



NDA 19758/S-047

Novartis Pharmaceuticals Corporations
Attention: James Rawls, Pharm.D.
Assistant Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Rawls:

Please refer to your supplemental new drug application dated February 28, 2002, received March 1, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clozaril (clozapine) tablets.

We acknowledge receipt of your submissions of March 29, May 17, June 24, and August 5, 2002.

This supplemental new drug application proposes the use of Clozaril (clozapine) tablets for the treatment of suicidality in patients with schizophrenia or schizoaffective disorder.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Issues for Study ABA 451 that Need to be Addressed:

While we agree that the results of this study, on face, suggest a benefit for Clozaril compared to Zyprexa in reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for such behavior, there are several issues that were identified in the course of the review that need further exploration before we can reach a final judgement about this application. Thus, we ask that you address the following concerns:

1. Change in Blinded Raters

We note that, for a substantial proportion of patients in this study (42% for Clozaril and 44% for Zyprexa), there was a change in the blinded raters who conducted the CGI-SS-BP ratings over the course of this 2-year study. Since it was data from the 7-point version of this instrument that were included in the defined primary endpoint for this study, i.e., the version that asked raters to categorize patients regarding their change from baseline on suicidality, the fact that almost half of the raters changed during the course of the study raises a concern about the reliability of these ratings. Thus, we ask that you comment on this finding and its potential impact on the validity of the results for this study.

2. SMB Performance

As part of our routine audit of data from this trial, we examined the clinical materials provided to the SMB for a random sample of patients to determine whether or not the events referred for these patients were appropriately classified by the SMB. We examined the materials in detail for 3 patients who were classified by the SMB as having a Type 1 event (Zyprexa patient 201-0004, Clozaril patient 127-0007, and Zyprexa patient 102-0012), since in each case the blinded psychiatrist, having reviewed the same data, did not classify the event as Type 1. In addition, we note that, for all 3 cases, one of the SMB members had initially voted that no event had occurred, but changed to vote that the event in question was in fact a Type 1 event. Our clinical reviewer, upon examining the material that presumably was provided to the SMB, found in each case that the information provided did not support designation as a Type 1 event. In 2 cases, the investigator had indicated a low risk of self-injury for patients who were hospitalized, and in the third case, the investigator had indicated that the suicide attempt was in fact a low risk attention-getting gesture. These random findings raise a concern about the performance of the SMB in classifying events.

Of course, it is possible that the cases were more complicated than appears from the materials available to us for this audit, and in fact we have already requested that you provide any additional documentation that might be available for these 3 cases, e.g., conference minutes for SMB, etc. (see 8-21-02 e-mail from Dr. Dubitsky). We have also requested an additional 25 patient endpoint packages from the 103 events for which there was disagreement between the blinded psychiatrist and the SMB (see 8-23-02 e-mail from Dr. Dubitsky). Such information may help to reassure us that potential events were correctly classified.

3. Unblinding of Blinded Psychiatrists

Apparently the CRFs provided a place for BP's to indicate if they became unblinded at any particular patient visit. A search of the entire database for such notations revealed a total of 6 BP's who indicated that they had become unblinded to 6 patients (110-0001, 117-0001, 119-0002, 122-0006, 131-0005, and 701-0001). Please provide any additional information regarding how unblinding occurred in these 6 cases, so we can better understand the approaches used to ensure blinding for the BP's.

4. Potential Bias in the Referral of Information to the SMB

We reviewed the data for the CGI-SS ratings and found that, for both versions of the CGI-SS, the p-values for the between-treatment contrasts using the ratings of the unblinded investigators were lower (in favor of clozapine) than those for the between-treatment contrasts using the ratings of the blinded psychiatrists. While clearly not proof of bias in the unblinded investigators, these findings raise a concern about the possibility of bias. Furthermore, it is our impression that the vast majority of events reviewed by the SMB were referred to the SMB by the unblinded investigators. The numbers of referrals and proportions of those referred who were judged to represent Type 1 events can be summarized as follows:

<u>Clozapine</u>	<u>Olanzapine</u>	<u>Difference</u>
# referred 122	157	35
# Type 1 84% (102/122)	90% (141/157)	39

It might be argued that, since the unblinded investigators had primary responsibility for deciding which events would be forwarded to the SMB, they may have, due to their bias for clozapine, forwarded more olanzapine events than clozapine events. Since there is clearly a high correlation between the number of referrals and the ultimate number of events judged to be Type 1, any bias in favor of clozapine in deciding which events to refer might have biased the overall results of this study in favor of clozapine.

This is an important concern and we ask that you fully address it. As part of your response, please fully clarify the source of referrals to the SMB. It is our understanding that staff from Ingenix conducted a review of the clinical database to identify any additional major events that might have been overlooked by the unblinded investigators, and they prepared information on these events similar to that prepared for the events referred by the investigators. Presumably, any additional events were then referred to the SMB for blinded evaluation. Thus, if there was a bias on the part of unblinded investigators, it could have been overcome by the detection of overlooked major events by Ingenix staff. However, if the Ingenix staff was unblinded to treatment assignment, a similar bias could be obtained. Therefore, we need clarification of whether or not these reviews were done by Ingenix, a detailed description of how the reviews were conducted, and an enumeration of how many additional major events were detected and referred to the SMB, beyond those referred by the investigators. It will also be critical to describe whether or not the Ingenix review was blinded, and, if not, how this affected the referral rate. Since it is also our understanding that the unblinded investigators had the final say in whether or not any particular event would be referred to the SMB (p. 39 of study report), we ask that you provide a listing of the events referred by Ingenix staff to the unblinded investigators and for which the unblinded investigators decided not to send them on to the SMB.

We would also like to make you aware of our plans to bring this application to the PDAC. While we believe that study ABA 451 could serve as support for a suicide related claim, there are a number of significant issues that we believe need to be discussed with the PDAC. Clearly there is no precedent for the claim being sought for Clozaril in this NDA. Furthermore, if supported, this claim will represent a major advance in the treatment of schizophrenic and schizoaffective patients judged to be at risk of experiencing suicidal behaviors. Thus, we feel it is paramount that we bring this application to the PDAC for their consideration, both of the claim generally, and more specifically to have them consider study ABA 451 as support for this claim, and whether this single study constitutes substantial evidence of effectiveness for this claim. We have scheduled a PDAC meeting on Monday, November 4, 2002, to discuss your application. In preparation for that meeting, we ask that you provide a complete briefing package by the third week in September. We will need to have the package at that time in order for us to have adequate time to review it prior to sending it to the committee before the deadline of October 5, 2002. The briefing package should include a detailed summary of the critical information in support of the claim, and in addition, it should address the concerns about study ABA 451 that we have raised in this letter.

In addition, it will be necessary for you to submit revised draft labeling (see attached) with all previous revisions as reflected in the most recently approved labeling included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CLOZARIL®

(clozapine) Tablets

Rx only

Prescribing Information

Before prescribing Clozaril® (clozapine), the physician should be thoroughly familiar with the details of this prescribing information.

WARNING

1. AGRANULOCYTOSIS

[We have modified the new claim to focus on what has actually been demonstrated, i.e., a reduction in the risk of emergent suicidal behavior, and not the treatment of active suicidal behavior.]

BECAUSE OF A SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT, **CLOZARIL® (CLOZAPINE)** SHOULD BE RESERVED FOR USE IN **(1) THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WITH SCHIZOPHRENIA WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, OR (2) FOR REDUCING THE RISK OF EMERGENT SUICIDAL BEHAVIOR THE TREATMENT OF SUICIDALITY IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHO ARE JUDGED TO BE AT RISK OF EXPERIENCING SUICIDAL BEHAVIOR. -H-**

PATIENTS BEING TREATED WITH CLOZAPINE MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT AS WELL AS REGULAR WBC COUNTS DURING TREATMENT AND FOR 4 WEEKS AFTER DISCONTINUATION OF TREATMENT.

CLOZAPINE IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WBC COUNTS ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION. (SEE WARNINGS)

2. SEIZURES

SEIZURES HAVE BEEN ASSOCIATED WITH THE USE OF CLOZAPINE. DOSE APPEARS TO BE AN IMPORTANT PREDICTOR OF SEIZURE, WITH A GREATER LIKELIHOOD AT HIGHER CLOZAPINE DOSES. CAUTION SHOULD BE USED WHEN ADMINISTERING CLOZAPINE TO PATIENTS HAVING A HISTORY OF SEIZURES OR OTHER PREDISPOSING FACTORS. PATIENTS SHOULD BE ADVISED NOT TO

ENGAGE IN ANY ACTIVITY WHERE SUDDEN LOSS OF CONSCIOUSNESS COULD CAUSE SERIOUS RISK TO THEMSELVES OR OTHERS. (SEE WARNINGS)

3. MYOCARDITIS

ANALYSES OF POSTMARKETING SAFETY DATABASES SUGGEST THAT CLOZAPINE IS ASSOCIATED WITH AN INCREASED RISK OF FATAL MYOCARDITIS, ESPECIALLY DURING, BUT NOT LIMITED TO, THE FIRST MONTH OF THERAPY. IN PATIENTS IN WHOM MYOCARDITIS IS SUSPECTED, CLOZAPINE TREATMENT SHOULD BE PROMPTLY DISCONTINUED. (SEE WARNINGS)

4. OTHER ADVERSE CARDIOVASCULAR AND RESPIRATORY EFFECTS

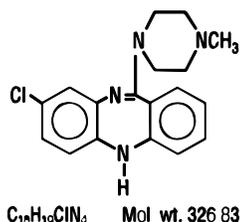
ORTHOSTATIC HYPOTENSION, WITH OR WITHOUT SYNCOPE, CAN OCCUR WITH CLOZAPINE TREATMENT. RARELY, COLLAPSE CAN BE PROFOUND AND BE ACCOMPANIED BY RESPIRATORY AND/OR CARDIAC ARREST. ORTHOSTATIC HYPOTENSION IS MORE LIKELY TO OCCUR DURING INITIAL TITRATION IN ASSOCIATION WITH RAPID DOSE ESCALATION. IN PATIENTS WHO HAVE HAD EVEN A BRIEF INTERVAL OFF CLOZAPINE, i.e., 2 OR MORE DAYS SINCE THE LAST DOSE, TREATMENT SHOULD BE STARTED WITH 12.5 mg ONCE OR TWICE DAILY. (SEE WARNINGS and DOSAGE AND ADMINISTRATION)

SINCE COLLAPSE, RESPIRATORY ARREST AND CARDIAC ARREST DURING INITIAL TREATMENT HAS OCCURRED IN PATIENTS WHO WERE BEING ADMINISTERED BENZODIAZEPINES OR OTHER PSYCHOTROPIC DRUGS, CAUTION IS ADVISED WHEN CLOZAPINE IS INITIATED IN PATIENTS TAKING A BENZODIAZEPINE OR ANY OTHER PSYCHOTROPIC DRUG. (SEE WARNINGS)

DESCRIPTION

CLOZARIL[®] (clozapine), an atypical antipsychotic drug, is a tricyclic dibenzodiazepine derivative, 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo [b,e] [1,4] diazepine.

The structural formula is:



CLOZARIL[®] (clozapine) is available in pale yellow tablets of 25 mg and 100 mg for oral administration.

25 mg and 100 mg Tablets

Active Ingredient: clozapine is a yellow, crystalline powder, very slightly soluble in water.

Inactive Ingredients: colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch (corn), and talc.

CLINICAL PHARMACOLOGY

Pharmacodynamics

CLOZARIL[®] (clozapine) is classified as an 'atypical' antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine mediated behaviors differ from those exhibited by more typical antipsychotic drug products. In particular, although CLOZARIL[®] (clozapine) does interfere with the binding of dopamine at D₁, D₂, D₃ and D₅ receptors, and has a high affinity for the D₄ receptor, it does not induce catalepsy nor inhibit apomorphine-induced stereotypy. This evidence, consistent with the view that CLOZARIL[®] (clozapine) is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of CLOZARIL[®] (clozapine) from extrapyramidal side effects.

CLOZARIL[®] (clozapine) also acts as an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors.

Absorption, Distribution, Metabolism and Excretion

In man, CLOZARIL[®] (clozapine) tablets (25 mg and 100 mg) are equally bioavailable relative to a clozapine solution. Following a dosage of 100 mg b.i.d., the average steady state peak plasma concentration was 319 ng/mL (range: 102-771 ng/mL), occurring at the average of 2.5 hours (range: 1-6 hours) after dosing. The average minimum concentration at steady state was 122 ng/mL (range: 41-343 ng/mL), after 100 mg b.i.d. dosing. Food does not appear to affect the systemic bioavailability of CLOZARIL[®] (clozapine). Thus, CLOZARIL[®] (clozapine) may be administered with or without food.

Clozapine is approximately 97% bound to serum proteins. The interaction between CLOZARIL[®] (clozapine) and other highly protein-bound drugs has not been fully evaluated but may be important. (*See PRECAUTIONS*)

Clozapine is almost completely metabolized prior to excretion and only trace amounts of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The demethylated, hydroxylated and N-oxide derivatives are components in both urine and feces. Pharmacological testing has shown the desmethyl metabolite to have only limited activity, while the hydroxylated and N-oxide derivatives were inactive.

The mean elimination half-life of clozapine after a single 75 mg dose was 8 hours (range: 4-12 hours), compared to a mean elimination half-life, after achieving steady state with 100 mg b.i.d. dosing, of 12 hours (range: 4-66 hours). A comparison of single-dose and multiple-dose administration of clozapine showed that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration dependent pharmacokinetics. However, at steady state, linearly dose-proportional changes with respect to AUC (area under the curve), peak and minimum clozapine plasma concentrations were observed after administration of 37.5 mg, 75 mg, and 150 mg b.i.d.

Human Pharmacology

In contrast to more typical antipsychotic drugs, CLOZARIL[®] (clozapine) therapy produces little or no prolactin elevation.

As is true of more typical antipsychotic drugs, clinical EEG studies have shown that CLOZARIL[®] (clozapine) increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs, and sharp wave activity and spike and wave complexes may also develop. Patients, on rare occasions, may report an intensification of dream activity during CLOZARIL[®] (clozapine) therapy. REM sleep was found to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.

[We have made a number of changes to this section:

-We have limited the new language to information we consider useful to prescribers.

-We have deleted all reference to outcomes not specified as primary.

-We have focused the claim on what was actually shown.

-We have mentioned the extensive use of concomitant psychotropics.]

Clinical Trial Data (Reducing the Risk of Emergent Suicidal Behavior in Patients with Schizophrenia or Schizoaffective Disorder Who are Judged to be at Risk of Experiencing Suicidal Behavior)Suicidality)

The effectiveness of CLOZARIL[®] (clozapine) in reducing the risk of ~~emergent suicidal behaviors~~suicide was assessed in the International Suicide Prevention Study (InterSePT study), ~~Study ABA 451,~~ which was a prospective, randomized, international, parallel-group comparison of CLOZARIL vs. Zyprexa[®] (olanzapine) ~~in the reduction of suicidality (See INDICATIONS)~~ in patients with schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be ~~at risk for emergent suicidal behaviors~~suicide. About 25% of these patients were considered resistant to standard antipsychotic drug treatment, and the remainder were not. ~~Males or females diagnosed with schizophrenia or schizoaffective disorder using DSM IV criteria and who were deemed at high risk for suicidal behaviors~~suicide were included in the trial [1]. ~~Patients met one of the following criteria that put them at high risk for suicidality:~~

- They had attempted suicide within the 3 years prior to their baseline evaluation.
- They had been hospitalized to prevent a suicide attempt within the 3 years prior to their baseline evaluation.
- They demonstrated moderate to severe suicidal ideation with a depressive component within 1 week prior to their baseline evaluation.
- They demonstrated moderate to severe suicidal ideation accompanied by command hallucinations to do self harm within 1 week prior to their baseline evaluation.

Dosing regimens for each treatment group were determined by individual investigators and were individualized by patient. Dosing was flexible, with a dose range of 200 to 900 mg/day for Clozaril and 5 to 20 mg/day for Zyprexa. For the 956 patients who received Clozaril or Zyprexa in this study, there was extensive use of concomitant psychotropics: 84% with antipsychotics; 65% with anxiolytics; 53% with antidepressants; and 28% with mood stabilizers.

The primary efficacy measure was time to (1) a significant suicide attempt, including a completed suicide, confirmed by the Suicide Monitoring Board (SMB, a blinded group of experts responsible for the final determination of a significant suicide attempt), (2) hospitalization due to imminent suicide risk (including increased level of surveillance for suicidality for patients already hospitalized), confirmed by the SMB, or (3) worsening of suicidality severity as demonstrated by “much worsening” or “very much worsening” from baseline in the Clinical Global Impression of Severity of Suicidality-Blinded Psychiatrist (CGI-SS-BP) scale. A determination of whether or not a reported event met criteria 1 or 2 above was made by the Suicide Monitoring Board (SMB, a blinded group of experts).

A total of 980 patients were randomized to the study and 956 received study medication. Sixty-two percent of the patients were diagnosed with schizophrenia and the remainder (38%) were diagnosed with schizoaffective disorder. Only about one-fourth of the total patient population (27%) was identified as “treatment resistant” at baseline. There were more males than females in the study (61% of all patients were male). The mean age of patients entering the study was 37 years (range 18-69). Most patients were Caucasian (71%), 15% were Black, 1% were Oriental, and 13% were classified as being of “other” races.

Data from this study indicate that Clozaril had a statistically significantly longer delay in the time to emergent suicidal behavior in comparison with Zyprexa. olanzapine, CLOZARIL reduced the risk of suicidality (as measured by suicide attempts and hospitalizations to prevent suicide) by 25% over a 2 year period. This beneficial effect is supported by a reduction in both the overall number of events and the number of recorded interventions necessary to prevent suicide, including the use of antidepressants and anxiolytics as concomitant medications.

These results are supported by analyses of the primary outcome measures and by numerous supportive analyses indicating that these effects occur at doses widely used clinically. In addition, a reduction in health care costs may be observed through a reduction in hospitalizations and the need for other interventions to prevent suicide.

Hazard ratios derived from the primary endpoint analysis indicate superiority of Clozaril over olanzapine (see table below).

Clozaril Study ABA 451—Primary analysis: Multiple event analysis of time to first occurrence of Type 1 and Type 2 events (ITT population)

<u>Event Type</u>	<u>Coefficient of Treatment Effect (Beta¹) (SE)</u>	<u>p-value</u>	<u>Hazard Ratio¹</u>	<u>95% C.I. for Hazard Ratio</u>
² Type 1	<u>-0.280 (0.130)</u>	<u>0.0316</u>	<u>0.76</u>	<u>0.58, 0.98</u>
³ Type 2	<u>-0.250 (0.121)</u>	<u>0.0388</u>	<u>0.78</u>	<u>0.61, 0.99</u>
⁴ Combined	<u>-0.265 (0.123)</u>	<u>0.0309</u>	<u>=</u>	<u>=</u>

¹ Beta < 0 and hazard ratio < 1 indicate superiority of Clozaril over olanzapine.

² Type 1 event = a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance), confirmed by SMB.

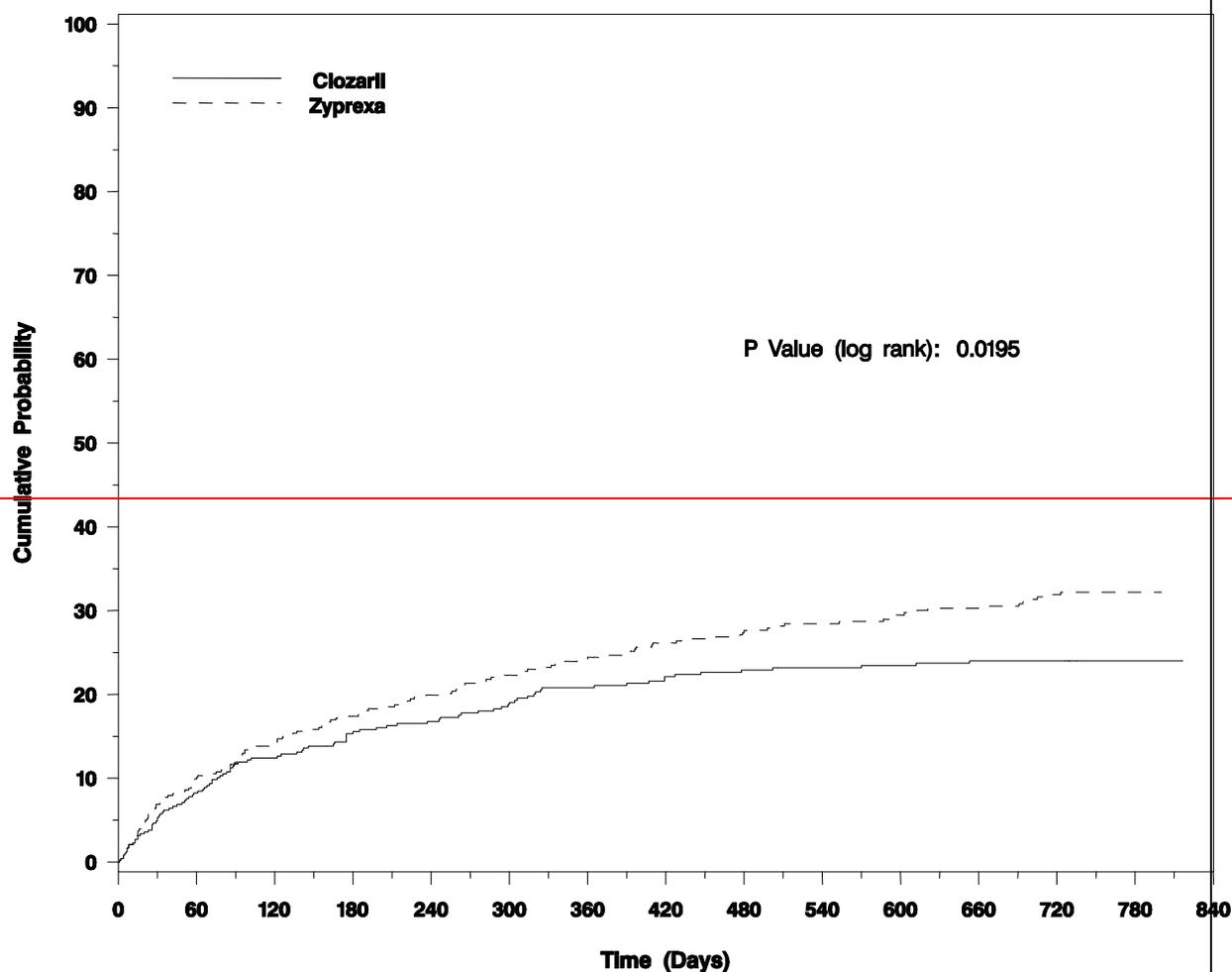
³ Type 2 event = worsening of suicidality severity as demonstrated by “much worsening” or “very much worsening” from baseline in the Clinical Global Impression of Severity of Suicidality-Blinded Psychiatrist (CGI-SS-BP) scale, or by implicit worsening of suicidality severity as demonstrated by occurrence of a Type 1 event.

⁴ The statistical methodology utilized to analysis the primary endpoint for this study was the Wei, Lin, and Weissfeld method with ‘c’ fixed at 0.5

As shown in the figure below, the probability (standard error) of experiencing (1) a significant suicide attempt, including a completed suicide, or (2) hospitalization due to imminent suicide risk (including increased level of surveillance for suicidality for patients already hospitalized) Type 1 event was lower for CLOZARIL patients than for Zyprexaolanzapine patients at all visits. The CLOZARIL treatment group demonstrated significantly lower probability of a Type 1 event at Week 104: than the olanzapine treatment group (Clozaril 24% vs. Zyprexa 32%; 95% C.I. of the difference: 2%, 14%).

Similarly, the probability (standard error) of experiencing a Type 2 event was lower for CLOZARIL patients than for olanzapine patients at all visits. The CLOZARIL treatment group demonstrated a significantly lower probability for a Type 2 event at Week 104 than the olanzapine treatment group (CLOZARIL 28% vs. olanzapine 37%; 95% C.I. of the difference: 2%, 15%).

Kaplan-Meier estimates for cumulative probability of Suicide Attempt or Hospitalization to Prevent Suicide as determined by the Suicide Monitoring Board



INDICATIONS AND USAGE

Treatment Resistant Schizophrenia

CLOZARIL[®] (clozapine) is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Because of the significant risk of agranulocytosis and seizure associated with its use, CLOZARIL[®] (clozapine) should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard drug, treatments for schizophrenia either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. (See *WARNINGS*)

The effectiveness of CLOZARIL[®] (clozapine) in a treatment resistant schizophrenic population was demonstrated in a 6-week study comparing CLOZARIL[®] (clozapine) and chlorpromazine. Patients meeting DSM-III criteria for schizophrenia and having a mean BPRS total score of 61 were demonstrated to be treatment resistant by history and by open, prospective treatment with haloperidol before entering into the double-blind phase of the study. The

superiority of CLOZARIL[®] (clozapine) to chlorpromazine was documented in statistical analyses employing both categorical and continuous measures of treatment effect.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated.

[We have modified the claim to focus on what was actually shown.]

Reduction in the Risk of Emergent Suicidal Behavior in Schizophrenia and Schizoaffective Disorder

CLOZARIL is indicated for reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for emergent suicidal behavior, based on history and recent clinical state (see Clinical Trials Data, under Clinical Pharmacology). ~~the treatment of suicidality in patients with schizophrenia or schizoaffective disorder, where suicidality—Suicidal behavior refers to is defined as actions by a patient committed either with willful intent or as a response to internal compulsions or disordered thinking that put him/herself at high risk for death—H.~~

CONTRAINDICATIONS

CLOZARIL[®] (clozapine) is contraindicated in patients with a previous hypersensitivity to clozapine or any other component of this drug, in patients with myeloproliferative disorders, uncontrolled epilepsy, or a history of CLOZARIL[®] (clozapine) induced agranulocytosis or severe granulocytopenia. As with more typical antipsychotic drugs, CLOZARIL[®] (clozapine) is contraindicated in severe central nervous system depression or comatose states from any cause.

CLOZARIL[®] (clozapine) should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The mechanism of CLOZARIL[®] (clozapine) induced agranulocytosis is unknown; nonetheless, it is possible that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression.

WARNINGS

General

[We have modified the language to focus on what was actually shown.]

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (*SEE FOLLOWING*), CLOZARIL[®] (clozapine) SHOULD BE RESERVED FOR USE (1) IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD DRUG TREATMENT FOR SCHIZOPHRENIA, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS, —OR (2) FOR REDUCING THE RISK OF EMERGENT SUICIDAL BEHAVIOR IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHO ARE JUDGED TO BE AT RISK OF EXPERIENCING SUICIDAL BEHAVIOR~~THE TREATMENT OF SUICIDALITY IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER—H.~~ CONSEQUENTLY, UNLESS THE PATIENT IS AT HIGH RISK FOR EMERGENT SUICIDAL BEHAVIOR/SUICIDE, BEFORE INITIATING TREATMENT WITH CLOZARIL[®] (clozapine), IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST 2 TRIALS, EACH WITH A DIFFERENT STANDARD

DRUG PRODUCT FOR SCHIZOPHRENIA, AT AN ADEQUATE DOSE, AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZARIL® (clozapine) MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK FOR THE FIRST SIX MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS (WBC greater than or equal to 3,000/mm³, ANC \geq 1500/mm³) HAVE BEEN MAINTAINED DURING THE FIRST 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNTS CAN BE MONITORED EVERY OTHER WEEK. WBC COUNTS MUST BE MONITORED WEEKLY FOR AT LEAST 4 WEEKS AFTER THE DISCONTINUATION OF CLOZARIL® (clozapine).

CLOZARIL® (clozapine) IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WBC COUNTS ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION.

Agranulocytosis

Agranulocytosis, defined as an absolute neutrophil count (ANC) of less than 500/mm³, has been estimated to occur in association with CLOZARIL® (clozapine) use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 US cases out of 1743 patients exposed to CLOZARIL® (clozapine) during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported worldwide in association with CLOZARIL® (clozapine) use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL® (clozapine) induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL® (clozapine) induced agranulocytosis, despite strict adherence to the required frequency of monitoring. In the U.S., under a weekly WBC monitoring system with CLOZARIL® (clozapine), there have been 585 cases of agranulocytosis as of August 21, 1997; 19 were fatal. During this period 150,409 patients received CLOZARIL® (clozapine). A hematologic risk analysis was conducted based upon the available information in the Clozaril® National Registry (CNR) for U.S. patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule, rose steeply during the first two months of therapy, peaking in the third month. Among Clozaril® (clozapine) patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree, so that by the sixth month the weekly incidence of agranulocytosis was reduced to 3 per 1000 person-years. After six months, the weekly incidence of agranulocytosis declines still further, however, never reaches zero. It should be noted that any type of reduction in the frequency of monitoring WBC counts may result in an increase incidence of agranulocytosis.

Because of the substantial risk for developing agranulocytosis in association with CLOZARIL® (clozapine) use, which may persist over an extended period of time, patients must have a blood sample drawn for a WBC count before initiation of treatment with CLOZARIL® (clozapine), and must have subsequent WBC counts done at least weekly for the first 6 months of continuous treatment. If WBC counts remain acceptable (WBC greater than or equal to 3000/mm³, ANC \geq 1500/mm³) during this period, WBC counts may be monitored every other week thereafter. After the discontinuation of Clozaril® (clozapine), weekly WBC counts should be continued for an additional 4 weeks.

If a patient is on Clozaril® (clozapine) therapy for less than 6 months with no abnormal blood events and there is a break on therapy which is less than or equal to 1 month, then patients can continue where they left off with weekly WBC testing for 6 months. When this 6 month period has been completed, the frequency of WBC count monitoring can be reduced to every other week. If a patient is on Clozaril (clozapine) therapy for less than 6 months with no abnormal blood events and there is a break on therapy which is greater than 1 month, then patients should be tested weekly for an additional 6 month period before biweekly testing is initiated. If a patient is on Clozaril® (clozapine) therapy for less than 6 months and experiences an abnormal blood event as described below but remains a rechallengeable patient

[patients cannot be reinitiated on Clozaril® (clozapine) therapy if WBC counts fall below 2000/mm³, or the ANC falls below 1000/mm³ during Clozaril® (clozapine) therapy], the patient must re-start the 6 month period of weekly WBC monitoring at day 0.

If a patient is on Clozaril® (clozapine) therapy for 6 months or longer with no abnormal blood events and there is a break on therapy which is 1 year or less, then the patient can continue WBC count monitoring every other week if Clozaril® (clozapine) therapy is reinitiated. If a patient is on Clozaril® (clozapine) therapy for 6 months or longer with no abnormal blood events and there is a break on therapy which is greater than 1 year, then, if Clozaril® (clozapine) therapy is reinitiated, the patient must have WBC counts monitored weekly for an additional 6 months. If a patient is on Clozaril® (clozapine) therapy for 6 months or longer and subsequently has an abnormal blood event, but remains a rechallengeable patient, then the patient must re-start weekly WBC count monitoring until an additional 6 months of Clozaril® (clozapine) therapy has been received. The distribution of Clozaril® (clozapine) is contingent upon performance of the required blood tests.

Treatment should not be initiated if the WBC count is less than 3500/mm³, or if the patient has a history of a myeloproliferative disorder, or previous CLOZARIL® (clozapine) induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initial treatment, the total WBC count has dropped below 3500/mm³ or it has dropped by a substantial amount from baseline, even if the count is above 3500/mm³, or if immature forms are present, a repeat WBC count and a differential count should be done. A substantial drop is defined as a single drop of 3,000 or more in the WBC count or a cumulative drop of 3,000 or more within 3 weeks. If subsequent WBC counts and the differential count reveal a total WBC count between 3000 and 3500/mm³ and an ANC above 1500/mm³, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000/mm³, or the ANC below 1500/mm³, CLOZARIL® (clozapine) therapy should be interrupted, WBC count and differential should be performed daily, and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL® (clozapine) therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000/mm³ and the ANC returns to levels above 1500/mm³. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500/mm³.

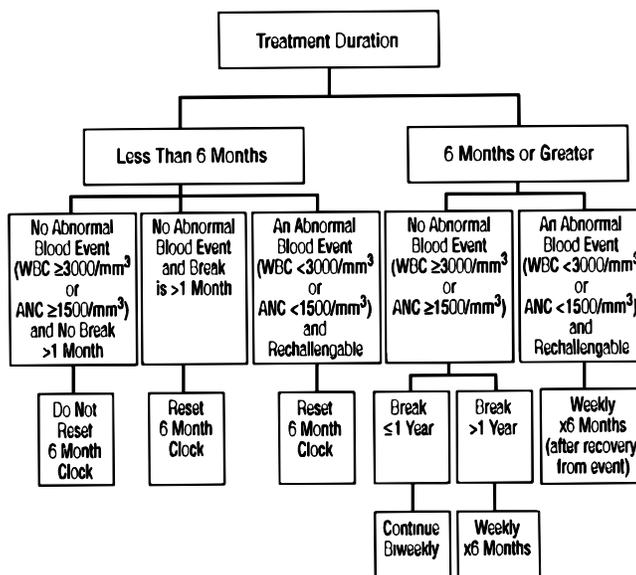
If the total WBC count falls below 2000/mm³ or the ANC falls below 1000/mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000/mm³, or ANCs below 1000/mm³ during CLOZARIL® (clozapine) therapy should have daily WBC count and differential. These patients should not be re-challenged with CLOZARIL® (clozapine). Patients discontinued from CLOZARIL® (clozapine) therapy due to significant WBC suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on re-exposure. To reduce the chances of rechallenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL® (clozapine) therapy, a single, national master file will be maintained confidentially.

Except for evidence of significant bone marrow suppression during initial CLOZARIL® (clozapine) therapy, there are no established risk factors, based on world-wide experience, for the development of agranulocytosis in association with CLOZARIL® (clozapine) use. However, a disproportionate number of the US cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during domestic development of CLOZARIL® (clozapine). Most of the US cases occurred within 4-10 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with CLOZARIL® (clozapine) use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with CLOZARIL® (clozapine).

To reduce the risk of agranulocytosis developing undetected, CLOZARIL® (clozapine) is available only through a distribution system that ensures monitoring of WBC counts according to the schedule described above prior to delivery of the next supply of medication.

**Interrupted Therapy (WBC < 3000/mm³
ANC < 1500/mm³) for Bi-Weekly Monitoring**



Eosinophilia

In clinical trials, 1% of patients developed eosinophilia, which, in rare cases, can be substantial. If a differential count reveals a total eosinophil count above 4,000/mm³, CLOZARIL® (clozapine) therapy should be interrupted until the eosinophil count falls below 3,000/mm³.

Seizures

Seizure has been estimated to occur in association with CLOZARIL® (clozapine) use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to CLOZARIL® (clozapine) during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher CLOZARIL® (clozapine) doses used.

Caution should be used in administering CLOZARIL® (clozapine) to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with CLOZARIL® (clozapine) use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Myocarditis

Post-marketing surveillance data from four countries that employ hematological monitoring of clozapine-treated patients revealed: 30 reports of myocarditis with 17 fatalities in 205,493 U.S. patients (August 2001); 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (April 2001); 30 reports of myocarditis with 8 fatalities in 24,108 U.K. patients (August 2001); 15 reports of myocarditis with 5 fatalities in 8,000 Australian patients (March 1999). These reports represent an incidence of 5.0, 16.3, 43.2, and 96.6 cases/100,000 patient years, respectively. The number of fatalities represent an incidence of 2.8, 2.3, 11.5, and 32.2 cases/100,000 patient years, respectively.

The overall incidence rate of myocarditis in patients with schizophrenia treated with antipsychotic agents is unknown. However, for the established market economies (WHO), the incidence of myocarditis is 0.3 cases/100,000 patient years and the fatality rate is 0.2 cases/100,000 patient years. Therefore, the rate of myocarditis in clozapine treated patients appears to be 17-322 times greater than the general population and is associated with an increased risk of fatal myocarditis that is 14-161 times greater than the general population.

The total reports of myocarditis for these four countries was 82 of which 51 (62%) occurred within the first month of clozapine treatment, 25 (31%) occurred after the first month of therapy and 6 (7%) were unknown. The median duration of treatment was 3 weeks. Of 5 patients rechallenged with clozapine, 3 had a recurrence of myocarditis. Of the 82 reports, 31 (38%) were fatal and 25 patients who died had evidence of myocarditis at autopsy. These data also suggest that the incidence of fatal myocarditis may be highest during the first month of therapy.

Therefore, the possibility of myocarditis should be considered in patients receiving Clozaril (clozapine) who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST- T wave abnormalities or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. Tachycardia, which has been associated with Clozaril (Clozapine) treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis.

Prompt discontinuation of Clozaril (clozapine) treatment is warranted upon suspicion of myocarditis. Patients with clozapine-related myocarditis should not be rechallenged with Clozaril (clozapine).

Other Adverse Cardiovascular and Respiratory Effects

Orthostatic hypotension with or without syncope can occur with CLOZARIL® (clozapine) treatment and may represent a continuing risk in some patients. Rarely (approximately 1 case per 3,000 patients), collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. When restarting patients who have had even a brief interval of CLOZARIL® (clozapine), i.e., 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25 mg tablet (12.5 mg) once or twice daily (*see DOSAGE AND ADMINISTRATION*).

Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even CLOZARIL® (clozapine) by itself. Although it has not been established that there is an interaction between CLOZARIL® (clozapine) and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking CLOZARIL® (clozapine), with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.

A minority of CLOZARIL® (clozapine) treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL® (clozapine). The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL® (clozapine), several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, arrhythmias and sudden death. In addition there have been postmarketing reports of congestive heart failure. Causality assessment was difficult in many of

these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown.

CLOZARIL[®] (clozapine) should be used with caution in patients with known cardiovascular and/or pulmonary disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

There have been several reported cases of NMS in patients receiving CLOZARIL[®] (clozapine) alone or in combination with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that CLOZARIL[®] (clozapine) may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. A few cases of tardive dyskinesia have been reported in patients on CLOZARIL[®] (clozapine) who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to CLOZARIL[®] (clozapine) alone. Nevertheless, it cannot be concluded, without more extended experience, that CLOZARIL[®] (clozapine) is incapable of inducing this syndrome.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptom suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, CLOZARIL[®] (clozapine) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic CLOZARIL[®] (clozapine)

use should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on CLOZARIL[®] (clozapine), drug discontinuation should be considered. However, some patients may require treatment with CLOZARIL[®] (clozapine) despite the presence of the syndrome.

PRECAUTIONS

General

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. Although it is not known whether the risk would be increased, it is prudent either to avoid CLOZARIL[®] (clozapine) or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.

Fever

During CLOZARIL[®] (clozapine) therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first 3 weeks of treatment. While this fever is generally benign and self limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of Neuroleptic Malignant Syndrome (NMS) must be considered. There have been several reports of NMS in patients receiving CLOZARIL[®] (clozapine), usually in combination with lithium or other CNS-active drugs. [See *Neuroleptic Malignant Syndrome (NMS)*, under *WARNINGS*]

Pulmonary Embolism

The possibility of pulmonary embolism should be considered in patients receiving CLOZARIL[®] (clozapine) who present with deep vein thrombosis, acute dyspnea, chest pain or with other respiratory signs and symptoms. As of December 31, 1993 there were 18 cases of fatal pulmonary embolism in association with CLOZARIL[®] (clozapine) therapy in users 10-54 years of age. Based upon the extent of use observed in the Clozaril National Registry, the mortality rate associated with pulmonary embolus was 1 death per 3450 person-years of use. This rate was about 27.5 times higher than that in the general population of a similar age and gender (95% Confidence Interval; 17.1,42.2). Deep vein thrombosis has also been observed in association with CLOZARIL[®] (clozapine) therapy. Whether pulmonary embolus can be attributed to CLOZARIL[®] (clozapine) or some characteristic(s) of its users is not clear, but the occurrence of deep vein thrombosis or respiratory symptomatology should suggest its presence.

Hyperglycemia

Severe hyperglycemia, sometimes leading to ketoacidosis, has been reported during CLOZARIL[®] (clozapine) treatment in patients with no prior history of hyperglycemia. While a causal relationship to CLOZARIL[®] (clozapine) use has not been definitively established, glucose levels normalized in most patients after discontinuation of CLOZARIL[®] (clozapine), and a rechallenge in one patient produced a recurrence of hyperglycemia. The effect of CLOZARIL[®] (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 CLOZARIL[®] (clozapine) who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycemia, the discontinuation of CLOZARIL[®] (clozapine) should be considered.

Hepatitis

Caution is advised in patients using CLOZARIL® (clozapine) who have concurrent 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 CLOZARIL® (clozapine) treatment, liver function tests should be performed immediately. If the elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with CLOZARIL® (clozapine) should be discontinued.

Anticholinergic Toxicity

Eye

CLOZARIL® (clozapine) has potent anticholinergic effects and care should be exercised in using this drug in the presence of narrow angle glaucoma.

Gastrointestinal

CLOZARIL® (clozapine) use has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction and paralytic ileus (*see ADVERSE REACTIONS*). On rare occasions, these cases have been fatal. Constipation should be initially treated by ensuring adequate hydration, and use of ancillary therapy such as bulk laxatives. Consultation with a gastroenterologist is advisable in more serious cases.

Prostate

CLOZARIL® (clozapine) has potent anticholinergic effects and care should be exercised in using this drug in the presence of prostatic enlargement.

Interference with Cognitive and Motor Performance

Because of initial sedation, CLOZARIL® (clozapine) may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness.

Use in Patients with Concomitant Illness

Clinical experience with CLOZARIL® (clozapine) in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using CLOZARIL® (clozapine) in patients with renal or cardiac disease.

Use in Patients Undergoing General Anesthesia

Caution is advised in patients being administered general anesthesia because of the CNS effects of CLOZARIL® (clozapine). Check with the anesthesiologist regarding continuation of CLOZARIL® (clozapine) therapy in a patient scheduled for surgery.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe CLOZARIL® (clozapine):

- Patients who are to receive CLOZARIL® (clozapine) should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required for the first 6 months, if acceptable WBC counts (WBC greater than or equal to $3000/\text{mm}^3$, ANC $\geq 1500/\text{mm}^3$) have been maintained during the first 6 months of continuous therapy, then WBC counts can be monitored every other week in order to monitor for the occurrence of agranulocytosis, and that CLOZARIL® (clozapine) tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.

- Patients should be informed of the significant risk of seizure during CLOZARIL[®] (clozapine) treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL[®] (clozapine).
- Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.
- Patients should be informed that if they stop taking CLOZARIL[®] (clozapine) for more than 2 days, they should not restart their medication at the same dosage, but should contact their physician for dosing instructions.
- Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol.
- Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should not breast feed an infant if they are taking CLOZARIL[®] (clozapine).

Drug Interactions

The risks of using CLOZARIL[®] (clozapine) in combination with other drugs have not been systematically evaluated.

Pharmacodynamic-related interactions

The mechanism of CLOZARIL[®] (clozapine) induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, CLOZARIL[®] (clozapine) should not be used with other agents having a well-known potential to suppress bone marrow function.

Given the primary CNS effects of CLOZARIL[®] (clozapine), caution is advised in using it concomitantly with other CNS-active drugs or alcohol.

Orthostatic hypotension in patients taking clozapine can, in rare cases (approximately 1 case per 3,000 patients), be accompanied by profound collapse and respiratory and/or cardiac arrest. Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even CLOZARIL[®] (clozapine) by itself. Although it has not been established that there is an interaction between CLOZARIL[®] (clozapine) and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

CLOZARIL[®] (clozapine) may potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug induced hypotension because of a possible reverse epinephrine effect.

Pharmacokinetic-related interactions

Clozapine is a substrate for many CYP 450 isozymes, in particular 1A2, 2D6, and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimized. Nevertheless, caution should be used in patients receiving concomitant treatment with other drugs which are either inhibitors or inducers of these enzymes.

Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine. Phenytoin, nicotine, and rifampin may decrease CLOZARIL[®] (clozapine) plasma levels, resulting in a decrease in effectiveness of a previously effective CLOZARIL[®] (clozapine) dose.

Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine. Cimetidine, caffeine, and erythromycin may increase plasma levels of CLOZARIL[®] (clozapine), potentially resulting in adverse effects. Although concomitant use of CLOZARIL[®] (clozapine) and

carbamazepine is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in CLOZARIL[®] (clozapine) plasma levels.

In a study of schizophrenic patients who received clozapine under steady state conditions, fluvoxamine or paroxetine was added in 16 and 14 patients, respectively. After 14 days of co-administration, mean trough concentrations of clozapine and its metabolites, *N*-desmethylclozapine and clozapine *N*-oxide, were elevated with fluvoxamine by about three-fold compared to baseline concentrations. Paroxetine produced only minor changes in the levels of clozapine and its metabolites. However, other published reports describe modest elevations (less than two-fold) of clozapine and metabolite concentrations when clozapine was taken with paroxetine, fluoxetine, and sertraline. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when CLOZARIL[®] (clozapine) is combined with these drugs, particularly with fluvoxamine. A reduced CLOZARIL[®] (clozapine) dose should be considered.

A subset (3%-10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isozyme P450 2D6. Such individuals are referred to as “poor metabolizers” of drugs such as debrisoquin, dextromethorphan, the tricyclic antidepressants, and clozapine. These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. In addition, certain drugs that are metabolized by this isozyme, including many antidepressants (clozapine, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isozyme, and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction.

Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6 may require lower doses than usually prescribed for either clozapine or the other drug. Therefore, co-administration of clozapine with other drugs that are metabolized by this isozyme, including antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses approximately 7 times the typical human dose on a mg/kg basis. Fertility in male and female rats was not adversely affected by clozapine. Clozapine did not produce genotoxic or mutagenic effects when assayed in appropriate bacterial and mammalian tests.

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses of approximately 2-4 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

Nursing Mothers

Animal studies suggest that clozapine may be excreted in breast milk and have an effect on the nursing infant. Therefore, women receiving CLOZARIL[®] (clozapine) should not breast feed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical studies of clozapine did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

Orthostatic hypotension can occur with CLOZARIL[®] (clozapine) treatment and tachycardia, which may be sustained, has been observed in about 25% of patients taking CLOZARIL[®] (clozapine) (see WARNINGS, Adverse Cardiovascular and Respiratory Effects). Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.

Also, elderly patients may be particularly susceptible to the anticholinergic effects of CLOZARIL[®] (clozapine), such as urinary retention and constipation. (See PRECAUTIONS, Anticholinergic Toxicity)

Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Other reported clinical experience does suggest that the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women. (See WARNINGS, Tardive Dyskinesia)

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Sixteen percent of 1080 patients who received CLOZARIL[®] (clozapine) in premarketing clinical trials discontinued treatment due to an adverse event, including both those that could be reasonably attributed to CLOZARIL[®] (clozapine) treatment and those that might more appropriately be considered intercurrent illness. The more common events considered to be causes of discontinuation included: CNS, primarily drowsiness/sedation, seizures, dizziness/syncope; cardiovascular, primarily tachycardia, hypotension and ECG changes; gastrointestinal, primarily nausea/vomiting; hematologic, primarily leukopenia/granulocytopenia/agranulocytosis; and fever. None of the events enumerated accounts for more than 1.7% of all discontinuations attributed to adverse clinical events.

Commonly Observed

Adverse events observed in association with the use of CLOZARIL[®] (clozapine) in clinical trials at an incidence of greater than 5% were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

Incidence in Clinical Trials

The following table enumerates adverse events that occurred at a frequency of 1% or greater among CLOZARIL[®] (clozapine) patients who participated in clinical trials. These rates are not adjusted for duration of exposure.

Treatment-Emergent Adverse Experience Incidence

Among Patients Taking CLOZARIL[®] (clozapine) in Clinical Trials (excluding the InterSePT Study-ABA 451)

(N = 842)

(Percentage of Patients Reporting)

Body System Adverse Event ^a	Percent
Central Nervous System	
Drowsiness/Sedation	39
Dizziness/Vertigo	19
Headache	7
Tremor	6
Syncope	6

Disturbed sleep/Nightmares	4
Restlessness	4
Hypokinesia/Akinesia	4
Agitation	4
Seizures (convulsions)	3 ^b
Rigidity	3
Akathisia	3
Confusion	3
Fatigue	2
Insomnia	2
Hyperkinesia	1
Weakness	1
Lethargy	1
Ataxia	1
Slurred speech	1
Depression	1
Epileptiform movements/Myoclonic jerks	1
Anxiety	1
<hr/>	
Cardiovascular	
Tachycardia	25 ^b
Hypotension	9
Hypertension	4
Chest pain/Angina	1
ECG change/Cardiac abnormality	1
<hr/>	
Gastrointestinal	
Constipation	14
Nausea	5
Abdominal discomfort/Heartburn	4
Nausea/Vomiting	3
Vomiting	3
Diarrhea	2
Liver test abnormality	1
Anorexia	1
<hr/>	
Urogenital	
Urinary abnormalities	2
Incontinence	1
Abnormal ejaculation	1
Urinary urgency/frequency	1
Urinary retention	1
<hr/>	
Autonomic Nervous System	
Salivation	31
Sweating	6
Dry mouth	6

Visual disturbances	5
Integumentary (Skin)	
Rash	2
Musculoskeletal	
Muscle weakness	1
Pain (back, neck, legs)	1
Muscle spasm	1
Muscle pain, ache	1
Respiratory	
Throat discomfort	1
Dyspnea, shortness of breath	1
Nasal congestion	1
Hemic/Lymphatic	
Leukopenia/Decreased WBC/Neutropenia	3
Agranulocytosis	1 ^b
Eosinophilia	1
Miscellaneous	
Fever	5
Weight gain	4
Tongue numb/sore	1

^aEvents reported by at least 1% of CLOZARIL[®] (clozapine) patients are included.

^bRate based on population of approximately 1700 exposed during premarket clinical evaluation of CLOZARIL[®] (clozapine).

[We have slightly edited the following statement.]

[The following table enumerates adverse events that occurred at a frequency of 10% for either treatment group in patients who took at least 1 dose of study medication during their participation in ~~Study ABA 451 \(the InterSePT study\)~~, which was an adequate and well-controlled 2-year study evaluating the efficacy of CLOZARIL[®] \(clozapine\) relative to Zyprexa in reducing the risk of emergent suicidal behavior in patients with schizophrenia \(including schizoaffective disorder\). These rates are not adjusted for duration of exposure ~~11~~.](#)

[Please make the following changes to this table:

-Delete the p-value column.

-Delete the total AE row.

-Please change the format of the table to include the sample size only once under the drug heading, and then include only the percentages, rounded to whole numbers, in the columns.

-Delete the following terms that have no relevance to this table: anxiety; depression; psychotic disorder NOS; suicidal ideation; suicide attempt; hallucinations.

-Move to a footnote all events for which the risk ratio, Clozaril to Zyprexa, is in a range of 2/3 to 3/2.

-Add a footnote explaining the abbreviations NEC and NOS.1

Treatment-Emergent Adverse Experience Incidence¹
Among Patients Taking CLOZARIL[®] (clozapine) or Zyprexa[®] (olanzapine) in
Study ABA-451 (the InterSePT study)
(N = 956)
(Percentage of Patients Reporting)

<u>Patients Studied</u>	<u>Clozaril</u>	<u>Zyprexa</u>	<u>p-value</u>
Total no. of patients	479 (100.0)	477 (100.0)	
Total no. with any AE	443 (92.5)	450 (94.3)	0.2971
<u>Adverse Events</u>			
Salivary hypersecretion	229 (47.8)	28 (5.9)	0.0000 ²
Somnolence	220 (45.9)	118 (24.7)	0.0000 ²
Weight increased	150 (31.3)	265 (55.6)	0.0000 ²
Anxiety NEC	143 (29.9)	169 (35.4)	0.0729
Depression NEC	137 (28.6)	173 (36.3)	0.0128 ²
Dizziness (excluding vertigo)	129 (26.9)	59 (12.4)	0.0000 ²
Psychotic disorder NOS	126 (26.3)	146 (30.6)	0.1518
Suicidal ideation	125 (26.1)	153 (32.1)	0.0461 ²
Constipation	120 (25.1)	46 (9.6)	0.0000 ²
Insomnia NEC	96 (20.0)	155 (32.5)	0.0000 ²
Headache NOS	93 (19.4)	99 (20.8)	0.6286
Nausea	79 (16.5)	47 (9.9)	0.0029 ²
Vomiting NOS	79 (16.5)	42 (8.8)	0.0004 ²
Dyspepsia	66 (13.8)	40 (8.4)	0.0098 ²
Agitation	61 (12.7)	70 (14.7)	0.3985
Fatigue	59 (12.3)	43 (9.0)	0.1158
Influenza	59 (12.3)	59 (12.4)	1.0000
Nasopharyngitis	59 (12.3)	65 (13.6)	0.5647
Hallucinations—auditory	58 (12.1)	71 (14.9)	0.2194
Diarrhea NOS	53 (11.1)	53 (11.1)	1.0000
Back pain	47 (9.8)	51 (10.7)	0.6710
Cough	44 (9.2)	58 (12.2)	0.1435
Suicide attempt	37 (7.7)	66 (13.8)	0.0024 ²

¹AEs are listed by frequency in Clozaril group

²Statistically significant difference between treatments

Other Events Observed During the Premarketing Evaluation of CLOZARIL[®] (clozapine)

This section reports additional, less frequent adverse events which occurred among the patients taking CLOZARIL[®] (clozapine) in clinical trials. Various adverse events were reported as part of the total experience in these clinical studies; a causal relationship to CLOZARIL[®] (clozapine) treatment cannot be determined in the absence of appropriate controls in some of the studies. The table above enumerates adverse events that occurred at a frequency of at least 1% of patients treated with CLOZARIL[®] (clozapine). The list below includes all additional adverse experiences reported as being temporally associated with the use of the drug which occurred at a frequency less than 1%, enumerated by organ system.

Central Nervous System: loss of speech, amentia, tics, poor coordination, delusions/hallucinations, involuntary movement, stuttering, dysarthria, amnesia/memory loss, histrionic movements, libido increase or decrease, paranoia, shakiness, Parkinsonism, and irritability.

Cardiovascular System: edema, palpitations, phlebitis/thrombophlebitis, cyanosis, premature ventricular contraction, bradycardia, and nose bleed.

Gastrointestinal System: abdominal distention, gastroenteritis, rectal bleeding, nervous stomach, abnormal stools, hematemesis, gastric ulcer, bitter taste, and eructation.

Urogenital System: dysmenorrhea, impotence, breast pain/discomfort, and vaginal itch/infection.

Autonomic Nervous System: numbness, polydipsia, hot flashes, dry throat, and mydriasis.

Integumentary (Skin): pruritus, pallor, eczema, erythema, bruise, dermatitis, petechiae, and urticaria.

Musculoskeletal System: twitching and joint pain.

Respiratory System: coughing, pneumonia/pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, and sneezing.

Hemic and Lymphatic System: anemia and leukocytosis.

Miscellaneous: chills/chills with fever, malaise, appetite increase, ear disorder, hypothermia, eyelid disorder, bloodshot eyes, and nystagmus.

Postmarketing Clinical Experience

Postmarketing experience has shown an adverse experience profile similar to that presented above. Voluntary reports of adverse events temporally associated with CLOZARIL[®] (clozapine) not mentioned above that have been received since market introduction and that may have no causal relationship with the drug include the following:

Central Nervous System: delirium; EEG abnormal; exacerbation of psychosis; myoclonus; overdose; paresthesia; possible mild cataplexy; and status epilepticus.

Cardiovascular System: atrial or ventricular fibrillation and periorbital edema.

Gastrointestinal System: acute pancreatitis; dysphagia; fecal impaction; intestinal obstruction/paralytic ileus; and salivary gland swelling.

Hepatobiliary System: cholestasis; hepatitis; jaundice.

Hepatic System: cholestasis.

Urogenital System: acute interstitial nephritis and priapism.

Integumentary (Skin): hypersensitivity reactions: photosensitivity, vasculitis, erythema multiforme, and Stevens-Johnson Syndrome.

Musculoskeletal System: myasthenic syndrome and rhabdomyolysis.

Respiratory System: aspiration and pleural effusion.

Hemic and Lymphatic System: deep vein thrombosis; elevated hemoglobin/hematocrit; ESR increased; pulmonary embolism; sepsis; thrombocytosis; and thrombocytopenia.

Vision Disorders: narrow angle glaucoma

Miscellaneous: CPK elevation; hyperglycemia; hyperuricemia; hyponatremia; and weight loss.

DRUG ABUSE AND DEPENDENCE

Physical and psychological dependence have not been reported or observed in patients taking CLOZARIL® (clozapine).

OVERDOSAGE

Human Experience

The most commonly reported signs and symptoms associated with CLOZARIL® (clozapine) overdose are: altered states of consciousness, including drowsiness, delirium and coma; tachycardia; hypotension; respiratory depression or failure; hypersalivation. Aspiration pneumonia and cardiac arrhythmias have also been reported. Seizures have occurred in a minority of reported cases. Fatal overdoses have been reported with CLOZARIL® (clozapine), generally at doses above 2500 mg. There have also been reports of patients recovering from overdoses well in excess of 4 g.

Management of Overdose

Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdosage. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. Additional surveillance should be continued for several days because of the risk of delayed effects. Avoid epinephrine and derivatives when treating hypotension, and quinidine and procainamide when treating cardiac arrhythmia.

There are no specific antidotes for CLOZARIL® (clozapine). Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

In managing overdosage, the physician should consider the possibility of multiple drug involvement.

Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physicians' Desk Reference®.*

DOSAGE AND ADMINISTRATION

Treatment Resistant Schizophrenia

Upon initiation of CLOZARIL® (clozapine) therapy, up to a 1 week supply of additional CLOZARIL® (clozapine) tablets may be provided to the patient to be held for emergencies (e.g., weather, holidays).

Initial Treatment

It is recommended that treatment with CLOZARIL® (clozapine) begin with one-half of a 25 mg tablet (12.5 mg) once or twice daily and then be continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day by the end of 2 weeks. Subsequent dosage increments should be made no more than once or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

In the multicenter study that provides primary support for the effectiveness of CLOZARIL[®] (clozapine) in patients resistant to standard drug treatment for schizophrenia, patients were titrated during the first 2 weeks up to a maximum dose of 500 mg/day, on a t.i.d. basis, and were then dosed in a total daily dose range of 100-900 mg/day, on a t.i.d. basis thereafter, with clinical response and adverse effects as guides to correct dosing.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of CLOZARIL[®] (clozapine) in treatment resistant patients, the mean and median CLOZARIL[®] (clozapine) doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated. CLOZARIL[®] (clozapine) can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizures threshold in a dose-dependent manner and may induce myoclonic jerks or generalized seizures. These symptoms may be likely to occur with rapid dose increase and in patients with pre-existing epilepsy. In this case, the dose should be reduced and, if necessary, anticonvulsant treatment initiated {1-5, 16, 17}.

Dosing should not exceed 900 mg/day.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided.

Maintenance Treatment

While the maintenance effectiveness of CLOZARIL[®] (clozapine) in schizophrenia is still under study, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on CLOZARIL[®] (clozapine), but at the lowest level needed to maintain remission. Because of the significant risk associated with the use of CLOZARIL[®] (clozapine), patients should be periodically reassessed to determine the need for maintenance treatment.

Discontinuation of Treatment

In the event of planned termination of CLOZARIL[®] (clozapine) therapy, gradual reduction in dose is recommended over a 1-2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as headache, nausea, vomiting, and diarrhea {6-10}.

Reinitiation of Treatment in Patients Previously Discontinued

When restarting patients who have had even a brief interval off CLOZARIL[®] (clozapine), i.e., 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25 mg tablet (12.5 mg) once or twice daily (*see WARNINGS*). If that dose is well tolerated, it may be feasible to titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment. However, any patient who has previously experienced respiratory or cardiac arrest with initial dosing, but was then able to be successfully titrated to a therapeutic dose, should be re-titrated with extreme caution after even 24 hours of discontinuation.

Certain additional precautions seem prudent when reinitiating treatment. The mechanisms underlying CLOZARIL[®] (clozapine) induced adverse reactions are unknown. It is conceivable, however, that re-exposure of a patient might enhance the risk of an untoward event's occurrence and increase its severity. Such phenomena, for example, occur when immune mediated mechanisms are responsible. Consequently, during the reinitiation of treatment, additional caution is advised. Patients discontinued for WBC counts below 2000/mm³ or an ANC below 1000/mm³ must *not* be restarted on CLOZARIL[®] (clozapine). (*See WARNINGS*)

[-We have modified the language to focus on what was actually shown.

-In addition, we ask that you address the question of what advice to give prescribers about non-refractory patients who respond when given Clozaril, and whose suicidality resolves. Should they stay on Clozaril, or switch back to another antipsychotic, and what data are there to support whatever advice is given?]

Reducing the Risk of Suicidal Behavior in Schizophrenia and Schizoaffective Disorder Suicidality

The dosage and administration recommendations outlined above regarding the use of CLOZARIL in patients with treatment-resistant schizophrenia should also be followed when treating patients with schizophrenia or schizoaffective disorder at risk for emergent suicidal behaviore.

Study ABA 451 (InterSePT study)- The InterSePT study demonstrated the efficacy of CLOZARIL in the treatment of patients with schizophrenia or schizoaffective disorder at risk for suicide where the mean daily dose was 300 mg (range 12.5 to 900 mg) [1].

HOW SUPPLIED

CLOZARIL® (clozapine) is available as 25 mg and 100 mg round, pale-yellow, uncoated tablets with a facilitated score on one side.

CLOZARIL® (clozapine) Tablets

25 mg

Engraved with “CLOZARIL” once on the periphery of one side.
Engraved with a facilitated score and “25” once on the other side.

- Bottle of 100.....NDC 0078-0126-05
- Bottle of 500.....NDC 0078-0126-08
- Unit dose packages of 100: 2 x 5 strips, 10 blisters per stripNDC 0078-0126-06

100 mg

Engraved with “CLOZARIL” once on the periphery of one side.
Engraved with a facilitated score and “100” once on the other side.

- Bottle of 100..... NDC 0078-0127-05
- Bottle of 500.....NDC 0078-0127-08
- Unit dose packages of 100: 2 x 5 strips, 10 blisters per strip.....NDC 0078-0127-06

Store and Dispense

Storage temperature should not exceed 86°F (30°C). Drug dispensing should not ordinarily exceed a weekly supply. If a patient is eligible for WBC testing every other week, then a two week supply of CLOZARIL® (clozapine) can be dispensed. Dispensing should be contingent upon the results of a WBC count.

*Trademark of Medical Economics Company, Inc.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2002-XX

REV: Month 2002

PRINTED IN USA

89004506

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References

1. ~~Clozaril. A prospective, randomized, international, parallel group comparison of Clozaril[®]/Leponex[®] vs. Zyprexa[®] in the reduction of suicidality in patients with schizophrenia or schizoaffective disorder who are at risk for suicide. Study ABA 451 Clinical Study Report. Novartis Pharmaceuticals Corporation. East Hanover, USA. Jan 2002.~~

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