CLOZAPINE

RECOMMENDATIONS TO PSYCHIATRISTS FOR CONVERSION OF BRAND NAME CLOZARIL TO GENERIC CLOZAPINE

1. INTENT

These recommendations are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns evolve. These parameters of practice should be considered recommendations only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

These recommendations have been developed by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involves in research or other academic endeavors. Contributors and reviewers have all been asked to base their recommendations on an objective evaluation of the available evidence. Consensus panel:

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2. BACKGROUND

Currently, there are two generic formulations of clozapine approved by the Food and Drug Administration and marketed in the United States.

These are manufactured by Mylan Laboratories Inc. and by Zenith-Goldline a subsidiary of Ivax Corporation. A third generic, manufactured by Geneva Pharmaceuticals, a unit of Novartis, has also been approved but is not yet marketed. Concerns have been expressed by patients, family members and physicians about switching patients stabilized on Clozaril manufactured by Novartis (formerly Sandoz) to a generic formulation. These concerns arise from concern for Clozaril patients who generally have had severe mental illness refractory to other treatments. In many cases, these patients' response to Clozaril has exceeded experience with all prior therapies. Naturally, a change in the care of these patients must be undertaken with caution.

As one means of testing the safety of switching from Clozaril to a generic formulation, two independent, scientific, investigations have examined the bioavailability of one formulation of generic clozapine (Zenith-Goldline) compared to Clozaril. Bioavailability is a measure of the rate, and extent of absorption of a drug into the body after ingestion. Each of these studies has concluded that there are differences in some of the measures of bioavailability between Clozaril and the generic formulation studied. However, the clinical significance of these differences in lab values was not demonstrated. In a critical review of these two studies, the Food and Drug Administration concluded that the neither study was designed to test whether the generic version of clozapine is unsafe or ineffective. It is important to note that the FDA continues to monitor the safety and efficacy of generic formulations, and despite thousands of patients currently receiving generic clozapine, no restrictions have been issued with respect to the generic products.

On December 1, 2000, Missouri Medicaid switched its reimbursement for clozapine to Maximum Allowable Cost (MAC). Medications reimbursed at Maximum Allowable Cost have a maximum reimbursement rate. As of February 2001, the MAC reimbursement rate for clozapine is less than the cost of Clozarilâ, but high enough to cover the cost of the two available generic clozapine products.

- For patients receiving Clozarilâ prior to December 1, 2000, Missouri Medicaid will continue to reimburse at full price if the prescriber contacts the Drug Prior Authorization Unit (800-392-8030) to obtain an override to the generic reimbursement limitation (Missouri Medicaid Bulletin, Vol. 23, No. 4).
- After December 1, 2000 prior authorization for a waiver of the MAC pricing for clozapine will expire for patients that have not

had a trial of generic clozapine. After this date, physicians treating patients that have had an unsuccessful trial of generic clozapine may seek an additional waiver to continue reimbursement for treatment with Clozaril (Medicaid prior authorization letter to physicians 11/00).

- We recommend that patients being newly started on clozapine be started on a generic to avoid having to be switched later.

At present, approximately one-third of the patients receiving clozapine in Missouri are receiving a generic formulation. Seven other states have also instituted Maximum Allowable Cost for reimbursement of clozapine. The vast majority of patients switched from Clozaril to generic clozapine have tolerated the change in formulation without incident. Nationally, there have been several reports of patients experiencing a change in symptom status or side effects coincidental to the change from Clozaril to a generic clozapine formulation. In evaluating these reports, it is important to be reminded that patients treated with Clozaril often have a chronic relapsing condition. Exacerbations of such an illness are not unusual for a minority of apparently stable patients.

3. MAKING THE SWITCH

1. Counseling of patients should be undertaken to familiarize them with the generic formulation. Also, patients' questions should be addressed. Therefore, additional time for a patient visit at the time of the switch may be scheduled. *Comment: Patient safety may be best protected by providing adequate personnel and time to explain the substitution that is being undertaken. Misunderstandings may be avoided if patients are given opportunity to identify and communicate their questions.*

2. Increased frequency of visits may be indicated on a patient-by-patient basis and should be determined clinically based on patient's presentation around the time of the switch (e.g. symptom status, medication tolerability and patient's acceptance of the change in formulation).

3. Establishing a trough concentration prior to formulation change in stable patients will be most helpful in guiding subsequent therapy should the patient's status change. To establish the trough concentration draw 2 samples 1 week apart. If the values differ by more than 50 ng/dl, draw a 3rd level.

Comment: When making clinical decisions based on the blood level monitoring data, consider the following:

1. All blood samples for clozapine concentration monitoring should be collected approximately 12 hours after the last clozapine dose and prior to taking the next clozapine dose (trough). In the case of patients taking clozapine as a single daily dose, blood sample collection should be done 12 hours after the dose.
2. A relationship between blood concentration and symptom outcome has not been demonstrated for clozapine. A trough concentration of at least 350 ng/mL is widely regarded as a desirable target for patients that are not adequately responding after 12 weeks of treatment.
3. For any patient on a stable dose of Clozarilâ, variability in blood concentration is expected day to day due to outside factors such as time since last dose, stomach contents, fluid status, and metabolic state. Therefore, it is important to make clinical decisions based primarily on patient status.
4. Clozapine is converted to the less active metabolite nor-clozapine. A clozapine blood concentration should include a nor-clozapine level. A change in the ratio of nor-clozapine to clozapine may indicate altered metabolic disposition for clozapine that could be due to normal environmental exposures (e.g. aryl hydrocarbons in diet and cigarette smoke).

4. Patients should be switched on an equal milligram per milligram basis. No adjustments in dose are indicated *a priori.*

   Comment: The Food and Drug Administration have indicated that the generic formulations are considered equivalent in the amount of drug delivered. Within the FDA guidelines for bioequivalence, it is possible that there could be differences in levels measured for a given patient in usual clinical practice. In the minority of patients where a difference may occur, it is impossible to predict either the direction (higher or lower concentration) or the magnitude of difference. Therefore, the best approach is to exchange the drugs on an equivalent

milligram for milligram basis. Subsequent adjustments in dose may be undertaken as indicated by patient status.

5. When writing for generic clozapine, physicians should realize that patients may be switched from one generic formulation to another when they have the prescription filled.

    - If the prescribing physician wants to assure a particular manufacturer's generic clozapine be used they should specify the manufacturer on each prescription written and be sure to sign the "make no substitution" signature line.
    - As part of patient education, patients need to be taught and encouraged to remember the manufacturer of the generic formulation of clozapine that they are taking. They should be instructed to question their pharmacist and call their physician if they are dispensed a pill of a different shape or color.

MYLAN

Clozapine 25 mg
IMPRINT CODE: M C 7
COLOR: PEACH
SHAPE: ROUND, SCORED
FORM: TABLET

Clozapine 100 mg
IMPRINT CODE: M C 11
COLOR: GREEN
SHAPE: ROUND, SCORED
FORM: TABLET

ZENITH GOLDLINE

Clozapine 25 mg
IMPRINT CODE: 4359 25
COLOR: PALE YELLOW
SHAPE: ROUND
FORM: TABLET

CLOZAPINE 100 MG

IMPRINT CODE: 4360 100
COLOR: PALE YELLOW
SHAPE: ROUND
FORM: TABLET

NOVARTIS

Clozapine 25 mg
IMPRINT CODE: CLOZARIL 25
COLOR: PALE YELLOW
SHAPE: ROUND, COMPRESSED, EMBOSSED
FORM: TABLET

Clozapine 100 mg
IMPRINT CODE: CLOZARIL 100
COLOR: PALE YELLOW
SHAPE: ROUND, COMPRESSED
FORM: TABLET

Comment: In a minority of patients, it may be possible to observe changes in blood levels in switching between generic formulations. To date, there is no evidence to address the safety and efficacy of switching between available generic formulations. By making sure that patients are knowledgeable of which generic formulation they are receiving, the risk of an inadvertent switch between formulations can be minimized.

6. Subsequent clozapine blood level monitoring should be considered only as warranted by a change in patient status that is unexplained by other factors. A Clozapine level that is significantly different from their established baseline pre-switch level (a suggested change of ± 50 ng/dl or 10% in higher ranges is provided as a guideline) should be managed with a dosage change based on clinical presentation. The upper range of dose and serum level is limited only by side effects.

   Comment:

   0. The patient's prior history of waxing and waning of symptoms should be taken into account in making this determination. Some patients with optimal treatment on brand name Clozaril continue to have exacerbations of symptoms or relapse to psychosis in spite of optimum dosing on brand medication.

   1. Some patients and families are very concerned about switching Clozapine preparations.

1. Symptoms related to those concerns such as anxiety, irritability and insomnia can be similar to early warning symptoms of psychosis.
2. Follow-up serum levels can be helpful in addressing these concerns.

7. Increased frequency of blood cell monitoring (i.e. CBC) is not indicated except as guided by FDA approved labeling for clozapine.

   Comment: Agranulocytosis associated with clozapine treatment is an idiosyncratic adverse drug reaction. It is not a predictable phenomenon. Experience in the last decade though, has shown that patients are at a decreased risk of agranulocytosis after the first six months of treatment. Therefore, the frequency of blood cell monitoring may be changed from weekly to every other week after six months (in the absence of sub-threshold CBC or ANC). There is no evidence to suggest that a switch in clozapine formulations will in any way alter the safety profile of clozapine treatment nor place patients at additional risk of agranulocytosis.

8. Duration of trial will vary by clinical circumstance but a suggested minimum trial of 4 weeks is provided as a guideline. An adequate trial of generic clozapine should be of sufficient duration to make a fair evaluation of outcome.

9. A waiver to return to brand name Clozaril should be requested if:
    0. If it is not possible to achieve the prior to switch serum level without side effects intervening.
    1. If there is significant deterioration from the level of function observed prior to the change of formulation, and this change does not appear related to outside factors, and the deterioration is of such rapidity and severity that the patient cannot be safely be managed by dose adjustment and further serum monitoring.