioners (CPP) may not possess a DEA registration, therefore limiting their ability to serve as VA clozapine prescribers in facilities using the VistA EHR; however, they may provide care coordination services in those facilities, including monitoring patients prescribed clozapine as an added resource to the healthcare team.

3. DEFINITIONS

a. **Clozapine.** Clozapine (CLZ) is a second-generation antipsychotic medication whose use is regulated by FDA REMS.

b. **Clozapine Prescriber.** A clozapine prescriber is a practitioner authorized to prescribe medications in accordance with their facility approved privileges or scope of practice and have experience and expertise in the management of mental health and clozapine monitoring. This may include physicians (e.g., psychiatrists, applicable neurologists, psychiatry medical residents), physician assistants (PA), advance practice nurses (Nurse Practitioners and Clinical Nurse Specialists), and CPPs. **NOTE:** *Software changes to the EHR (i.e., VistA) are required to allow prescribing of clozapine by all clozapine prescribers. However, VA facilities utilizing the Cerner EHR do not require an individual clozapine prescriber to possess a DEA registration to prescribe clozapine, consistent with the Clozapine REMS program, and therefore would allow prescribing by all clozapine prescribers described in this definition.*

c. **Absolute Neutrophil Count.** Absolute neutrophil count (ANC) is a measure of the number of neutrophil granulocytes present in the blood. **NOTE:** *Use of clozapine may result in a reduction of ANC and the body's ability to resist infections. ANCs must be measured and evaluated before clozapine can be prescribed. Test results must be reported to the Clozapine Products Manufacturers' Group (CPMG) as part of REMS protocols. As a check on the validity of ANCs, VHA requires submission of white blood cell (WBC) counts together with ANCs (i.e., ANC with matching WBC count) and the date and time of each blood test.*

4. POLICY

It is VHA policy that the safe and effective use of clozapine is in compliance with the requirements by the Food and Drug Administration (FDA) and the mandatory use of the FDA registry system, Clozapine REMS, clozapine access is ensured across the continuum, and that clozapine is made available when clinically indicated to any eligible Veteran who may benefit at all VA medical facilities, including Community-Based Outpatient Clinics, and other related sites.

5. RESPONSIBILITIES

a. **Under Secretary for Health.** The Under Secretary for Health is responsible for ensuring overall compliance with this directive.

b. **Assistant Under Secretary for Health for Patient Care Services.** The Assistant Under Secretary for Health for Patient Care Services is responsible for supporting the PBM program office with implementation and oversight of this directive.

c. **Assistant Under Secretary for Health for Operations.** The Assistant Under Secretary for Health for Operations is responsible for:

(1) Communicating the contents of this directive to each of the Veterans Integrated Services Networks (VISN).

(2) Assisting VISN Directors in resolving implementation and compliance challenges in all VA medical facilities within that VISN.

(3) Providing oversight of VISNs to ensure compliance with this directive and its effectiveness.

d. **VHA Chief Consultant, Pharmacy Benefits Management Services.** The VHA Chief Consultant, PBM Services is responsible for:

(1) Serving as an advisor to the Under Secretary for Health, Assistant Under Secretary for Health for Patient Care Services, program offices, other governmental agencies and VA medical facilities on issues related to clozapine prescribing.

(2) Developing VHA policies and procedures to ensure the safe and effective use of clozapine in compliance with FDA Clozapine REMS requirements.

(3) Communicating with Clozapine Product Manufacturers Group (CPMG), and the FDA Clozapine REMS administrator regarding clozapine-related issues.

(4) Providing oversight of the NCCC. This includes audit and oversight of clozapine prescribers and prescribing.

(5) Advising VA medical facilities, pharmacies and clozapine prescribers on areas of compliance and corrective action required consistent with Clozapine REMS, this directive and applicable processes and guidance available at:

https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/NCCC/SitePages/NCCC.aspx. **NOTE:** *This is an internal VA website that is not available to the public.*

(6) Registering all VA pharmacies with Clozapine REMS and maintaining documents supplied by individual pharmacies as required by Clozapine REMS.

(7) Serving as the intermediary between VA pharmacies and the FDA Clozapine REMS administrator.

(8) Collaborating with VHA central office program offices to include the Office of Mental Health and Suicide Prevention (OMHSP), Pathology and Laboratory Medicine Services (P&LMS), and the Office of Information and Technology (OI&T) to support clozapine prescribing across VA medical facilities.

(9) Conducting quality improvement studies to optimize the safe and effective use of clozapine in VHA and communicate practice changes to VISN's and medical centers.

(10) Partnering with the Office of Research and Development (OR&D) to develop new knowledge about the treatment of serious mental illnesses.

e. **Executive Director, Office of Information and Technology.** The Executive Director, OI&T is responsible for:

(1) Maintaining the Clozapine Management System and updating this system at regular intervals when requirements change.

(2) Collaborating with PBM when changes are needed to the Clozapine Management System or relevant reports.

(3) Ensuring reports are generated and reported at agreed upon intervals between VA and the Clozapine REMS.

f. **Executive Director, Office of Mental Health and Suicide Prevention.** The Executive Director, OMHSP is responsible for collaborating with PBM on clozapine patient management and providing subject matter expertise on the prescribing of clozapine.

g. **National Clozapine Coordinating Center Team.** *NOTE: The NCCC is a program under the direction and oversight of PBM service and provides VA oversight of Clozapine REMS.* The NCCC is responsible for:

(1) Serving as the authorized VA representative for Clozapine REMS certification of VA pharmacies.

(2) Identifying VA medical facilities, pharmacies and clozapine prescribers not in compliance with Clozapine REMS and advising on corrective action plans as required. All applicable processes and guidance are available at:

https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/NCCC/SitePages/NCCC.aspx. *NOTE: This is an internal VA website that is not available to the public.*

(3) Ensuring data on clozapine prescribers, patients, and prescriptions are entered into and maintained within the Clozapine Management System.

(4) Providing training and technical assistance to VHA staff involved with the prescribing and dispensing of clozapine.

h. **Veterans Integrated Service Network Director.** The VISN Director is responsible for:

(1) Ensuring all VA medical facilities within the VISN comply with this directive and to inform PBM and NCCC when barriers to compliance are identified.

(2) Ensuring VA medical facilities and clozapine prescribers within the VISN take corrective action when areas of noncompliance are identified.

i. **VA Medical Facility Director.** The VA medical facility Director is responsible for:

(1) Ensuring the VA medical facility and clozapine prescribers comply with Clozapine REMS requirements for prescribers and patients as outlined in this directive and applicable processes and guidance available at: https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/NCCC/SitePages/NCCC.aspx. **NOTE:** *This is an internal VA website that is not available to the public.*

(2) Developing and timely completion of corrective action plans when areas of noncompliance are identified including timely response to NCCC and the VISN Director.

j. **VA Medical Facility Chief of Staff and VA Medical Facility Associate Director for Patient Care Services (ADPCS).** The VA medical facility Chief of Staff and ADPCS are responsible for:

(1) Ensuring VA medical facility procedures comply with this directive and Clozapine REMS.

(2) Ensuring that the requirements of this directive are communicated to all VA medical facility clozapine prescribers and mental health staff.

(3) Ensuring psychiatrists and other trained mental health practitioners serve as clozapine prescribers.

(4) Ensuring clozapine prescribers follow VA National Formulary requirements and evidence-based guidance outlined in VHA Directive 1108.08(1), Formulary Management Process, dated November 2, 2016. This includes ensuring:

(a) Clozapine is an available treatment option to any Veteran who may benefit.

(b) Transitioning Service members who transfer their care to VA are appropriately assessed by the clozapine prescriber and clozapine is continued when clinically appropriate in accordance with VHA Directive 1108.15, Continuation of Mental Health Medications Initiated by Department of Defense Authorized Providers, dated August 2, 2019.

k. **VA Medical Facility Chief of Mental Health.** The VA Medical Facility Chief of Mental Health is responsible for:

(1) Serving as an advisor to the VA medical facility Chief of Staff and ADPCS regarding clozapine prescribing and providing oversight of mental health staff regarding local procedures to ensure that clozapine prescribing complies with this directive and Clozapine REMS.

(2) Designating a psychiatrist or clinical pharmacist practitioner (CPP) to serve as the Clozapine Treatment Manager (CTM). **NOTE:** *This may be a shared role when appropriate.*

l. **VA Medical Facility Clozapine Treatment Manager.** The VA Medical Facility Clozapine Treatment Manager (CTM) is responsible for:

NOTE: *The Clozapine Treatment Manager (CTM) is a clozapine prescriber and the designated VA medical facility lead responsible for authorizing clozapine prescribers within their respective facility.*

(1) Serving as the facility lead responsible for ensuring education and training requirements have been completed prior to authorizing the practitioner as a clozapine prescriber.

(2) Providing oversight and issuance of standard permission key software keys to clozapine prescribers.

(3) Providing technical assistance to clozapine prescribers related to the safe and effective use of clozapine.

(4) Collaborating with the VA medical facility Director and Pharmacy Clozapine Manager in developing and deploying corrective action plans when required or when noncompliance is identified. This includes timely communication with NCCC and PBM as appropriate.

m. **VA Medical Facility Chief of Pharmacy.** The VA Medical Facility, Chief of Pharmacy is responsible for:

(1) Ensuring that the dispensing of clozapine is monitored and in compliance with this directive, VHA Directive 1108.08(1), VHA Formulary Management Process, Clozapine REMS requirements, and applicable processes and guidance available at: - https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/NCCC/SitePages/NCCC.aspx. **NOTE:** *This is an internal VA website that is not available to the public.*

(2) Ensuring the VA pharmacy is approved and enrolled for REMS certification nationally by the PBM. Within VA, authorization by NCCC is required to dispense clozapine from a VA pharmacy. **NOTE:** *Direct patient application or registration with Clozapine REMS will not enable delivery of clozapine at VA medical facilities.*

(3) Designating the facility Pharmacy Clozapine Manager (PCM). This must be a clinical pharmacist who possesses appropriate training and experience in the Clozapine Management System and ensuring that the PCM has appropriate permissions and software keys in the EHR.

(4) Ensuring CPPs who serve as clozapine prescribers comply with all requirements outlined in this directive.

(5) Identifying additional pharmacist coverage with appropriate permissions and software keys to support the PCM to ensure continuity of care in special clinical and emergency situations.

n. **VA Medical Facility, Pharmacy Clozapine Manager.** The VA medical facility PCM is a clinical pharmacist responsible for:

(1) Maintaining and distributing appropriate permissions and software keys to ensure timely and appropriate clozapine dispensing is not interrupted.

(2) Collaborating with the VA medical facility Director and CTM to develop and deploy corrective action plans when required or noncompliance is identified. This includes timely communication with NCCC and PBM as appropriate.

o. **Clozapine Prescriber.** The Clozapine prescriber is responsible for:

NOTE: Clozapine prescribers should possess formal training or equivalent experience and knowledge in assessment of patients with mental health conditions; understanding the established indications and risks for clozapine; awareness of alternative evidence-based treatments including pharmacological and psychosocial strategies; monitoring for and treating adverse effects of clozapine; and evaluating clozapine treatment outcomes.

(1) Certifying with Clozapine REMS and the NCCC. For detailed information on the Clozapine REMS Program and registration, see https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/NCCC/SitePages/NCCC.aspx. Obtaining, maintaining, and reporting to NCCC all valid qualifications to prescribe clozapine including certification with the FDA Clozapine REMS administrator. ***NOTE: This is an internal VA website that is not available to the public.***

(2) Informing patients, families and caregivers, when appropriate, about the risks and benefits of clozapine and the procedures required to prescribe clozapine treatment.

(3) Prior to starting clozapine treatment, providing each patient, family or caregiver as appropriate with Clozapine REMS required educational materials including *A Guide for Patients and Caregivers: What You Need to Know about Clozapine and Neutropenia* https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/NCCC/SitePages/NCCC.aspx ***NOTE: This is an internal VA website that is not available to the public.***

(4) Prescribing clozapine in accordance with this directive, applicable processes and guidance available at: https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/NCCC/SitePages/NCCC.aspx. ***NOTE: This is an internal VA website that is not available to the public.***

(5) Evaluating patients to establish or confirm mental health diagnoses as authorized by their individual clinical privileges or scope of practice, planning treatment, performing necessary assessments, and monitoring for both therapeutic benefits and adverse

effects including, but not limited to, clozapine-induced neutropenia. Prescribers are responsible for responding appropriately to out of range ANC markers.

(6) Ensuring all required documentation is complete, accurate and submitted in a timely manner.

(7) Enrolling prescriber designee(s) to act on their behalf as appropriate and in accordance with the FDA Clozapine REMS to ensure timely and continuous patient care.

6. TRAINING

There are no mandatory VHA training requirements associated with this directive.

NOTE: FDA required training is separate. All clozapine prescribers must complete all required training and registration requirements by Clozapine REMS outlined at: https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/NCCC/SitePages/NCCC.aspx. This is a VA website that is not available to the public.

7. RECORDS MANAGEMENT

All records regardless of format (e.g., paper, electronic, electronic systems) created by this directive shall be managed as required by the National Archives and Records Administration (NARA) approved records schedules found in VHA Records Control Schedule (RCS) 10-1. Questions regarding any aspect of records management should be addressed to the appropriate Records Officer.

8. REFERENCES

- a. 21 U.S.C. § 355-1.
- b. 38 U.S.C. § 7301(b).
- c. VHA Handbook 1160.01, Uniform Mental Health Services in VA Medical Centers and Clinics, dated September 11, 2008.
- d. VHA Directive 1108.08(1), VHA Formulary Management Process, dated November 2, 2016.
- e. VHA Handbook 1108.11(1), Clinical Pharmacy Service, dated July 1, 2015.
- f. VHA Directive 1108.15, Continuation of Mental Health Medications Initiated by Department of Defense Authorized Providers, dated August 2, 2019.
- g. VHA National Clozapine Coordination Center Documents:
https://dvagov.sharepoint.com/sites/VHAPBM/VA_MedSAFE/NCCC/SitePages/NCCC.aspx. **NOTE:** This is an internal VA website that is not available to the public.

h. Clozapine Risk Evaluation and Mitigation Strategy:
<https://www.newclozapinerems.com/home>. **NOTE:** *This website is outside VA control and may not conform to Section 508 of the Rehabilitation Act of 1973.*