CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 19-758/S-035

Trade Name: Clozaril Tablets

Generic Name: clozapine

Sponsor: Novartis

Approval Date: 09/19/1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-758/S-035

CONTENTS

Reviews / Information Included in this NDA Review.	
Approval Letter	X
Approvable Letter	
Labeling	X
Medical Review(s)	X
Chemistry Review(s)	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/ Biopharmaceutics Review(s)	
Administrative and Correspondence Document(s)	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

I.O.

Food and Drug Administration
Rockville MD 20857

NDA 19-758 / SLR-035

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

SEP 19 1997

Dear Ms. Witham:

Please refer to your supplemental new drug application dated September 3, 1997, received September 11, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clozaril (clozapine) 25 mg and 100 mg Tablets.

The supplemental application provides for the addition of a statement in labeling for patients who are on Clozaril therapy and develop symptoms of hyperglycemia. The statement, added to PRECAUTIONS, is as follows:

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 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.

We have completed our review of supplemental application SLR-035 and it is approved.

Labeling changes of this kind are permitted by section 314.70(c) of the regulations, and may be established prior to approval of the supplement. We note that these changes have been effected.

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

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

Sincerely yours,

9/19/97

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-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)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)

Final: sdh/September 18, 1997/

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APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-758/S-035

LABELING

[redacted]

128 BAR CODE AREA
FOR POSITION ONLY

NOVARTIS

30118907

CLOZARIL®

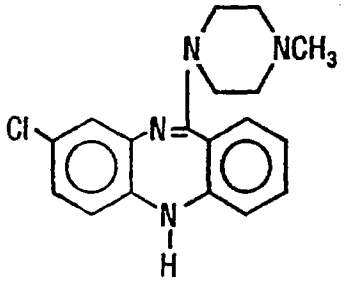
(clozapine) Tablets

Caution: Federal law prohibits dispensing without prescription.

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.

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 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 THROUGHOUT TREATMENT, AND FOR 4 WEEKS AFTER THE DISCONTINUATION OF CLOZARIL® (clozapine).

CLOZARIL® (clozapine) IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES WEEKLY WBC TESTING PRIOR TO DELIVERY OF THE NEXT WEEK'S SUPPLY OF MEDICATION.

Agranulocytosis

Agranulocytosis, defined as an absolute neutrophil count (ANC) of less than 500/mm^3, 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 recommendation for weekly monitoring of WBC counts. In the US, under a weekly WBC monitoring system with CLOZARIL® (clozapine), there have been 317 cases of agranulocytosis as of January 1, 1994; 11 were fatal. During this period, over 68,000 patients received CLOZARIL® (clozapine).

Because of the substantial risk of 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 duration of therapy, as well as for 4 weeks thereafter. The distribution of CLOZARIL® (clozapine) is contingent upon performance of the required blood tests.

reatment should not be initiated if the WBC count is less than 3500/mm^3, 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/mm^3 or it has dropped by a substantial amount from baseline, even if the count is above 3500/mm^3, 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/mm^3 and an ANC above 1500/mm^3, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 3000/mm^3 or the ANC below 1500/mm^3, 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/mm^3 and the ANC returns to levels above 1500/mm^3. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500/mm^3.

If the total WBC count falls below 2000/mm^3 or the ANC falls below 1000/mm^3, 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/mm^3, or ANCs below 1000/mm^3 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 weekly WBC testing prior to delivery of the next week's supply of medication.

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/mm^3, CLOZARIL® (clozapine) therapy should be interrupted until the eosinophil count falls below 3,000/mm^3.

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.

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 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.

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
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

In order to minimize the risk of agranulocytosis, CLOZARIL® (clozapine) is available only through a distribution system that ensures weekly WBC testing prior to delivery of the next week's supply of medication. 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 only through a distribution system that ensures weekly WBC testing prior to delivery of the next week's supply of medication.

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. Dispensing should be contingent upon the results of a WBC count.

*Trademark of Medical Economics Company, Inc.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

REV: JUNE 1997 PRINTED IN USA 30118907

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-758/S-035

MEDICAL REVIEW

SEP 17 1997

Review and Evaluation of Clinical Data
NDA # 19,758

Sponsor:	Novartis Pharmaceuticals Corporation
Drug:	CLOZARIL (clozapine)
Indication:	Schizophrenia
Material Reviewed:	SLR-035: Special Supplement-Changes Being Effected (Precautionary statement re: hyperglycemia)
Date Submitted:	September 3, 1997
Date Received:	September 11, 1997

Based on multiple spontaneous and published reports of hyperglycemia associated with Clozaril treatment, we had sent a letter to the sponsor on March 24, 1997, suggesting that the event "hyperglycemia" be moved from the Postmarketing Clinical Experience section of product labeling to PRECAUTIONS in order to more prominently describe these occurrences.

This supplement provides final printed labeling incorporating our suggested precautionary text regarding hyperglycemia.

This version of labeling also incorporates previously approved pharmacology text regarding dopamine receptors, removal of the "Sandopak®" reference in the HOW SUPPLIED section,[1] and the change in the company name to Novartis.

These changes are acceptable.

Gregory M. Dubitsky, M.D.
September 16, 1997

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

9-17-97

[1]This change is acceptable, based on informal consultation with the chemistry reviewer, Mona Zarifa, Ph.D., and the chemistry group leader, Maryla Guzewska, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 19-758/S-035

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date SEP 15 1997

NDA No. 19-758

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

Attention: Susan Witham

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-035

Date of Supplement: September 3, 1997

Date of Receipt: September 11, 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 10, 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. Hardman 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)

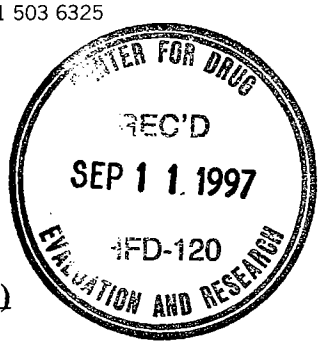
Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 201 503 7500
Fax 201 503 6325

NOVARTIS

ORIGINAL

NDA NO. 19-758 REF. NO. SLR-035
NDA SUPPL FOR Labeling (FPL)



September 3, 1997

Paul Leber, MD
Director
Division of Neuropharmacological
Drug Products/HFD-120
Office of Drug Evaluation I
Attn: Document Control Room
Center for Drug Evaluation and Research
Woodmont II, 1451 Rockville Pike
Rockville, Maryland 20852

NDA No. 19-758
CLOZARIL® (clozapine) Tablets

"SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED"

FINAL PRINTED LABELING

No changes other than those specified by sponsor.
Steven D. Harduny
Project Manager
9/18/97

Dear Dr. Leber:

Per the Division's request, in accordance with 21 CFR §314.60 (c)(2), Novartis Pharmaceuticals Corporation herewith submits a "SPECIAL SUPPLEMENT-CHANGES BEING EFFECTED" labeling supplement for Clozaril® (clozapine) Tablets which provides for a precautionary statement for patients who are on Clozaril® therapy and develop symptoms of hyperglycemia. Novartis has incorporated the Division's recommended text to the PRECAUTIONS section of the package insert.

Enclosed are 16 copies of final printed labeling (#30118907). This version of the package insert also includes the approved clinical pharmacology text regarding the dopamine receptors (approved on April 25, 1997), removal of "Sandopak® " reference in the HOW SUPPLIED section, and changed the company name to Novartis. Novartis will implement this package insert this month.

If there are any questions or comments, please contact me at (973) 503-7758.

Sincerely,

Susan Witham

Susan Witham
Associate Director
Drug Regulatory Affairs

Attachments: 1 Archival
15 Acco