

July 29, 1999

CLOZAPINE PATIENT MANAGEMENT PROTOCOL (CPMP)

1. PURPOSE: This Veterans Health Administration (VHA) Directive provides updated guidance on the use of clozapine within the VHA, specifically addressing:

- a. Revisions in the Federal Drug Administration (FDA) monitoring requirements for the use of clozapine, including the provision for bi-weekly blood monitoring in selected patients.
- b. Additional FDA information on risk factors.
- c. Some modifications regarding drug procurement and distribution.
- d. The retention of previous modifications facilitating the use of clozapine in facilities and Veterans Integrated Service Networks (VISNs).

2. POLICY: The use of clozapine by VHA patients is in accordance with the attached Clozapine Patient Management Protocol.

***NOTE:** Additional Veterans Health Information Systems Technology Architecture (VistA) computer patches will be distributed to automate the bi-weekly white blood cell monitoring activity and facilitate monitoring activities of the field and VHA's National Clozapine Coordinating Center (NCCC).*

3. ACTION: All VHA facilities prescribing clozapine will implement the use and monitoring of clozapine in accordance with the following instructions until the new VistA patches are in place. After the new computer patches are in place, the use and monitoring of clozapine will be in accordance with the instructions in Attachment A.

a. The Department of Veterans Affairs (VA) National Clozapine Coordinating Center (NCCC) will prepare a list of active clozapine patients whose records in the VA database meet the FDA criteria for white blood count (WBC) testing every-other-week. In order to qualify, a clozapine patient must have a WBC sample drawn and tested once each week for at least 6 months. All of these samples must produce "acceptable" results (WBC count > 3000 per cubic millimeter (mm³) and absolute neutrophil count (ANC) > 1500/mm³). Qualification will be made electronically, based on data available at the NCCC, and separate lists will be prepared for each active clozapine site.

b. The lists of patients approved by the NCCC for WBC monitoring every-other-week will be forwarded to each individual clozapine facility via facsimile. It is the responsibility of the facility Clozapine Treatment Team (CTT) to ensure that prescribing clinicians and pharmacy staff receive the list of approved patients. ***NOTE:** If a clozapine facility does not receive the list, contact the NCCC at 214-857-0068 or fax FTS 214-857-0339.*

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c. Site clozapine prescribers are to review each patient listed on the NCCC qualification list to decide which patients are appropriate candidates. It is important to verify accuracy of qualification:

(1) Because of chronic problems with computer and/or facsimile data transmissions, the NCCC list will be prepared on data at least three weeks old. If the qualified patient has experienced an abnormal blood event (WBC < 3000 per mm³ and/or ANC < 1500 per mm³) since the date of the qualification list, contact the NCCC before starting WBC testing every-other-week.

(2) If the site feels a patient is qualified, but not listed as accepted by the NCCC, please contact the NCCC for review. Do not accept any clozapine patient for every-other-week WBC monitor without specific approval of NCCC.

d. Clozapine patients listed may begin the WBC testing and clozapine prescriptions may begin on an “every-other-week basis.”

(1) Do Not, Under Any Circumstances, Permit a Prescription for Clozapine to be Based on a White Blood Cell Count More than 6 Days Old. Overrides of the current Pharmacy computer safety interlocks for this purpose are not acceptable. The Chief of Psychiatry or the designated Chief of the Clozapine Treatment Team may authorize an override only when administrative problems prevent an acceptable WBC count (< 6 days old) from being entered into the laboratory computer. Each override must be fully documented by the pharmacist coding the override. Full justification must be provided to the NCCC at any time. The FDA and Novartis Pharmaceuticals are also following such information.

(2) Patients who are approved for bi-weekly blood monitoring shall have this approval noted in the VistA Pharmacy Outpatient Narrative Statement field (e.g., by noting a letter “B” in this field). It is the responsibility of the Chief of Pharmacy Service to see that this notation is accomplished and updated as necessary.

(3) The required weekly or bi-weekly data (SSN, Initials, WBC test date, WBC test result, prescription date, daily dose, and physician’s DEA) should be transmitted to the NCCC via facsimile with clear indications noting which patients have started the every-other-week clozapine schedule

e. Using macro-driven programs, the NCCC reviews incoming electronic data and a weekly report is prepared noting how much time has passed since the last WBC count report for each active clozapine patient. This report will be used to follow the WBC reports for every-other-week clozapine users.

f. A new listing of clozapine patients qualified for every-other-week WBC monitor will be prepared on a monthly basis. Clozapine sites may feel free to request NCCC review and approval of individual patients to be included in the program at any time.

4. REFERENCES: See Attachment A

5. FOLLOW-UP RESPONSIBILITY: The Associate Chief Consultant for Psychiatry, Mental Health Strategic Healthcare Group, VA Central Office (116), is responsible for the content of this Directive.

6. RECESSIONS: This Directive expires July 31, 2004.

S/ by M. L. Murphy for
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Acting Under Secretary for Health

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ATTACHMENT A

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CLOZAPINE PATIENT MANAGEMENT PROTOCOL (CPMP)

1. USING CLOZAPINE IN A VA FACILITY

a. **Intent.** The intent of the Clozapine Patient Management Protocol (CPMP) is to:

(1) Create a structure at each Department of Veterans Affairs (VA) facility to monitor the safe and effective use of clozapine.

(2) Ensure that VA physicians prescribing clozapine are properly trained as required by the Federal Drug Administration (FDA) and VA contract with the Clozaril National Registry.

(3) Establish a communication system between the National Clozapine Coordinating Center (NCCC) and individual VA facilities using clozapine.

b. **Organization.** A Clozapine Treatment Team (CTT) will be organized by the Chief of Psychiatry Service and will be headed by the Chief of Psychiatry Service, or designee.

(1) The CTT can represent a single facility, a Health Care System (HCS), or a Veterans Integrated Service Network (VISN). The FDA must be notified and the clozapine patient must be reauthorized to receive clozapine each time care is transferred between facilities. Therefore, combining single facility CTTs into multiple facility CTTs is highly advised when clozapine patients move back and forth between facilities that share services. The financial and administrative relationship of the HCS or VISN CTT to the single facility CTTs will be worked out in each network to facilitate the timely and efficient use of clozapine for that network's patients.

(2) A Chairman will represent each CTT. Team members should include active representatives from Psychiatry, Pharmacy, and Nursing Services and consulting members from Laboratory and Medical (hematologist preferred) Services. An initial meeting may help to plan for human and fiscal resources, educational activities, and the assignment of service responsibilities.

c. **Preparation and Team Registration.** Clozapine may not be prescribed for any patient until the following items have been completed:

(1) The CTT will develop an educational program (documented on VA Form 10-0363G) to establish minimum qualifications and knowledge requirements for prescribers of clozapine. The educational program should include:

(a) Pharmacology and clinical efficacy of clozapine.

(b) Adverse effects associated with clozapine.

(c) Risk management procedures described in this protocol.

(d) Guidelines for dosing and patient education.

(2) Each clozapine prescriber must:

(a) Be a psychiatrist or neurologist, Board Certified by the American Board of Psychiatry and Neurology or Board Eligible in Psychiatry. **NOTE:** *Non-psychiatric VA physicians may not prescribe clozapine.*

(b) Have expertise with clozapine that includes, at a minimum, successful completion of the clozapine educational program as outlined in subparagraph 1c(1).

(3) The CTT will register the facility with the NCCC by completing two forms: VA Form 10-0363G, and VA Form 10-0363H, Clozapine Treatment Team (CTT) Documentation Form. Any change in the information on these forms should be communicated to the NCCC.

(4) The CTT will arrange for Information Resource Management (IRM) staff at their facility to install the most current version of the Veterans Health Information System Technology Architecture (VistA) Outpatient Pharmacy Package, the Mental Health Package, and the Clozapine Patch. Installation is mandatory at all VA facilities.

(5) The CTT will coordinate with Laboratory Service at their facility to ensure that clozapine related data are appropriately entered into VistA.

(6) The NCCC will review registration paperwork and installation of software, then provide approval for the CTT to become active.

d. **Operation.** The CTT is a working team entrusted at each facility with the responsibility for ensuring the safe and appropriate use of clozapine within the requirements of VA and FDA. Such responsibilities will include:

(1) Reviewing the use of clozapine in individual patients to ensure that risk management procedures are being followed according to protocol. This includes:

(a) Careful review of the initial enrollment package to ensure the patient is properly qualified to receive clozapine within the VA guidelines.

(b) Meeting semi-annually to review the treatment regimen, patient response, and present status of each individual patient who has been treated with clozapine by the CTT since the last meeting. Such a meeting can be formal or informal, but the CTT must reach a consensus and document its results in the patient's medical record. The CTT also officially summarizes its responses to patient safety problems.

(2) Maintaining and using valid clozapine authorization numbers on written and computer transmissions. **NOTE:** *See Subparagraph 2.b. (2).*

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(3) Collecting and forwarding information and documents to the NCCC, including:

(a) The initial patient application

(b) Weekly clozapine data via facsimile to comply with FDA mandatory requirements. The reporting form is the option of the local CTT. **NOTE:** See Attachment B for a sample Summary Weekly Tracking Sheet. The report must include:

1. Clozapine Authorization Number.
2. Social Security Number (SSN).
3. Date of white blood cell (WBC) test.
4. WBC test result (including granulocyte count if WBC <5000 per cubic millimeter (mm³)).
5. Date prescription was dispensed.
6. Dose per day prescribed, based on the WBC test result.
7. Drug Enforcement Agency (DEA) number of the prescriber.
8. VA facility number.

(c) VA Form 10-0363F, Termination of Clozapine Treatment, whenever clozapine therapy has been stopped or interrupted for more than 4 days.

(d) Notification of the death, including cause and circumstances, of any VA registered clozapine patient. **NOTE:** The NCCC will perform the data reporting required by the FDA and the Clozaril National Registry, including termination notification.

2. APPLYING TO PRESCRIBE CLOZAPINE TO A VA PATIENT

a. **Intent.** The intent of an application to prescribe clozapine is to:

- (1) Guide the clinician in the choice to use clozapine.
- (2) Establish a monitoring structure within VA that adheres to the FDA requirements.
- (3) Institute safety procedures to protect the health and well-being of VA clozapine patients.

b. **Review, Evaluate, Assess Risk, and Consider Alternatives (Administrative Issues)**

- (1) **Patient Status.** The patient must be registered to receive services in the local facility.

(2) **Authorization Numbers.** The FDA requires all clozapine patients to be registered with the Clozaril National Registry. The NCCC arranges for this registration; however, certain rules apply. **NOTE:** *VA agreements with the Clozapine National Registry require a new authorization number when a clozapine patient changes to the jurisdiction of another Clozapine Treatment Team. Do not, under any circumstances, use the clozapine authorization number from another facility to dispense clozapine.*

(a) A new authorization number is needed when:

1. The patient is starting clozapine.
2. Clozapine is not started within 30 days after initial registration.
3. Clozapine treatment is administratively or medically interrupted for more than 30 days.
4. The patient is transferred to another VA facility (including short-term medical or vacation care).
5. The patient has temporarily left VA care and has received clozapine from another source.

(b) A new authorization number is not needed when:

1. Clozapine treatment is interrupted but reinitiated within 30 days of interruption.
2. The patient is assigned to another CTT psychiatrist within the same VA facility.

(c) Each time a new clozapine authorization number is needed, the CTT must prepare VA Form 10-0363A, Selection Criteria for Clozapine Treatment, including any changes in patient information.

(3) **Limitations of Use.** The FDA and VA recommend clozapine trials for patients with severe schizophrenia who are either treatment-resistant or treatment-intolerant. Although clozapine may be superior to traditional antipsychotics in selected situations, the potential side effects preclude use as first-line therapy in most patients.

(4) **Extended Use of Clozapine.** Some research studies support the use of clozapine for other purposes. With special documentation, clozapine may be used in VHA for unlabeled reasons, such as Schizoaffective Disorder, Bipolar Affective Disorder, the tremor and/or dementia of Parkinson's Disease, or the negative symptoms of schizophrenia. **NOTE:** *See VA Form 10-0363J, Special VA Application to Use Clozapine for Unlabeled Purposes.*

(5) **Patient Variables.** Clozapine should be avoided if weekly monitoring and ethical treatment could be jeopardized because of:

- (a) Geographic distance from the CTT,

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- (b) Social situation,
- (c) Substance abuse,
- (d) Noncompliance,
- (e) Lack of follow-up care, or
- (f) Other factors, as documented by the CTT or psychiatrist

(6) **Extended Service Area.** Clozapine is not available through the fee-basis program, the Civilian Health and Medical Program of VA (CHAMPVA), or any other paid service provider procedure, except as monitored and directed by the CTT. However, if appropriate, the CTT can administrate patient-specific plans to provide clozapine treatment for veterans who cannot reasonably (because of medical condition or distance) visit VA on a weekly basis.

(a) Qualifications

1. A minimum of 18 weeks on clozapine with stable white blood cell counts $>4,500$ per mm^3 , granulocyte count $> 2,500$ per mm^3 dosage change in last 8 weeks.
2. No history of blood disorders, lymphatic system disorders, or seizure disorders while on clozapine.
3. Good family or social service support at the distant site.
4. Psychosis in partial remission with stable dosage for 8 weeks and clinical stability on clozapine.
5. Inability (CTT documented) to return to the medical center for weekly monitoring.
6. Eligibility for fee-basis medical care.
7. Availability to return to the VA medical center immediately if the CTT determines that questions have arisen concerning the patient's physical or mental condition.

(b) For such veterans, CTTs can make special contract arrangements with a distant physician for weekly or bi-weekly WBC and side effect monitoring. Such agreements between the CTT and distant physicians and facilities require CTT evaluation and certification that:

1. The treating physician meets the same standard required for VA clozapine prescribing psychiatrists (except psychiatrist status). This practitioner may be paid by fee-basis funds.
2. The distant laboratory monitoring WBC and granulocyte count meet the standards of the Clinical Laboratory Improvement Act (CLIA) of 1988 - specifically, a Laboratory Registration

Certificate from the Department of Health and Human Services (HHS) for Moderate to High Complexity Tests. This laboratory testing may also be paid by fee-basis funds. *NOTE: The expenditure of fee-basis funds for pharmacy or medication is not allowed. All clozapine used by VA patients must be dispensed by a VA pharmacy.*

(c) The fee-basis, CTT-approved local care practitioner is responsible for evaluating the patients' current condition, perform the weekly phlebotomy, and arrange for the WBC count and side effect evaluation information to be faxed to the local CTT.

(d) The CTT will review the information, enter the WBC count into the VA laboratory computer, enter the prescription into the VA pharmacy computer, and dispense a 7-day supply (or 14 days if patient is qualified by subparagraph 3.c.) of clozapine by mail, with an optional one-time basis, 4-day supply for emergency backup.

(e) The CTT will report the data to the NCCC.

(f) Patients being treated using this method should be evaluated by the CTT at the supervising VA medical center at least once each 6-month period for verification of efficacy.

(6) **Patient Transfers.** Patients from other clozapine treatment systems can be accepted for treatment without interrupting medication. Self-explanatory VA Form 10-0363I, VA/Non-VA Clozapine Patient Transfer Registration, must be completed and forwarded to the NCCC, which will issue a new authorization number. All clozapine patient transfers require:

(a) A hard copy (e.g., fax) transmission from the referring facility signed by the attending physician about the treatment plan, giving the latest confirmed laboratory data, is not sufficient. A new form 10-0363I from the accepting facility is required.

(b) Clozapine informed consent form signed by the patient before the prescribing of clozapine by the receiving facility.

NOTE: The VA agreements with the Clozapine National Registry require a new authorization number when a clozapine patient change to the jurisdiction of another CTT. Do not, under any circumstances, use the clozapine authorization number from another facility to dispense clozapine.

c. **Review, Evaluate, Access Risk, and Consider Alternatives (Medical Issues).** Patients beginning clozapine must have a physical examination, liver function tests (Aspartate Aminotransferase (AST), Alanine Aminotrasferase (ALT), Blood Urea Nitrogen (BUN), and creatinine, complete blood count (CBC) and differential, blood pressure, temperature, pulse, pregnancy test (in fertile women), and Electrocardiogram (EKG) within 30 days prior to clozapine initiation as part of the baseline examination. Any abnormal results should be evaluated thoroughly.

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(1) **Agranulocytosis.** Clozapine has a clear association with granulocytopenia, leukopenia, neutropenia, and agranulocytosis (less than 500 per mm³) Absolute Neutrophil Count (ANC).

(a) General Risk. The cumulative incidence of agranulocytosis has been estimated to occur in association with clozapine use to at a cumulative incidence at 1 year of approximately 1.3 percent.

1. The incidence rates of agranulocytosis based upon a weekly monitoring schedule rises steeply during the first two months of therapy, peaking in the third month. Most of the cases occur within 4 to 10 weeks of initial exposure.

2. After 6 months, the weekly incidence of agranulocytosis declines almost completely, however, it never reaches zero. Some cases have been reported in the 165th week of clozapine treatment.

3. Neither dose nor duration is a reliable predictor of agranulocytosis.

4. Any reduction in the frequency of monitoring weekly WBC counts will result in an increase in the incidence of agranulocytosis.

(b) Demographic Risks. No patient characteristics have been clearly linked to the development of agranulocytosis in association with clozapine use, but data reported to the FDA shows a greater frequency of agranulocytosis in women. Agranulocytosis induced by clozapine also increases with age, with significant increase in risk above age 40 and the highest risk in patients over 65 years old. Risk of agranulocytosis is also increased in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with clozapine.

(c) Medical Risks. Due to its granulocytopenia potential, clozapine is contraindicated in patients who have pre-existing leukopenia, history of hematologic reactions to drugs, or lymphoproliferative disorders.

(d) Drug Interactions Risks. Clinicians should carefully weigh the risks versus benefits of administering clozapine to patients who also take drugs that potentially suppress bone marrow function. Examples of such drugs include carbamazepine, penicillamine, antineoplastics, antiretrovirals, protease inhibitors, and some antifungatives. Because clozapine is known to cause respiratory depression or apnea in some patients, its use with benzodiazepines and other potential respiratory depressants should proceed with great caution, especially in the first 72 hours of clozapine treatment. Furthermore, caution is advised when combining clozapine with other sedating, anticholinergic, or hypotensive drugs.

(2) **Cardiac Symptoms.** Clozapine may cause hypotension, especially when combined with an anti-hypertensive medication, and increased heart rate. An electrocardiogram (EKG) to detect potential cardiac problems is required before clozapine is started. No linkage to cardiac failure has been established; however, sudden cardiac arrest deaths have

occurred in VA patients taking clozapine. Cardiac failure is the leading cause of death among VA patients taking clozapine and has been implied in many other unexplained sudden deaths. If abnormalities in cardiac functioning are detected, particularly the existence of arrhythmia or ischemia, a cardiology consultation is needed to fully evaluate the risk to the patient. Clozapine should be titrated with great caution and close observations on patients with a history of cardiovascular disease

(3) **Pulmonary Embolism.** The possibility of pulmonary embolism should be considered in patients receiving clozapine, especially those who present with deep vein thrombosis, acute dyspnea, chest pain or with other respiratory signs and symptoms. Fatal pulmonary embolism has been associated with clozapine therapy. The Clozaril National Registry reports the mortality rate associated with pulmonary embolus was 27.5 times higher in clozapine patients than that in the general population. Pulmonary illness has been the second most frequent cause of death among VA clozapine patients. Deep vein thrombosis has also been observed in clozapine therapy. Whether pulmonary embolus can be attributed to clozapine or some characteristic(s) of its users is not clear, but caution must be used in any clozapine patient presenting deep vein thrombosis or respiratory symptomatology.

(4) **Hepatitis.** Caution is advised in patients using clozapine who have concomitant hepatic disease. Hepatitis has been reported in both patients with normal and pre-existing liver function abnormalities. In patients who develop nausea, vomiting, and/or anorexia during clozapine treatment, liver function tests should be performed immediately. If elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with clozapine should be discontinued.

(5) **Hyperglycemia.** Severe hyperglycemia, sometimes leading to ketoacidosis, has been reported during clozapine treatment in patients with no prior history of hyperglycemia. While a causal relationship to clozapine use has not been definitively established, glucose levels normalized in most patients after discontinuation of clozapine, and a rechallenge in one patient produced a recurrence of hyperglycemia. The effect of clozapine on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving clozapine who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycemia, the discontinuation of clozapine should be considered.

(6) **Anticholinergic Toxicity.** Clozapine has very potent anticholinergic effects and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. In addition, clozapine use has been associated with varying degrees of intestinal peristalsis impairment, ranging from constipation to intestinal obstruction, fecal impaction, and paralytic ileus. On rare occasions, these cases have been fatal. Ensuring adequate hydration and using ancillary therapy such as bulk laxatives should initially treat constipation. Consultation with a gastroenterologist is advisable in more serious cases.

(7) **Seizure Disorder.** Clozapine must be used cautiously in patients with pre-existing epilepsy since its use is associated with the lowering of the seizure threshold. Seizure risk

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increases with clozapine dose, especially when clozapine doses exceed 600 milligrams (mg) per day. Two medications used to treat seizure disorders (carbamazepine and phenytoin) have shown evidence of potentially harmful interactions with clozapine. Neurology consultation may be needed to assess this risk in patients with epilepsy controlled by drugs.

(8) **Sleep Apnea.** During initial titration, clozapine patients are generally very sedated and may not startle to an acute hypoxic event. In the case of sleep apnea, continuous positive airway pressure (CPAP) monitor should be considered, especially during initial titration.

(9) **Renal Impairment.** Approximately 50 percent of the administered dose of clozapine is excreted in the urine. Patients with renal impairment should be monitored for symptoms of clozapine toxicity.

NOTE: In the event a patient receiving clozapine dies, next of kin should be asked for permission to have an autopsy performed.

d. Document, Obtain Consent, Approval and Authorizations

(1) **Documentation.** Complete VA Form 10-0363-A, Selection Criteria for Clozapine Treatment, following the self-explanatory directions. *NOTE: See Brief Psychiatric Ratings Scale (BPRS), the Abnormal Involuntary Movement Scale (AIMS), and the chlorpromazine equivalence table are found in VistA.*

(2) **Informed Consent**

(a) Patients selected for clozapine therapy (or the patient's representative, under the circumstances described in VHA Handbook 1004.1, and local requirements), must be educated by their primary care provider of the potential risks and benefits associated with clozapine therapy. Information on clozapine that is shared with the patient should include:

1. Indications for use.
2. The need to avoid drugs of abuse.
3. Recognizing and responding to side effects.
4. Risks associated with clozapine, especially seizures and granulocytopenia.
5. The need for patient compliance with bi-weekly blood tests and the prescribed medication dose.
6. The need for immediate follow-up in the case of granulocytopenia.
7. How the VA clozapine system is monitored by the NCCC and the manufacturer.

NOTE: *A progress note must be written in the patient's medical record indicating that this information was explained to the patient and that the patient (or representative, as appropriate) accepted the risks.*

(b) While the clozapine prescriber is responsible for primary patient education about clozapine, the pharmacist must also speak with the patient and:

1. Describe some of the common side effects and provide some practical advice for relieving the distress.
2. Describe the signs of neutropenia, including sustained temperature elevation with flu-like symptoms or sore throat.
3. Explain the importance of strict compliance with bi-weekly laboratory tests.
4. Explain the importance of notifying the clozapine prescriber and pharmacy if problems are suspected.
5. Document the discussion with the patient in the medical record. Due to the requirement for reporting patient data to the manufacturer, the patient will need to sign a release of information form (VA Form 3288, Request for and Consent to Release of Information From Claimant's Records) to authorize the transmittal of relevant clinical information. The manufacturer requires notification of SSN, patient initials, date of birth, ZIP Code, gender, race, weekly WBC counts, and weekly doses. **NOTE:** *All releases of information will be consistent with procedures outlined in M-1, part 1, Chapter 9.*

(3) Special Clozapine Use Informed Consent

(a) In addition to the Informed Consent described in the preceding, special informed consent must be obtained to use clozapine to treat illnesses not listed on the FDA product labeling. This special informed consent can be completed using the attached examples, or by developing a local alternative. In either case, the patient or the patient's special informed consent must show that the risks and benefits of clozapine and at least one alternative treatment have been fully explained. The patient, or the patient's representative, must consent to the use of clozapine and sign the form, witnessed by a co-signer.

(b) The CTT must review and approve this special use. VA Form 10-0363A, VA Form 10-0363J, and the special informed consent form must be forwarded to the NCCC. Such a special use approval from the NCCC is valid for a 3-month trial period, unless a longer period is specified by the facility. If the patient has documented improvement that warrants continuation of clozapine, the NCCC must be so informed. If the target criteria established by the facility clinicians and their CTT have not been met, sufficient time must be allowed for tapering of clozapine.

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(4) **Obtain CTT Approval.** Before any patient is started on clozapine, the local CTT must authorize the patient. The CTT Chair, or designee:

(a) Ensures that the patient meets VA criteria for the use of clozapine.

(b) Reviews the treatment plan to ensure it has been properly prepared and follow-up has been considered. The treatment plans for each clozapine patient must be documented by the CTT and provided to the NCCC at their request.

(c) Authorizes the enrollment of individual patients into the clozapine management protocol.

(d) Reviews and signs the forms.

(5) **Process Application.** The CTT sends the application to the NCCC by facsimile or mail. If the submitted forms comply with the requirements of the CPMP, the NCCC secures a new patient clozapine authorization code from the manufacturer for drug initiation and reporting purposes. The NCCC provides its endorsement of the enrollment packet, together with the clozapine authorization code, to the CTT for initiation of clozapine. This review is usually accomplished within 24 hours.

3. MONITORING USE OF CLOZAPINE

a. General Monitoring Rules

(1) **Monitor Frequency**

(a) Clozapine patients must have a baseline WBC count and differential count before starting clozapine.

(b) Clozapine patients must have one WBC count for every week of treatment for the first 6 months.

(c) Clozapine patients may qualify for WBC counts and clozapine prescriptions every-other-week if there have been no abnormal blood events during the first 6 months of continuous therapy. **NOTE:** An "abnormal blood event" is defined as a WBC count less than 3000 per mm^3 or a granulocyte count (ANC) less than 1500 per mm^3 .

(d) Rules to qualify for bi-weekly WBC monitor. The following are the parameters for a veteran to qualify for the bi-weekly WBC monitoring:

1. For patients with clozapine treatment less than 6 months:

a. If a patient has no abnormal blood events and there is a break in therapy which is greater than 1 month, patients should be tested weekly for an additional 6-month period before bi-weekly WBC testing is initiated.

b. If a patient is in clozapine therapy for less than 6 months and experiences an abnormal blood event (see subparagraph 3a(1)(c)), but remains rechallengeable (patients cannot be reinitiated on clozapine therapy if WBC counts fall below 2000 per mm³ or the ANC falls below 1000 per mm³ during clozapine therapy), the patient must restart the 6-month period of weekly WBC monitoring at day zero.

2. For patients with clozapine treatment greater than 6 months who have met the biweekly test criteria:

a. If there is a break in clozapine therapy which is 1 year or less, then the patient can continue WBC count monitoring every-other-week if clozapine therapy is reinitiated.

b. If there is a break in clozapine therapy which is greater than 1 year, then if clozapine therapy is reinitiated, the patient must have WBC counts monitored weekly for an additional 6 months.

c. If a bi-weekly monitor qualified patient has an abnormal blood event, the patient must restart weekly WBC count monitoring until an additional 6 months of clozapine therapy has been completed (without additional abnormal blood events).

d. WBC counts must be followed and reported to the NCCC until 4 weeks following cessation of clozapine treatment.

(2) **Prescription Rules.** All clozapine (inpatient and outpatient) must be dispensed through the VistA Outpatient Pharmacy Package.

(a) Clozapine cannot be dispensed to a patient who has not registered with the local CTT and the NCCC.

(b) Only one prescription may be filled for a given WBC count. A written prescription for clozapine is required for a weekly or bi-weekly visit.

(c) The number of tablets dispensed cannot exceed the amount used in 7 days.

(d) Prescriptions with refill orders are not permitted. **NOTE:** *Because dosing data is not properly gathered until the VistA Clozapine patch can be corrected, the "RENEW" option should not be used.*

(e) Clozapine orders are subject to an automatic 7-day stop-order policy. The pharmacist may fill a clozapine prescription only after verification of the white blood cell count from blood samples drawn on the day of dispensing or within the previous 6 days.

(f) Four days' supply of clozapine may be provided to outpatient veterans as an emergency backup in the case of anticipated severe weather or delays in receiving clozapine by mail from the VA pharmacy. Each time this four-day supply is dispensed, the pharmacist

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must document the patient's medical record. This supply is only to be used for emergencies and never to circumvent the weekly or bi-weekly WBC count requirement.

(g) Maximum Clozapine Dose per Day is 900 mg. If the patient does not appear to respond, daily doses above 900 mg could be approved if:

1. The patient's clozapine plasma level is below 350 nanograms (ng) per ml.
2. The patient, or representative, is specifically informed that the high dosage has not been approved by the FDA and may result in unknown side effects.
3. The patient or representative provides written informed consent for the dosage above 900 mg per day.

(3) **Outpatient Monitoring Logistics.** For safety reasons, the WBC sample should be drawn, tested, and reviewed immediately (same day) before dispensing the medication. Outpatient treatment of patients on clozapine should be synchronized with the laboratory and pharmacy so that all laboratory tests, mental health evaluations, and pharmacy distributions are performed on the same day of the week. Weekly WBC counts and corresponding face-to-face evaluation of side effects and efficacy are highly recommended for the first 20 weeks of clozapine treatment, especially due to the risk of agranulocytosis.

(a) Optionally, the patient's blood may be sampled several days prior to the weekly clinic visit to be available to the clinician to review before the prescription is written.

(b) For clozapine patients who have completed 20 weeks without significant hematological problems, dispensing clozapine by mail is permitted after review of the WBC by the prescribing physician.

(4) **Inpatient Monitoring Logistics.** To ensure proper hematologic monitoring, dispensing of clozapine to inpatients must be entered into the VistA Outpatient Pharmacy Package. Continuation of inpatient orders is left to the decision of the treating facility. However, at a minimum, the treating psychiatrist and/or neurologist must write a progress note for each week of clozapine treatment, specifically showing a review of the WBC count for that week, the clozapine dose for that week, estimate of efficacy, and signs of side effects.

(5) **Documentation of Monitoring.** Treatment of a clozapine patient must be fully documented, from initial application to termination of treatment. **NOTE:** *The numbered VHA clozapine forms referenced in this directive may be placed into the patient's medical record.* With the advent of electronic records, the CTT may organize its own forms for recording clozapine information. At a minimum, the following data must be placed in the patient's hard copy and/or electronic medical record:

- (a) Patient application with backup documentation.
- (b) Evidence that the practitioner has seen the patient on a weekly or bi-weekly basis.

(c) Evidence that weekly or bi-weekly WBC counts, value entry and side-effect monitoring have been performed.

(d) Evidence of semi-yearly, ongoing efficacy evaluations (BPRS, AIMS suggested).

(e) Reason for terminating clozapine therapy.

b. **Specific Rules for Monitoring WBC Counts**

(1) Treatment cannot be initiated if the WBC is less than 3500 per mm^3 .

(2) If the patient's white blood cell count falls below 5000 per mm^3 , a complete WBC and differential must be ordered and monitored. The treating physician or the VA or non-VA laboratory should notify the CTT leader, or designee, that a differential is required. The WBC count and the granulocyte count must be reported to the NCCC on the Weekly Tracking Sheet.

(3) If a differential count reveals a total eosinophil count above 4000 per mm^3 , clozapine treatment should be interrupted until the total eosinophil count falls below 3000 per mm^3 . Clozapine therapy has been associated with transient eosinophilia and the count may possibly be related to precursors of leukopenia.

(4) If the patient's white blood cell count falls to a level of less than 5000 per mm^3 in 3 consecutive weeks, it is likely that leukopenia has developed. Clozapine may be continued at the discretion of the treating physician. A WBC and differential must be ordered and monitored on a twice-weekly basis until the WBC stabilizes above 5000 per mm^3 .

(5) If the white blood cell count drops more than 3000 per mm^3 in 1 week, especially if immature forms are present in the differential count (e.g., bands greater than 8 to 10, or bands increasing), a repeat WBC should be performed immediately with acceptance based on the parameters listed as follows. Since sharp plunges in WBC have been identified as possible precursors to leukopenia, WBC counts on a twice-per-week basis are strongly recommended until the WBC stabilizes.

(6) If the patient's white blood cell count falls to a level between 3000 per mm^3 and 3500 per mm^3 and the granulocyte count is above 1500 per mm^3 , leukopenia has developed. Clozapine may be continued at the discretion of the treating physician. A WBC and differential must be ordered and monitored on a twice weekly basis until the WBC stabilizes above 5000 per mm^3 .

(7) If the patient has a WBC less than 3000 per mm^3 or a granulocyte count of less than 1500 per mm^3 , clozapine must be stopped. Evidence implies that most critical factor effecting recovery from a moderate leukopenia may how soon clozapine is stopped after WBC reduction is discovered.

(a) The patient must be evaluated medically and consultations arranged with Hematology and Infectious Disease Services.

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(b) CTT leader is responsible for documenting the following actions in the patient's medical record within the first 24 hours after notification. Documentation should include:

1. The primary prescriber was notified.
2. Steps were taken to notify the patient.
3. The patient was located and brought to the hospital.
4. Medication administration was stopped (medication returned to the pharmacy for disposal).
5. Appropriate service consultations were requested.
6. The NCCC was notified.

(c) Clozapine may be restarted when the WBC stabilizes above 5000 per mm³ at the discretion of the treating physician. However, the clinician should consider that patients who have developed a moderate leukopenia while on clozapine and recover have a 4 times greater risk of developing agranulocytosis if restarted on clozapine.

(8) If the WBC falls below 2000 per mm³ or the granulocyte count falls below 1,000 per mm³, clozapine must be stopped. In addition to the actions listed in the preceding subparagraph 3b(7):

(a) The patient requires immediate hospitalization.

(b) The patient must be evaluated medically and consultations arranged with Hematology and Infectious Disease Services with consideration to bone marrow aspiration and analysis, third and fourth generation antibiotic support, and growth factors Granulocyte-Colony Stimulating Factor (G-CSF).

(c) Neutropenia precautions should be instituted. In general, the severity of symptom presentation coincides with the mortality rate (i.e., febrile neutropenia has a much higher mortality rate than afebrile neutropenia).

(d) Clozapine may not be restarted on any patient whose WBC has fallen below 2000 per mm³ or whose granulocyte count has fallen below 1,000 per mm³ while on clozapine. The CTT should ensure that the patient's permanent medical record is clearly marked to prevent any accidental clozapine rechallenge.

c. **Side Effect Monitoring Points.** The following adverse effects should be monitored, especially during titration, to assess whether the patient can tolerate therapy:

(1) **Granulocytopenia.** Granulocytopenia is defined as an abnormal reduction of granulocytes in the blood. The risk of granulocytopenia is approximately 0.3 percent or a

cumulative index of 2 percent. Since granulocytopenia is a potentially fatal disorder, physician monitoring by laboratory testing, consisting of weekly WBC counts with differential and/or granulocyte count, are mandatory before each week's supply of medication can be dispensed.

(2) **Tachycardia.** Tachycardia is a common side effect of clozapine treatment and is rarely a significant concern unless the heart rate rises abnormally high or the patient complains of discomfort. If patient history permits, low dose beta-blockers have been used as an adjunct.

(3) **Sedation.** Sedation is another common side effect that usually forces adjustment to the rate of titration. The overall effect tends to disappear when steady state plasma levels are achieved during titration.

(4) **Sialorrhea.** Sialorrhea is a common side effect during titration. Studies suggest that the sialorrhea is the result of interruption in the swallowing reflex rather than the result of an actual overproduction of saliva. Generally, this condition improves as steady state plasma level is achieved. However, patients with swallowing problems should be carefully monitored for aspiration.

(5) **Seizures.** Seizures during clozapine use are generally the result of a lowering of the seizure threshold. The risk increases with dose and becomes most significant in doses above 600 mg/day. If a patient has a seizure while taking clozapine, immediately decrease the clozapine dosage by 50 percent and initiate valproic acid medication. Evaluate the patient to rule out epileptiform foci or consult Neurology Services, as appropriate. After the patient is stabilized on valproate, clozapine dosage may be increased to control psychosis by 25 mg to 50 mg per day with close observation. **NOTE:** *This protocol is based on recommendations from Novartis Pharmaceuticals.*

(6) **Hypotension.** Hypotension seems to be closely related to sedation during the early titration of clozapine. The problem is most significant when clozapine interacts with other medications that lower blood pressure. Patients on antihypertensive medication should be monitored carefully.

(7) **Fever.** The use of clozapine is frequently associated with a mild rise in temperature that resolves over time. Unfortunately, if neutropenia is developing in the patient, a similar rise in temperature may be expected. Any sign of fever in a newly-started clozapine patient should be thoroughly evaluated immediately to rule out underlying infectious process, (i.e., pancreatitis), development of agranulocytosis, or neuroleptic malignant syndrome before designating clozapine as the causal factor.

(8) **ECG Repolarization.** Some clozapine patients have experienced ECG repolarization changes, including S-T segment depression and flattening or inversion of T waves. All of these changes normalize when clozapine is discontinued.

(9) **Non-response.** Occasionally, clozapine patients do not appear to respond, even at the maximum dose (900 milligrams per day (mg/day)). Daily doses above 900 mg could be approved if:

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(a) The patient's clozapine plasma level is below 350 ng/ml.

(b) The patient, or representative, is specifically informed that the high dosage has not been approved by the FDA and may result in unknown side effects. The patient or representative provides written informed consent for the dosage above 900 mg per day.

d. **Efficacy Monitoring.** Improvement in the patient's condition, if any, should be carefully documented on the serial VA Form 10-0363C, Brief Psychiatric Rating Scale (BPRS), and VA Form 10-0363D, Abnormal Involuntary Movement Scale (AIMS), and filed in the medical record. An initial trial of clozapine of 8 weeks is generally recommended to determine whether to continue clozapine therapy or not. If the patient has mild clinical response, the CTT may assist in the decision to continue therapy to possibly benefit late responders. An adequate clozapine trial may take up to 6 months. If the patient does not respond as evidenced on the BPRS and AIMS, then clozapine should be tapered off over 1 to 2 weeks to avoid potential withdrawal reactions consisting of confusion, emotional withdrawal, or an intensified resurgence of psychotic symptoms. The CTT will continue to monitor the patient with WBC counts for 4 weeks after discontinuing clozapine.

4. DRUG PROCUREMENT AND DISTRIBUTION

a. **VA Sites Registered with the NCCC.** VA sites registered with the NCCC as described in Section 1 are permitted to purchase and dispense clozapine. Consolidated Mail Outpatient Pharmacies (CMOPs) may purchase clozapine for supply to a VA registered clozapine site; however, CMOPs are not authorized to dispense clozapine directly to VA patients.

b. **Drug Procurement.** Clozapine may be purchased through the current appropriate federal contract, either directly from the manufacturer or from any acceptable drug wholesaler. The VA contract with the clozapine supplier and the FDA requires the VA (NCCC) to provide certain types of patient data to the Clozapine National Registry on a weekly basis. Failure of the VA site to report to the NCCC on a weekly basis jeopardizes VA agreements and policy.

NOTE: The VA has a current contract that permits purchase of clozapine directly or by companies supplied by Novartis Pharmaceuticals. VA currently approves no other source of clozapine.

c. **Service Procurement.** Optionally, a VA medical center may seek a contract for an external blood monitoring system. Contracting officials must ensure that the data collection and forwarding which are specified as part of the contract are consistent with the requirements set forth by this directive. Contracts must specify a requirement for data transmittal to the NCCC.

d. **Pharmacy Service.** The Pharmacy Service has responsibility for dispensing outpatient or inpatient medication supplies after verification that the WBC count and the granulocyte count are within acceptable limits. *NOTE: See subpar. 3.b. for a description of these limits.*

(1) All orders must be entered into the VistA Pharmacy Outpatient Package as outpatient order after the computer and pharmacist verifies that a proper, acceptable blood test was

performed. **NOTE:** *The number of tablets dispensed cannot exceed the total needed for 7 days.*

(a) For inpatients, actual drug distribution may be through the regular unit dose or ward stock systems. When the ward stock system is employed, the patient's clozapine will be dispensed to the ward in patient-specific containers with 7 days of medication.

(b) For outpatients, the pharmacist entering the outpatient physician's order must also verify the patient's current address and telephone number on each clozapine prescription so that the patient may be contacted if case problems arise. The Chief, Pharmacy Service, is responsible for entering a note in the message field of the drug file to cue pharmacists to verify the patient's address and telephone number.

(2) When the pharmacist enters the physician's order into the computer, a software program will verify that the patient's WBC data from the last 6 days has been entered into the computer system and that the WBC is within acceptable limits. If both conditions are true, the computer allows the entry of the physician's order. Otherwise, the computer will automatically lock out entry of the physician's order to prevent the patient from receiving clozapine.

(a) The CTT leader may decide to override a computer lock out and permit the pharmacy to dispense clozapine. The CTT leader must provide a clear, documented explanation for the override on the information sent to the NCCC each week and in the patient's medical record.

(b) The pharmacist will enter the override code as instructed by the CTT leader. The pharmacist will maintain a permanent record of all lock out overrides of the clozapine safety software and will print a weekly report for the CTT. The CTT will review the circumstances of each override to ensure that the override was justified and properly documented in the medical record.

(c) The pharmacist will generate a report 24 hours after entry of the physician's order(s), listing the patient(s) who received clozapine, date of the visit, and results of the WBC. After review, the pharmacist will forward the report to the CTT.

(3) The pharmacist will generate a date and results. After review, the pharmacist will forward the report to the CTT.

(4) Anytime the patient's WBC = <5000 per mm^3 , the VA or non-VA laboratory and/or VA Pharmacy will be responsible to notify the prescriber and CTT leader.

NOTE: *All clozapine orders, inpatient or outpatient, are subject to subparagraph 3.a. (2).*

e. **IRM Service.** IRM Service assists with questions on the pharmacy local computer program. Subsets of patient information, including the patient's registration number, clozapine doses, and WBC results are transferred electronically from the medical center computer to the national data bank. IRM Service also assists if problems develop in data transfer. The data is used to partially fulfill national contract obligations for reporting data to the manufacturer and by

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the NCCC for post-marketing surveillance and national quality assurance purposes. The weekly information transmitted to the NCCC via facsimile is needed to supplement the computer transmission and meet manufacturer's information requirements.

5. QUALITY MANAGEMENT

a. **Responsibility for Each Clozapine Patient.** The responsibility for each clozapine patient rests with the individual prescriber and the local CTT. Procedures and information outlined in this directive and attachment provide a system and structure for supporting the safe use of clozapine in VA patients. However, the CPMP is not to be considered a substitute for clinical judgment and expertise.

b. **Review by Medical Center Drug Use Evaluation (DUE) Committee.** At the medical center level, data on the activities of the CTT (monitors, determinations, actions) shall be collected and summarized for review by the medical center's DUE Committee as part of the facility's Quality Assurance plan. Data collection is assisted by the special clozapine lock-out software reports patients on clozapine, their WBC values, and reports of lock-out overrides. Incorporation of clozapine into the facility's DUE plan is consistent with the Joint Commission on Accreditation of Healthcare Organization's (JCAHO) requirements for monitoring a high-risk and problem-prone drug.

c. **National Clozapine Coordinating Center.** The activities of the NCCC are guided by an expert panel of VA clinicians (the VA Clozapine Task Force) organized from the offices of the Associate Director for Psychiatry, Mental Health, and Behavioral Sciences Service, and the Chief, Clinical Pharmacy for Quality Management, VA Headquarters. At the national level, the NCCC will:

(1) Serve as primary information and data liaison between the VA clozapine sites and the Clozaril National Registry.

(2) Monitor medical center compliance with procedures outlined through this circular, documenting that structures and procedures are instituted at each site to ensure the safe and appropriate use of clozapine.

(3) Conduct quality improvement studies based on data that is electronically gathered by pooling of patient information into a central VA data bank.

(4) Refine risks and benefits of clozapine in VA patients through post-marketing surveillance. Serve as a resource for consultation on difficult cases.

(5) Maintain a national database on VA patients receiving clozapine to prevent any unauthorized rechallenge of clozapine at a different VA site, and prevent simultaneous clozapine treatment on the same patient at two or more facilities.

(6) Maintain a national database of demographic information of VA clozapine patients that can be referenced for data and research.

6. PATIENTS ENROLLED IN RESEARCH STUDIES

Individual arrangements must be made between clinical investigators and research sponsors for protocols, approvals through appropriate committees, and drug procurement. However, VA patients enrolled in a clozapine research protocol must be monitored using the procedures outlined in this circular and its attachment. This includes participation of the local CTT and data transmittal to the NCCC.

7. COMPLIANCE WITH PROTOCOL

a. Individual prescribers who fail to comply with the CPMP jeopardize the national VA clozapine initiative. Individual physician compliance failures are reportable to the Chief of the relevant Service (Psychology, Neurology) and may be considered in reversing privileges for clozapine prescribing.

b. Upon identification of major compliance failure or patient management and safety concerns that cannot be resolved through communication with the CTT:

(1) The NCCC will:

(a) Notify the VISN Clinical Manager and medical center Chief of Staff of the specific problem.

(b) Withhold authorization of new patients at the site.

(2) The VISN Clinical Manager and medical center Chief of Staff will:

(a) Assume full responsibility for clozapine patient safety and proper risk management procedures until the problem is resolved.

(b) Investigate the problem and institute corrective actions, as warranted.

(c) Notify the NCCC of the results of the investigation.

WEEKLY TRACKING INFORMATION FOR _____ WEEK _____ THRU _____ PAGE _____
VA FACILITY MONDAY SUNDAY

NOTE-- GRANULOCYTE COUNT RECOMMENDED AT ALL TIMES, BUT REQUIRED IF WBC LESS THAN 5000/MM3

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Department of Veterans Affairs
National Clozapine Coordinating Center
FTS/COMM 214-857-0068 FAX 214-857-0339

WEEKLY TRACKING INFORMATION FOR _____ WEEK _____ THRU _____ PAGE _____
VA FACILITY MONDAY SUNDAY

NOTE-- GRANULOCYTE COUNT RECOMMENDED AT ALL TIMES, BUT REQUIRED IF WBC LESS THAN 5000/MM3

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