CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

019758Orig1s034

Trade Name:	CLOZARIL
Generic or Proper Name:	(clozapine)
Sponsor:	Novartis
Approval Date:	March 3, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

019758Orig1s034

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	**X**
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019758Orig1s034

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-758 / SLR-034

Novartis Pharmaceuticals Corporation
Attention: Susan Witham
59 Route 10
East Hanover, NJ 07936-1080

MAR 3 1998

Dear Ms. Witham:

Please refer to your supplemental new drug application dated September 3 1997, received September 5, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clozaril (clozapine) 25mg and 100mg tablets.

Refer also to your submission (response to approvable letter) of January 14, 1998, received January 15, 1998, and to your fax of February 13, 1998, with agreed upon changes in the draft labeling. We also refer to your letter of February 13, 1998, regarding the issue of the requirement in clozapine labeling for a "distribution system that ensures (b) (4) (b) (4) supply of medication." We will respond to the approval of SLR-034 and to your February 13, 1998 inquiry separately.

SLR-034

The supplemental application provides for a decrease in the required white blood count (WBC) monitoring from weekly to biweekly after the first 6 months of continuous Clozaril therapy.

We have completed the review of this supplemental application, as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling submitted by fax on February 13, 1998. Accordingly, the supplemental application is approved effective on the date of this letter. We acknowledge that the implementation of these labeling changes will occur on or about March 10, 1998.

The final printed labeling (FPL) must be identical to the attached draft labeling which includes the minor changes as agreed upon in the teleconference of February 13, 1998.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 19-758 / SLR-034. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

February 13, 1998 Inquiry Regarding the Requirement in Clozapine Labeling for a Distribution System that Ensures (b) (4) Supply of Medication

(b) (4)

(b) (4)

(b) (4) You requested a teleconference to discuss this matter, and you asked that we delay a final decision on your supplement (SLR-034) until we had an opportunity to reconsider this matter.

We have decided not to delay action on SLR-034, since there has been no change in our policy regarding the general principle of a distribution system that ensures monitoring, but rather, only a change in the frequency of required monitoring after six months. For the same reason, we have opted to respond to your inquiry by letter, rather than granting a teleconference. If our response does not address your question, a teleconference is still a possibility.

The current language in labeling requiring that a distribution system be in place that will ensure WBC testing at a predefined frequency does not specify how compliance with such monitoring will be insured, but only that any sponsor for a clozapine product will accept this burden. There are undoubtedly many approaches to ensuring compliance with such monitoring and FDA does not presume that it knows the best approach. Your approach to ensuring compliance with monitoring appears to have been successful, and we applaud your decision to continue with your program. It is our understanding that OGD will have a similar expectation regarding the responsibility of generic manufacturers of clozapine to have some program in place that fulfills this requirement of labeling.

If you have any questions, please contact Steven D. Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Sincerely yours,

3/2/95

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

cc:
Original NDA 19-758
HFD-120/Div. files
HFD-100/Temple
HFD-120/CSO/Hardeman
HFD-120/Leber/Laughren/Dubitsky
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

2-26-98

SW 2/25/98

Drafted: 2/24/98
Final: 2/25/98

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019758Orig1s034

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-758 / S-034

Novartis Pharmaceuticals Corporation
Attention: Susan Witham
59 Route 10
East Hanover, NJ 07936-1080

NOV 25 1997

Dear Ms. Witham:

Please refer to your supplemental new drug application of September 3, 1997, received September 5, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clozaril (clozapine) 25mg and 100mg tablets.

The goal date for this application is March 4, 1998.

This draft labeling supplement provides for a decrease in the required white blood count (WBC) monitoring from weekly to biweekly after the first 6 months of continuous Clozaril therapy.

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

1. Implementation of reduced WBC testing after six months of continuous therapy requires a mechanism for tracking the duration of continuous drug exposure over time for each patient. Such a plan should allow the physician, the pharmacist, and the Clozaril National Registry to readily and accurately determine the treatment status of a Clozaril-treated patient (i.e., $\leq$ 6 months versus $>$6 months) in order to determine the required monitoring frequency for that patient at any point in time. This mechanism should be explicitly described by you as part of a modified monitoring plan.

2. Occasional, brief interruptions of therapy (e.g., accidentally missed doses) are expected in this patient population. You should carefully consider the maximum duration of treatment interruption that can be tolerated before treatment can no longer be considered continuous, a circumstance that would require resetting the exposure "clock." Limits for defining continuous use of Clozaril should be specified in this plan and perhaps in labeling as well.

3. We request that you commit to providing us with another risk analysis after the plan for reduced monitoring has been in place for 1-2 years to assess the safety of reduced testing and to provide data for consideration of further modifications to WBC monitoring requirements.

4. With respect to the proposed labeling changes, the following changes should be considered:

   a. [redacted] WBC monitoring:

      1) The last sentence of the paragraph under General WARNINGS states that Clozaril "is available only through a distribution system that ensures [redacted] supply of medication." For those patients in treatment over six months, testing will be biweekly and the dispensing of a two-week supply of medication to these patients is reasonable. Thus, the phrases [redacted], and [redacted] supply of medication" should be amended accordingly.

      2) The sixth sentence in the first paragraph in the boxed WARNING for agranulocytosis refers to "strict adherence to the [redacted]" This phrase should be revised.

      3) The final paragraph in the boxed WARNING for agranulocytosis again states that Clozaril "is available only through a distribution system that ensures [redacted] supply of medication." As noted above, this phrase should be modified.

   b. The first paragraph of the material in the "Agranulocytosis" box needs to be updated to the April '95 cutoff date, and it should include sufficient details on the shape of the hazard curve for agranulocytosis to justify for prescribers why 6 months is a reasonable time to switch to biweekly monitoring.

   c. The following language has been proposed for addition to [redacted] and to [redacted]: [redacted] This language is redundant with language already in labeling and unnecessary.

In addition, all previous revisions as reflected in the most recently approved package inserts must be 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 such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Steven D. Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Sincerely yours,

11/25/97

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

cc:

Original NDA 19-758
HFD-120/Div. Files
HFD-92/DDM-DIAB
DISTRICT OFFICE
HFD-120/CSO/Hardeman
HFD-120/Leber/Laughren/Dubitsky

10-9-97

10/9/97

Final: 10/7/97

n:\hardeman\clozaril\S-034.AE

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

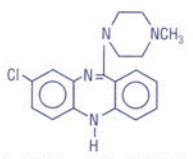
019758Orig1s034

LABELING

CLOZARIL®
(clozapine) Tablets

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

The structural formula is:



$C_{18}H_{19}ClN_4$ Mol. wt. 326.83

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, NF; lactose, NF; magnesium stearate, NF; povidone, USP; starch, NF; and talc, USP.

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 D_1, D_2, D_3 and D_5 receptors, and has a high affinity for the D_4 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.

APR 17 1998

128 BAR CODE AREA
FOR POSITION ONLY

30718909

NOVARTIS

CLOZARIL®
(clozapine) Tablets

Caution: Federal law prohibits dispensing without prescription.

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.

INDICATIONS AND USAGE
CLOZARIL® (clozapine) is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment. 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 antipsychotic drugs, 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.

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
BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT *(SEE FOLLOWING)*, CLOZARIL® (clozapine) SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZARIL® (clozapine), IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST 2 TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, 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 ≥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 reducton 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 ≥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 initiation of 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.

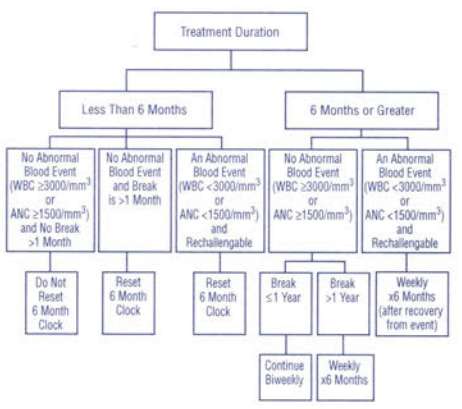
If the total WBC count falls below 2000/mm³ or the ANC falls below 1000/mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop,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

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 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 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, myocarditis, with or without eosinophilia, and pericarditis/pericardial effusions in association with CLOZARIL® (clozapine) use. 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
CLOZARIL® (clozapine) has very potent anticholinergic effects and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. In addition, 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.

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/mm^3, ANC ≥ 1500/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.

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.

Because CLOZARIL® (clozapine) is highly bound to serum protein, the administration of CLOZARIL® (clozapine) to a patient taking another drug which is highly bound to protein (e.g., warfarin, digitoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound CLOZARIL® (clozapine) by other highly bound drugs.

Cimetidine and erythromycin may both 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. Phenytoin may decrease CLOZARIL® (clozapine) plasma levels, resulting in a decrease in effectiveness of a previously effective CLOZARIL® (clozapine) dose.

Elevated serum levels of clozapine have been observed when CLOZARIL® (clozapine) is administered with selective serotonin reuptake inhibitors (SSRI's), e.g. fluoxetine and fluvoxamine. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when CLOZARIL® (clozapine) is combined with an SSRI. 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.

CLOZARIL® (clozapine) may also 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.

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.

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 (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
Cardiovascular	
Tachycardia	25[b]
Hypotension	9
Hypertension	4
Chest pain/Angina	1
ECG change/Cardiac abnormality	1

(Continued)

Treatment-Emergent Adverse Experience Incidence Among Patients Taking CLOZARIL® (clozapine) in Clinical Trials (N = 842) (Percentage of Patients Reporting)

Body System Adverse Event[a]	Percent
Gastrointestinal	
Constipation	14
Nausea	5
Abdominal discomfort/Heartburn	4
Nausea/Vomiting	3
Vomiting	3
Diarrhea	2
Liver test abnormality	1
Anorexia	1
Urogenital	
Urinary abnormalities	2
Incontinence	1
Abnormal ejaculation	1
Urinary urgency/frequency	1
Urinary retention	1
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

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

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

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, polydypsia, 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.

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
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 antipsychotic drug treatment, 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.

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 antipsychotic drugs. 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.

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/mm^3 or an ANC below 1000/mm^3 must *not* be restarted on CLOZARIL® (clozapine). *(See WARNINGS)*

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

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).
Unit dose packages of 100: 2 × 5 strips, 10 blisters per strip (NDC 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).
Unit dose packages of 100: 2 × 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.

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East Hanover, New Jersey 07936

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

SEP 30 1997

Review and Evaluation of Clinical Data
NDA # 19,758

Sponsor:	Novartis Pharmaceuticals Corporation
Drug:	CLOZARIL (clozapine)
Indication:	Schizophrenia
Material Reviewed:	**1)** SLR-034: Labeling Supplement for reduced WBC monitoring. **2)** Summary Minutes from the July 14, 1997, PDAC meeting. **3)** Transcript of the July 14, 1997, PDAC meeting as received from Neal R. Gross & Co., Inc.
Date Submitted:	September 3, 1997
Date Received:	September 5, 1997

I. Background

Clozapine (Clozaril®) was approved in the U.S. on September 26, 1989, for the treatment of neuroleptic-resistant schizophrenia. This drug was discovered to be associated with agranulocytosis during premarketing evaluation and a mandatory, controlled distribution system was instituted to ensure that white blood cell (WBC) counts would be monitored weekly throughout clozapine treatment.

(b) (4)

Further epidemiological analyses were provided on May 9, 1994; September 11, 1995; and most recently, May 30, 1997 to evaluate cumulative safety data with larger patient samples and longer durations of exposure. The latest report, which encompasses 96,821 patients treated with Clozaril in the U.S. as of April 30, 1995, with up to 5.5 years of follow-up, was reviewed by Judith Racoosin, M.D., M.P.H., an epidemiologist in the Division Safety Group. Her review is included in a Memorandum dated July 7, 1997, and the reader is referred to her report for details of this analysis, which will not be repeated here.

The Psychopharmacologic Drugs Advisory Committee convened on July 14, 1997, to consider the risks and potential benefits of various options for reducing WBC monitoring during Clozaril therapy. This submission serves [redacted] (b) (4) to present the sponsor's draft labeling which recommends for WBC monitoring in accordance with the recommendations of the PDAC.

II. PDAC Recommendations

The Committee meeting included presentations by representatives of both Novartis (Noel Weiss, M.D., Ph.D. and Ravi Anand, M.D.) and the FDA (Dr. Racoosin). Key information considered by the Committee included the following:

1) The background rate of agranulocytosis in the general population seems to be in the range of about 3-7 cases/million persons/year. No similar data in the schizophrenic population was available but, in treatment-resistant patients, a rate higher than that in the general population would not be surprising given exposure to drugs which may have a toxic effect on bone marrow.

2) In U.S. Clozaril-treated patients, the agran rate in the period 0-6 month after treatment initiation was 8.6 cases/1,000 person-years, with a peak between months 2-3 at 29.1 cases/1,000 person-years. The agran rate then falls rapidly in the 6 month-2 year period to 0.7 cases/1,000 person-years. Rates continue to fall to 0.4/1,000 person-years (after 2-3.5 years) and to 0.2 cases/1,000 person-years (after 3.5-5.5 years). This rate is approximately 100-fold higher than the background rate in the general population.

3) Based on model described by Dr. Weiss for projecting the number of cases of agran under various conditions of reduced WBC monitoring, the upper 95% confidence limit for the agran rate with discontinuation of all monitoring after six months of weekly testing (i.e., the "worst case scenario") is 3.6 cases/1,000 person-years. This rate is within the range of rates reported with two marketed drugs associated with agranulocytosis (neutrophils <~500/cmm) but <u>without</u> mandatory WBC monitoring: ticlopidine (≥8 cases/1,000 person-years) and sulfasalazine (3 cases/1,000 person-years). Even if one assumed that all Clozaril-treated patients who experience moderate or severe leukopenia[1] progressed to agran, the agran rate would be 5.2 cases/1,000 person-years.

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[1]Moderate leukopenia = 2,000-3,000 WBC/cmm and severe leukopenia = 500-2,000 WBC/cmm.

After considerable discussion, the Committee reached agreement that mandatory WBC monitoring should continue on a weekly basis for the first six months of treatment, then be reduced to every two weeks. The Committee was not prepared, at the consclusion of the meeting, to recommend discontinuation of monitoring after some time point or further reduction in monitoring frequency or conversion to voluntary monitoring after the first 12 months. They indicated that these questions should be revisited at a later date.

Additionally, the Committee recommended that the sponsor maintain the Clozaril National Registry and undertake an investigation to ascertain population subgroups at increased risk for agranulocytosis.

III. Proposed Labeling Changes

The sponsor proposes to amend product labeling to provide for weekly WBC monitoring for the first six months of continuous Clozaril therapy, followed thereafter by monitoring every two weeks thereafter. Draft labeling is included and was reviewed.

Specifically, notation of this modified WBC monitoring plan would be added to the following sections of labeling:

1) end of the paragraph under General WARNINGS,

2) second paragraph in the boxed WARNING for agranulocytosis,

3) paragraph discussing agranulocytosis under Information for Patients in PRECAUTIONS,

4) (b) (4)

5)

IV. Conclusions/Recommendations

Based my own consideration of the risk analysis presented by the sponsor, Dr. Racoosin's excellent review, and the recommendations of the PDAC, I feel that it is reasonable to reduce WBC monitoring with Clozaril treatment as proposed by the sponsor. However, it is recommended that the following issues be addressed by the sponsor prior to approval of this supplement:

1) Implementation of reduced WBC testing after six months of continuous therapy requires a mechanism for tracking the duration of continuous drug exposure over time for each patient. Such a plan should allow the physician, the pharmacist, and the Clozaril National Registry to readily and accurately determine the treatment status of a Clozaril-treated patient (i.e., ≤6 months versus > 6 months) in order to determine the required monitoring frequency for that

patient at any point in time. This mechanism should be explicitly described by the sponsor as part of a modified monitoring plan.

2) Occasional, brief interruptions of therapy (e.g., accidentally missed doses) are expected in this patient population. The sponsor should carefully consider the maximum duration of treatment interruption that can be tolerated before treatment can no longer be considered continuous, a circumstance that would require resetting the exposure "clock." Limits for defining continuous use of Clozaril should be specified in this plan and perhaps in labeling as well.

3) Novartis should commit to providing us with another risk analysis after the plan for reduced monitoring has been place for 1-2 years to assess the safety of reduced testing and to provide data for consideration of further modifications to WBC monitoring requirements.

4) With respect to the proposed labeling changes, while the proposed changes are acceptable, further changes should be considered:

a) It may be useful to the clinician to provide in labeling a summary of the rationale for reduced WBC monitoring after the first six months. It is recommended that the sponsor propose the addition of such text.

b) Also, [redacted] (b)(4) WBC monitoring that should be revised:

i) The last sentence of the paragraph under General WARNINGS states that Clozaril "is available only through a distribution system that ensures [redacted] (b)(4) supply of medication." For those patients in treatment over six months, testing will be biweekly and the dispensing of a two-week supply of medication to these patients is reasonable. Thus, the phrases [redacted] (b)(4) and [redacted] (b)(4) supply of medication" should be amended accordingly.

ii) The sixth sentence in the first paragraph in the boxed WARNING for agranulocytosis refers to "strict adherence to the [redacted] (b)(4)" This phrase should be revised.

iii) The final paragraph in the boxed WARNING for agranulocytosis again states that Clozaril "is available only through a distribution system that ensures [redacted] (b)(4) supply of medication." As noted above, this phrase should be modified.

It is recommended that this Labeling Supplement be given APPROVABLE status at this time. Final APPROVAL should be contingent on a satisfactory response from the sponsor regarding the above issues.

Gregory M. Dubitsky, M.D.
September 18, 1997

9-30-97

The only change for which there was solid agreement from the PDAC (7-14-97) was changing from weekly to biweekly WBC monitoring at six months. There was not agreement on subsequent step-downs to less frequent monitoring or on going to a voluntary monitoring system. Some may be disappointed at this change, but I agree that it is a reasonable change at this point in time. I also agree that the sponsor needs to make additional labeling changes and needs to commit to modifying the distribution system to accomodate the revised monitoring schedule and to providing a subsequent update on the neutropenia/agranulocytosis database after a reasonable interval to permit us to assess the effects of the change and to consider additional changes if appropriate. I have 2 brief comments on proposed labeling changes:

-The first paragraph of the material in the "Agranulocytosis" box needs to be updated to the April, 95' cutoff date, and it should include sufficient details on the shape of the hazard curve for agranulocytosis to justify for prescribers why 6 months is a reasonable time to switch to biweekly monitoring.

-The following language has been proposed for addition to [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4) **This language is redundant with language already in labeling and unnecessary.**

cc: NDA# 19,758
HFD-120
HFD-120/GDubitsky
TLaughren
SHardeman

Thomas P. Laughren, MD
TL, PDP

JAN 27 1998

Review and Evaluation of Clinical Data
NDA # 19,758

Sponsor:	Novartis Pharmaceuticals Corporation
Drug:	CLOZARIL (clozapine)
Indication:	Schizophrenia
Material Reviewed:	Amendment to SLR-034
Date Submitted:	January 14, 1998
Date Received:	January 15, 1998

I. Background

The Psychopharmacologic Drugs Advisory Committee convened on July 14, 1997, to consider the risks and benefits of possible options for reducing the frequency of WBC monitoring during Clozaril therapy. It was recommended that the frequency be decreased from weekly to biweekly (every two weeks) after six months of treatment. (This recommendation was discussed in further detail in my September 18, 1997, clinical review.)

In response, Novartis submitted a supplemental application (SLR-034) on September 3, 1997, which provided draft labeling to incorporate this recommendation. This supplement was reviewed by the division and a letter was issued to the firm on November 25, 1997, which indicated that it was approvable and specified a number of issues to be addressed before the supplement could be approved.

This amendment contains Novartis's response to our approvable letter.

II. Novartis Response to Issues/Reviewer Discussion

A. Tracking Clozaril Exposure Status

We had requested that the sponsor provide a mechanism for tracking the duration of drug exposure over time for all patients treated with Clozaril. Such a plan would allow the physician, pharmacist, and Clozaril National Registry (CNR) to readily ascertain the exposure status (≤6 months versus >6 months) of any patient at any point in time to insure that the patient was being appropriately monitored with respect to WBC count.

The response appears to include only their modified rules for monitoring compliance with WBC testing.[1] It is not clear that the sponsor could readily determine the status of a given patient at any point in time nor is it clear how a pharmacist will track or otherwise be informed of exposure status in a timely fashion.

However, bearing in mind that the physician has ultimate responsibility for prescribing Clozaril in accordance with the monitoring described in labeling, it is not considered critical that the pharmacist be capable of verifying the exposure status of his patients. The obligation of the pharmacist is to insure, before dispensing drug, that a current WBC count has been done and that the results do not contraindicate continued use, regardless of whether the patient is being tested weekly or biweekly.

Furthermore, it is not of vital importance that the sponsor have immediate access to information regarding treatment status for Clozaril patients. The key responsibility of the sponsor is the maintenance of the non-rechallenge master file, which should not be affected by reduced monitoring in a number of patients. Another Novartis function, monitoring compliance, requires only access to recent WBC data and the ability to analyze that data. Again, this function does not require the continuous tracking of exposure status for each patient.

Thus, in retrospect, this issue may have been overstated in our approvable letter and, in my opinion, it requires no further attention.

B. Provisions for Interruptions in Treatment

We requested that the sponsor carefully consider the maximum duration of treatment interruption that could be tolerated before treatment could no longer be considered continuous during the first six months, a circumstance that would require resetting the exposure clock and a six month period of exposure from that point forward before monitoring could be reduced.

The sponsor has addressed this request in the inclosed revised labeling (see the third and fourth paragraphs in the "Agranulocytosis" boxed warning). In essence, therapy with a

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1 [redacted] (b) (4)

(b) (4)

break of one month or less during the initial six months can still be considered continuous. In patients who have received greater than six months of treatment without a hematological event, a break less than one year can be tolerated without reinstituting weekly monitoring. However, in patients who have experienced a hematological event and recovered, a break of greater than one month would necessitate reversion to weekly testing. For clarity, this information has been summarized in the algorithm attached to this review.

No rationale for the lengths of these interruption periods is provided. Ideally, the duration of acceptable gaps in therapy would be decided on the basis of clinical data. However, it is unlikely that this question can be credibly addressed by an analysis of existing data. Furthermore, a clinical study to systematically investigate the risk of agranulocytosis as a function of varying periods of treatment and treatment interruption early in the course of Clozaril therapy would be very difficult, given the large numbers of patients likely to be needed. Such a study would be burdened by ethical considerations as well.

The concern behind this issue was to avoid probable misjudgement in extreme cases. For example, it would probably be unreasonable to require a patient who missed two doses during month #5 of treatment to undergo an additional six months of treatment before permitting biweekly testing. Similarly, a patient who, after three months of treatment, discontinued Clozaril for a year and then restarted treatment should probably be tested weekly for six months (not three) from that point onward. In this context, the durations proposed by the sponsor, while apparently arbitrary and quite possibly not optimal, are not unreasonable.

C. Commitment RE: Updated Risk Analysis

Novartis states that they will provide us with another risk analysis after the plan for reduced monitoring has been in place for 1-2 years, as we had requested.

D. Proposed Labeling

There are some points in the sponsor's labeling proposal that merit clarification:

1) The discussion of the hazard curve for agranulocytosis in the first paragraph of the boxed "Agranulocytosis" warning should include the cutoff data for that analysis (April 30, 1995). Also, it may be preferable to cite the incidence of agranulocytosis in units of person-years instead of (b) (4) (b) (4) to make it consistent with other sections of labeling (e.g., the precaution regarding pulmonary embolism).

2) In the second paragraph, the sixth line uses the phrase "if WBC counts remain acceptable." It may be advisable to define what is meant by acceptable [redacted]

3) In the third paragraph, although implied, it should be specifically stated that patients within the first six months of treatment who interrupt therapy for longer than one month and have no hematological event should be tested weekly for an additional six month period before biweekly testing is initiated.

4) Regarding the discussion of patients with greater than six months of exposure to Clozaril (fourth paragraph in the boxed warning), the sponsor should be asked to provide the rationale for [redacted]

Admittedly, the risk of a recurrent, precipitous decline in WBC count in such patients is not known. Nonetheless, a more conservative choice may be worthy of consideration [redacted]

5) [redacted] a) the first line should refer to patients on Clozaril therapy for 6 months or longer (not [redacted], b) the second line should refer to "a break on therapy which is 1 year or less" (not [redacted], and c) the phrase in the tenth line should refer to "a break on therapy which is [redacted]

6) We had noted that the [redacted] sections discussed [redacted]. It was felt that this was redundant, given discussions in earlier parts of labeling. This language should be removed from both sections.

Otherwise, the proposed labeling appears acceptable.

III. Recommendations

It is recommended that the sponsor be requested to address items 1) through 6) under section II.D. above. Final approval of this supplement should await mutually satisfactory resolution of these labeling issues.

Gregory M. Dubitsky, M.D.
January 23, 1998

1-27-98

I agree with the above recommendations. One additional suggestion would be to replace the text regarding breaks in therapy with a diagram, like that proposed by Dr. Dubitsky or some alternative. I further recommend that we attempt to work resolution of agreement on final labeling informally (fax & phone) rather than by letter.

T. Laughren, MD
TL, PhD

cc: NDA# 19,758
HFD-120
HFD-120/GDubitsky
TLaughren
SHardeman

Attachments: One (algorithm)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page.

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: November 25, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Clozaril WBC monitoring frequency

TO: File NDA 19- 758

This memorandum conveys to the administrative file the Division's determination to allow Novartis to modify Clozaril product labeling to reduce the frequency of white blood cell count monitoring required under the clozapine "no blood, no drug" distribution system. The details of the findings and the basis for the Division's action are nicely presented in Dr. Dubitsky's 9/18/97 review and the 9/30/97 addendum to that document appended by Dr. Laughren.

The decision to reduce the recommended frequency of white blood cell monitoring from weekly to biweekly intervals after six months of continuous treatment is justified by several findings, among them that 1) the risk (i.e., hazard) of agranulocytosis among clozapine recipients (participating in the monitoring program) decreases substantially (after the first 6 weeks of use) as the duration of continuous exposure to clozaril increases, and 2) the estimated risk to patients on treatment after 6 months, even without monitoring, although well above the estimated rate for the general population, is at a level within the range reported in association with the use of other marketed drug products (ticlopidine, sulfasalazine) that are not subject to mandatory white blood testing requirements.[1]

These conclusions in large part derive from the work of the sponsor's

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[1] The worst case estimate, 5.2 cases per 1000 PY, derives from a model developed by Dr. Weiss who served as a consultant for Novartis. (See Dr. Dubitsky's review of 9/18/97)

primary consultant, Dr. Noel Weiss, (a medical epidemiologist from the University of Washington) and from the work of Dr. Judith Racoosin (her review of July 7, 1997) of the Division's safety unit.

Although the action is technically taken at the request of the sponsor, it also reflects the Division's desire to reduce monitoring requirements to the minimum consistent with the safe use of this unusual antipsychotic drug product. Further modifications of recommendations for monitoring frequency will be entertained upon review of the consequences, if any, of the current labeling change.

Action taken

As of this date, I am issuing an approvable action letter developed for my signature by Dr. Laughren and his review team.

Paul Leber, M.D.
November 25, 1997

NDA 19-758
cc:
HFD-101
Temple
HFD -120
Katz
Laughren
Burkhart
Dubitsky
Racoosin
Hardeman

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

019758Orig1s034

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-758 / SLR-034

APR 17 1998

Novartis Pharmaceuticals Corporation
Attention: Susan Witham
59 Route 10
East Hanover, NJ 07936

Dear Ms. Witham:

We acknowledge the receipt of your April 6, 1998, submission containing final printed labeling in response to our March 3, 1998, letter approving your supplemental new drug application for Clozaril (clozapine) Tablets.

We have reviewed the labeling that you have submitted in accordance with our March 3, 1998, letter, and we find it acceptable.

Sincerely yours,

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

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 13, 1998

FROM: Gregory M. Dubitsky, M.D.
Medical Reviewer

SUBJECT: Revised Clozaril Labeling RE: Reduced WBC Testing

TO: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products Group

CC: Steve Hardeman, CSO

Attached is revised labeling for Clozaril to reflect decreased requirements for WBC count monitoring after six months of continuous treatment with clozapine. Included is an algorithm to address breaks in treatment continuity which will be inserted in FPL after the "Agranulcytosis" boxed warning. This version reflects recommendations made in my January 23, 1998, Review and Evaluation of Clinical Data as well as those documented in my February 10, 1998, Memorandum of Telephone Conversation. This draft and algorithm are acceptable to me but for the following:

1) In the "Agranulocytosis" boxed warning, the third from the last sentence in the first paragraph contains a misspelled word, "substantcial."

2) Under PRECAUTIONS, Information for Patients, the definition of acceptable WBC counts in the first hyphenated paragraph has ommitted the "≥" sign between ANC and 1500/mm^3.

The following comments refer to the algorithm.

3) In the title, the parenthetic phrase should read "WBC<3000/mm^3."

4) In the third row of boxes, the second box from the right should indicate that the ANC count is per mm^3 ("..1500/mm^3").

5) In the fourth row of boxes, the box on the right contains a misspelled word, "form."

These changes are not substantial and have been communicated telephonically to Susan Witham, of Novartis Regulatory Affairs, who has no objection to making these corrections in the FPL.

Thus, the labeling and algorithm are forwarded to you for further comment.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page.

cc:

Original NDA 19-758
HFD-120/Div. Files
HF-2/Medwatch (with labeling)
HFD-101/Office Director (with labeling) 4/16/98
HFD-120/CSO/S.Hardeman /Dubitsky/Laughren/Leber
HFD-40/DDMAC (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)

Final: 4/16/98

4/16/98

c:\docs\nda\clozaril\SLR-034.AR

ACKNOWLEDGE AND RETAIN (AR)

MEMORANDUM OF TELEPHONE CONVERSATION

Date of Call:	February 10, 1998; 11:05AM
NDA #:	19-758
Drug Name:	Clozaril
Sponsor:	Novartis
Point of Contact:	Susan Witham Associate Director Drug Regulatory Affairs
Phone #:	973-781-7758
Subject of Call:	Labeling revision RE: reduced WBC monitoring.

Susan Witham was contacted to communicate my comments on draft Clozaril labeling that was FAX'd to us on February 5, 1998. The following revisions were recommended:

1) The proposed labeling indicates that for patients whose WBC counts remained acceptable (defined as (b) (4) /cmm) during the first six months of continuous Clozaril therapy, biweekly WBC testing could be instituted (see General WARNINGS, the boxed "Agranulocytosis" WARNING, and Information for Patients under PRECAUTIONS). However, (b) (4) (b) (4) (b) (4). To resolve this incongruency, Ms. Witham planned to change the total WBC threshold from (b) (4) to "3000/cmm" and to add that ANC's, if obtained,[1] must be greater than 1500/cmm for a six month period of continuous therapy. I informed her that this seemed acceptable to me.

2) I requested that the description of the hematological analysis, which is presented in the first paragraph of the "Agranulocytosis" boxed WARNING, include the cut-off date for the relevant data (April 30, 1995). She agreed to add this information.

3) I pointed out four typographical errors within the "Agranulocytosis" boxed WARNING. She agreed to correct these.

Ms. Witham requested that the approval letter for this supplement stipulate a specific date for implementation (not earlier than March 10, 1998) to allow Novartis to work out the details of putting the new monitoring requirements in place. I informed her

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[1] (b) (4) (b) (4)

that the CSO (Steve Hardeman) would convey this request to Drs. Leber and Laughren for their consideration.

In addition, she also requested a telephonic conference, to include Drs. Laughren and Leber, to discuss the actual implementation of reduced monitoring and how this would dovetail with reduced monitoring of patients taking generic clozapine. I recommended that she put this request in writing and that this include an agenda for the telecon as well as any specific questions Novartis would like to pose. She agreed to follow this recommendation.

Ms. Witham stated that she would revise labeling as per my recommendations and FAX a revision to us within a few days. Since placement in labeling of an algorithm for addressing treatment interruptions has not been finalized with their printers, the revision would not be identical to FPL but would indicate with an asterisk (*) the placement of this display.

She thanked me for my feedback and the conversation was terminated.

Gregory M. Dubitsky, M.D.
February 10, 1998

cc: HFD-120/GDubitsky
/TLaughren
/SHardeman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

107.1

Food and Drug Administration
Rockville MD 20857

Date SEP -8 1997

NDA No. 19-758

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Attention: Susan Withman

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Clorazil Tablets

NDA Number: 19-758

Supplement Number: S-034

Date of Supplement: September 3, 1997

Date of Receipt: September 5, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on November 4, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

Steven D. Hardeman, R.Ph.

(For) John Purvis
Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

FORM FDA 3217b (11/95)

★ U.S. GPO: 1995-404-897/20714

A Monitoring Requirements

USER FEE DATA ENTRY/VALIDATION FORM Ver.2(9/1/93)

NDA # 19-758 DOCUMENT ID/LETTER DATE SLR-034, 9-3-97

APPLICANT NAME Novartis

PRODUCT NAME Clozaril Tablets

FORM MUST BE COMPLETED BY (10 DAYS FROM DOCUMENT RECEIPT): Sept 14, 1997

1. YES (NO) **CLINICAL DATA?**
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data" do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?**

IF SUPPLEMENT and NO CLINICAL DATA INCLUDED, SKIP TO ITEM 11!

2. YES NO **505(b)(2) NDA?** An application in which one or more of the pivotal studies (rather than all) was not conducted or sponsored by the applicant and the applicant does not have a right of reference to that study. In addition, the firm must have made a patent certification under section 505(b)(2)(A) and (B) of the Act and must have cited a reference listed drug on which it is basing its application.

YES NO **If 505(b)(2) NDA - FEE APPLIES?**
[Check YES if application is for a new chemical entity or Indication. Check NO if application is for a previously approved drug substance or indication.]

3. YES NO **LARGE VOLUME PARENTERAL APPROVED BEFORE 9/1/92?** [Check YES only if a supplement with clinical data submitted to an LVP application first approved before 9/1/92.]

4. YES NO **505(j) NDA?** Abbreviated Application IF YES, SKIP TO ITEM 11!

5. YES NO **506 NDA?** Insulin Product IF YES, SKIP TO ITEM 11!

6. YES NO **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE** (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION		
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

7. YES NO **BUNDLING POLICY APPLIED CORRECTLY?** NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

8. YES NO **SMALL BUSINESS EXCEPTION GRANTED?** [Check YES only if the NDA contains a copy of a written notice from the FDA Waiver Officer that a exception has been granted.]

9. YES NO **WAIVER GRANTED?** [Check YES only if the NDA contains a copy of a written notice from the FDA Waiver Officer that a waiver has been granted.]

10. YES NO **PRIORITY SUBMISSION?** [Check YES if Priority. Check NO if Standard.]

Steve D Hardman 9/8/97
11. CSO SIGNATURE/DATE

John L. Lewis 9/10/97
SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-1-1