CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 74949

Trade Name Clozapine Tablets 25mg and 100mg

Generic Name Clozapine Tablets 25mg and 100mg

Sponsor Zenith Goldline Pharmaceuticals, Inc.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 74949

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Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74949

APPROVAL LETTER

ANDA 74-949

Zenith Goldline Pharmaceuticals, Inc.
Attention: Jason A. Gross, Pharm. D.
140 Legrand Ave.
Northvale, NJ 07647

Dear Sir:

This is in reference to your abbreviated new drug application dated August 22, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Clozapine Tablets, 25 mg and 100 mg.

Reference is also made to your amendments dated May 28, June 2, June 20, July 30, September 12, October 17, November 5, and November 21, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Clozapine Tablets, 25 mg and 100 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Clozaril Tablets, 25 mg and 100 mg, respectively, of Novartis Pharmaceuticals Corporation). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74949

FINAL PRINTED LABELING

P141

Zenith Goldline

NDC 0172-4359-85

CLOZAPINE
TABLETS
25 mg

Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL ADULT DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
NDC **0172-4359-85**
Each Tablet Contains:
Clozapine 25 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0597J

N 3 0172-4359-85 7

LOT:

EXP:

Zenith Goldline

NDC 0172-4359-80

1000 TABLETS (Pale Yellow)

CLOZAPINE
TABLETS
25 mg

Store at controlled room temperature 15° - 30°C (59° - 86°F).
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Manufactured by:
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FT. LAUDERDALE, FL 33309
0597J

N 3 0172-4359-80 2

LOT:

EXP:

Zenith Goldline

NDC 0172-4359-70

500 TABLETS (Pale Yellow)

CLOZAPINE
TABLETS
25 mg

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0597J

N 3 0172-4359-60 4

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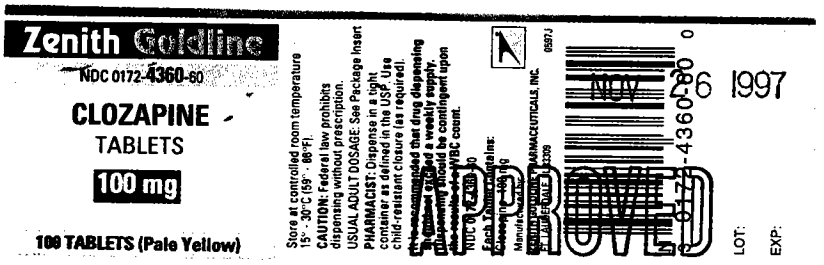
EXP: NOV 20


Zenith Goldline
NDC 0172-4360-60
CLOZAPINE
TABLETS
100 mg
100 TABLETS (Pale Yellow)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
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NDC 0172-4360-60
Each Tablet Contains:
Clozapine USP 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0597J
NOV 26 1997
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LOT:
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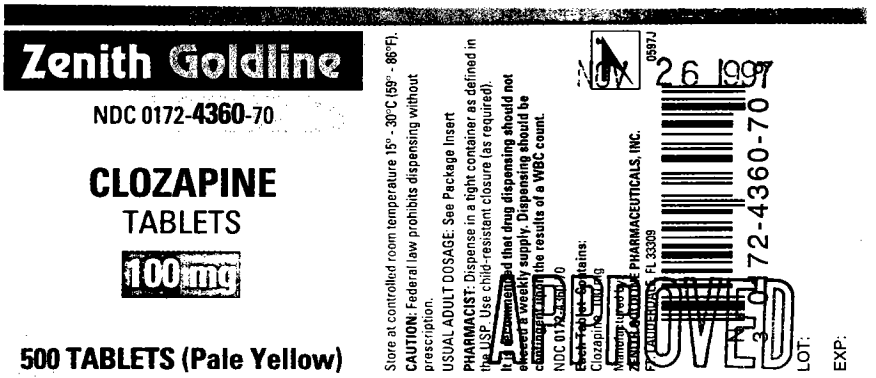
Zenith Goldline
NDC 0172-4360-70
CLOZAPINE
TABLETS
100 mg
500 TABLETS (Pale Yellow)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
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Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0597J
NOV 26 1997
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APPROVED
LOT:
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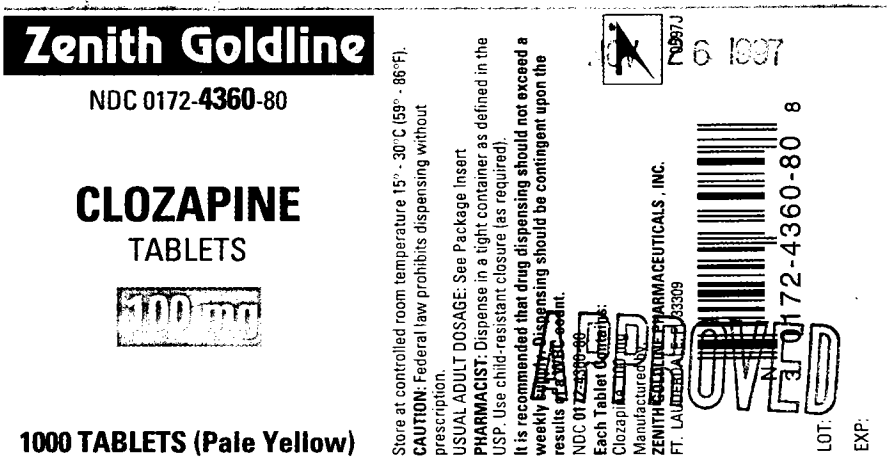
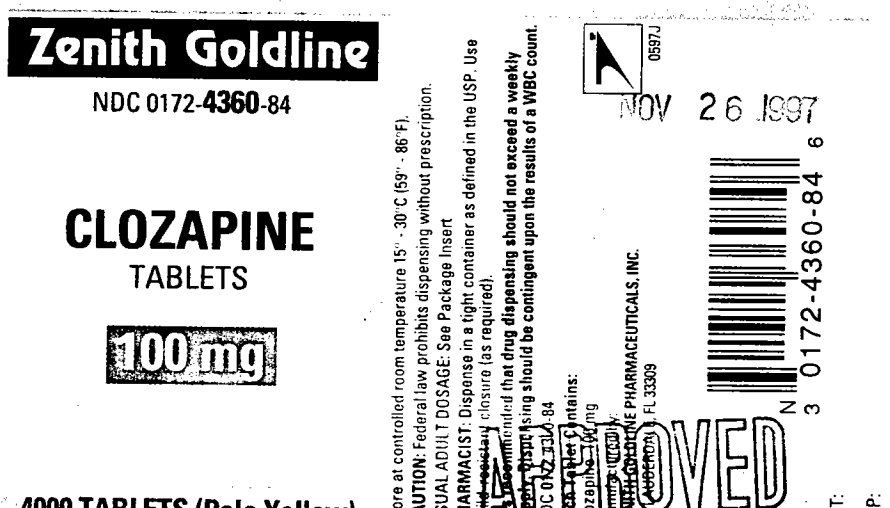

Zenith Goldline
NDC 0172-4360-80
CLOZAPINE
TABLETS
100 mg
1000 TABLETS (Pale Yellow)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL ADULT DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
NDC 0172-4360-80
Each Tablet Contains:
Clozapine USP 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0597J
NOV 26 1997
N 3 0172-4360-80 8
APPROVED
LOT:
EXP:


Zenith Goldline
NDC 0172-4360-84
CLOZAPINE
TABLETS
100 mg
4000 TABLETS (Pale Yellow)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL ADULT DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
NDC 0172-4360-84
Each Tablet Contains:
Clozapine USP 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0597J
NOV 26 1997
N 3 0172-4360-84 6
APPROVED
LOT:
EXP:

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Zenith Goldline

NDC 0172-**4360**-60

CLOZAPINE

TABLETS

100 mg

100 TABLETS (Pale Yellow)

Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL ADULT DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
NDC 0172-4360-60
Each Tablet Contains:
Clozapine 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0597J

N 3 0172-4360-60 0

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EXP:

Zenith Goldline

NDC 0172-**4360**-70

CLOZAPINE

TABLETS

100 mg

500 TABLETS (Pale Yellow)

Store at controlled room temperature 15° - 30°C (59° - 86°F).
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NDC 0172-4360-70
Each Tablet Contains:
Clozapine 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0597J

N 3 0172-4360-70 9

LOT:

EXP: 26 [illegible]7

Zenith Goldline

NDC 0172-**4360**-80

CLOZAPINE

TABLETS

100 mg

1000 TABLETS (Pale Yellow)

Store at controlled room temperature 15° - 30° C (59° - 86°F).
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USUAL ADULT DOSAGE: See Package Insert
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NDC 0172-4360-80
Each Tablet Contains:
Clozapine 100 mg
Manufactured by
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0597J

N 3 0172-4360-80 8

LOT:

EXP: 26 [illegible]7

Zenith Goldline

NDC 0172-**4360**-84

CLOZAPINE

TABLETS

100 mg

4000 TABLETS (Pale Yellow)

Store at controlled room temperature 15° - 30°C (59° - 86°F).
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It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
NDC 0172-4360-84
Each Tablet Contains:
Clozapine 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0597J

N 3 0172-4360-84 6

LOT:

EXP: [illegible] 26 [illegible]7

142d

Zenith Goldline

CLOZAPINE
TABLETS
25 mg

Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL ADULT DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
NDC 0172-4359-60
Each Tablet Contains:
Clozapine 25 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0597J

N 3 0172-4359-60 4

LOT:
EXP: NOV 26 1997

Zenith Goldline

NDC 0172-4359-70

CLOZAPINE
TABLETS
25 mg

500 TABLETS (Pale Yellow)

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1000 TABLETS (Pale Yellow)

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0597J

N 3 0172-4359-80 2

LOT:
EXP:

Zenith Goldline

NDC 0172-4359-85

CLOZAPINE
TABLETS
25 mg

5000 TABLETS (Pale Yellow)

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Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0597J

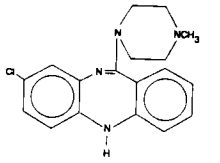
N 3 0172-4359-85 7

LOT:
EXP:

CLOZAPINE TABLETS

DESCRIPTION

Clozapine, an atypical antipsychotic drug, is a tricyclic dibenzodiazepine derivative. The chemical name of clozapine is 8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo [*b,e*][1,4] diazepine and it has the following structural formula:



$C_{18}H_{19}ClN_4$

M.W.326.83

Clozapine is a yellow, crystalline powder, very slightly soluble in water. Each tablet, for oral administration, contains 25 mg or 100 mg clozapine. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, povidone, pregelatinized starch and talc.

CLINICAL PHARMACOLOGY

Pharmacodynamics

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 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 clozapine is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of clozapine from extrapyramidal side effects.

Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors.

Absorption, Distribution, Metabolism and Excretion

In man, 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 clozapine. Thus, clozapine may be administered with or without food.

Clozapine is approximately 97% bound to serum proteins. The interaction between 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, clozapine therapy produces little or no prolactin elevation.

As is true of more typical antipsychotic drugs, clinical EEG studies have shown that 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 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

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, 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 clozapine in a treatment resistant schizophrenic population was demonstrated in a 6-week study comparing 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 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

Clozapine is contraindicated in patients with myeloproliferative disorders, uncontrolled epilepsy, or a history of clozapine induced agranulocytosis or severe granulocytopenia. As with more typical antipsychotic drugs, clozapine is contraindicated in severe central nervous system depression or comatose states from any cause.

Clozapine should not be taken simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The mechanism of 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*), 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 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 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 CLOZAPINE.

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/mm³, has been estimated to occur in association with 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 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 clozapine use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of 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 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 clozapine, there have been 317 cases of agranulocytosis as of January 1, 1994; 11 were fatal. During this period, over 68,000 patients received clozapine.

Because of the substantial risk of agranulocytosis in association with 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 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 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 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, 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. 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 clozapine therapy should have daily WBC count and differential. These patients should not be rechallenged with clozapine. Patients discontinued from 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 clozapine therapy, a single, national master file will be maintained confidentially.

Except for evidence of significant bone marrow suppression during initial clozapine therapy, there are no established risk factors, based on world-wide experience, for the development of agranulocytosis in association with 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 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 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 clozapine.

To reduce the risk of agranulocytosis developing undetected, 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 of 4,000/mm³, clozapine therapy should be interrupted until the eosinophil count falls below 3,000/mm³.

Seizures

Seizure has been estimated to occur in association with 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 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 clozapine doses used.

Caution should be used in administering clozapine to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with 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 clozapine treatment and may represent a continuing risk in some patients. Rarely (approximately 1 case per 3,000 patients), collapse can be profound and 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 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 clozapine by itself. Although it has not been established that there is an interaction between 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 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 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 clozapine. The clinical significance of these changes is unclear. However, in clinical trials with 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 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.

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 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 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 clozapine who had been previously treated with other antipsychotic drugs, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to clozapine alone. Nevertheless, it cannot be concluded, without more extended experience, that 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, clozapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic 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 clozapine, drug discontinuation should be considered. However, some patients may require treatment with 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 clozapine or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.

Fever

During 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 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 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 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 clozapine therapy. Whether pulmonary embolus can be attributed to 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 clozapine treatment in patients with no prior history of hyperglycemia. While a causal relationship to clozapine use has not been definitively established, glucose levels normalized in most patients after discontinuation of clozapine, and a rechallenge in one patient produced a recurrence of hyperglycemia. The effect of clozapine on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving clozapine who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycemia, the discontinuation of clozapine should be considered.

Hepatitis

Caution is advised in patients using 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 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 clozapine should be discontinued.

Anticholinergic Toxicity

Clozapine has very potent anticholinergic effects and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. In addition, clozapine use has been associated with varying degrees of 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, 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 clozapine in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using 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 clozapine. Check with the anesthesiologist regarding continuation of 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 clozapine:

- Patients who are to receive 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 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 clozapine treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking clozapine.
- Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

...its use, 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 clozapine in a treatment resistant schizophrenic population was demonstrated in a 6-week study comparing 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 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

Clozapine is contraindicated in patients with myeloproliferative disorders, uncontrolled epilepsy, or a history of clozapine induced agranulocytosis or severe granulocytopenia. As with more typical antipsychotic drugs, clozapine is contraindicated in severe central nervous system depression or comatose states from any cause.

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 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*), 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 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 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 CLOZAPINE.

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 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 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 140 cases of agranulocytosis reported worldwide in association with clozapine use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of 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 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 clozapine, there have been 317 cases of agranulocytosis as of January 1, 1994; 11 were fatal. During this period, over 68,000 patients received clozapine.

Because of the substantial risk of agranulocytosis in association with 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 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 clozapine is contingent upon performance of the required blood tests.

Treatment 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 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, 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. 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 clozapine therapy should have daily WBC count and differential. These patients should not be rechallenged with clozapine. Patients discontinued from 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 clozapine therapy, a single, national master file will be maintained confidentially.

Except for evidence of significant bone marrow suppression during initial clozapine therapy, there are no established risk factors, based on world-wide experience, for the development of agranulocytosis in association with 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 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 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 clozapine.

To reduce the risk of agranulocytosis developing undetected, clozapine is available only through a distribution system that ensures weekly WBC testing prior to delivery of the next week's supply of medication.

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 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 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 clozapine alone. Nevertheless, it cannot be concluded, without more extended experience, that 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, clozapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic 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 clozapine, drug discontinuation should be considered. However, some patients may require treatment with 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 clozapine or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.

Fever

During 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 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 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 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 clozapine therapy. Whether pulmonary embolus can be attributed to 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 clozapine treatment in patients with no prior history of hyperglycemia. While a causal relationship to clozapine use has not been definitively established, glucose levels normalized in most patients after discontinuation of clozapine, and a rechallenge in one patient produced a recurrence of hyperglycemia. The effect of clozapine on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving clozapine who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycemia, the discontinuation of clozapine should be considered.

Hepatitis

Caution is advised in patients using 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 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 clozapine should be discontinued.

Anticholinergic Toxicity

Clozapine has very potent anticholinergic effects and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. In addition, clozapine use has been associated with varying degrees of 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, 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 clozapine in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using 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 clozapine. Check with the anesthesiologist regarding continuation of 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 clozapine:

- Patients who are to receive 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 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 clozapine treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking clozapine.
- Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

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TABLETS

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TABLETS

- Patients should be informed that if they stop taking 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 clozapine.

Drug Interactions

The risks of using clozapine in combination with other drugs have not been systematically evaluated.

The mechanism of 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, clozapine should not be used with other agents having a well-known potential to suppress bone marrow function.

Given the primary CNS effects of 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 clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Because clozapine is highly bound to serum protein, the administration of 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 clozapine by other highly bound drugs.

Cimetidine and erythromycin may both increase plasma levels of clozapine, potentially resulting in adverse effects. Although concomitant use of clozapine and carbamazepine is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in clozapine plasma levels. Phenytoin may decrease clozapine plasma levels, resulting in a decrease in effectiveness of a previously effective 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.

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

Teratogenic Effects

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 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 clozapine in premarketing clinical trials discontinued treatment due to an adverse event, including both those that could be reasonably attributed to 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 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 clozapine patients who participated in clinical trials. These rates are not adjusted for duration of exposure.

Treatment-Emergent Adverse Experience Incidence Among Patients Taking Clozapine in Clinical Trials (N=642)

(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]
Rapidity	3
Akathesia	3
Confusion	3
Fatigue	2
Insomnia	2
Hypertonesia	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 clozapine patients are included.

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

Other Events Observed During the Premarketing Evaluation of Clozapine

This section reports additional, less frequent adverse events which occurred among the patients taking clozapine in clinical trials. Various adverse events were reported as part of the total experience in these clinical studies; a causal relationship to 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 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, hemolemesis, 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 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 clozapine.

OVERDOSAGE

Human Experience

The most commonly reported signs and symptoms associated with 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 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 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 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, 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 clozapine therapy, up to a 1 week supply of additional 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 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 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 the 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 clozapine in treatment resistant patients, the mean and the median 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 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 clozapine, but at the lowest level needed to maintain remission. Because of the significant risk associated with the use of clozapine, patients should be periodically reassessed to determine the need for maintenance treatment.

Discontinuation of Treatment

In the event of planned termination of 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 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 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 count below 1000/mm^3 must *not* be restarted on clozapine. (See **WARNINGS**)

HOW SUPPLIED

Clozapine Tablets are available only through a distribution system that ensures weekly WBC testing prior to delivery of the next week's supply of medication.

Clozapine Tablets are available as pale yellow, round tablets, debossed "4359" on one side and "25" and a bisect on the other, containing 25 mg clozapine packaged in bottles of 100, 500, 1000 and 5000 tablets.

Clozapine Tablets are available as pale yellow, round, flat-faced, beveled-edge tablets with a bisect, debossed "4360" on one side and "100" on the other, containing 100 mg clozapine packaged in bottles of 100, 500, 1000, and 4000 tablets.

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

Drug dispensing should not ordinarily exceed a weekly supply.

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

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

* Trademark of Medical Economics Company, Inc.

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ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

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CLOZAPINE TABLETS

Among Patients Taking 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
Akathesia	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
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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

4

...Recommended initial treatment with clozapine begins with one-half of a 25 mg tablet [illegible] 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.

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CAUTION: Federal law prohibits dispensing without prescription.

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FT. LAUDERDALE, FL 33309

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CLOZAPINE TABLETS

0193-03
CLOZAPINE
TABLETS

0193-03
CLOZAPINE
TABLETS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74949

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMISTRY REVIEW NO.

   Two (2)

2. ANDA #74-949

3. NAME AND ADDRESS OF APPLICANT

   Zenith Goldline Pharmaceuticals, Inc.,
   Attention: Jason Gross
   140 Legrand Avenue,
   Northvale, NJ 07647

4. LEGAL BASIS FOR SUBMISSION

   The listed reference product is Clozaril® Tablets, 25mg and 100mg Manufactured by Novartis (used to be Sandoz) Pharmaceuticals, Corporation. Clozaril® is not covered by any patents or exclusivity provisions.

5. SUPPLEMENT(s)

   None

6. PROPRIETARY NAME

   None

7. NONPROPRIETARY NAME

   Clozapine Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

   None

9. AMENDMENTS AND OTHER DATES:

   Minor Amendment - June 2, 1997
   Telephone amendment (bioequivalence) - July 30, 1997
   Telephone amendment - November 5, 1997
   Telephone amendment - November 21, 1997

10. PHARMACOLOGICAL CATEGORY

    Antipsychotic

11. Rx or OTC

    Rx

12. RELATED IND/NDA/DMF(s)

DMF#(type)	Product	DMF holder	LOA
(b)(4)(CC)			

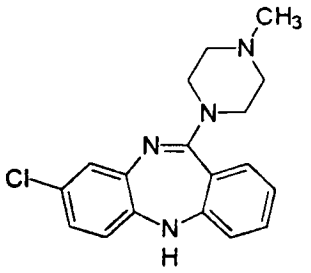
13. DOSAGE FORM

Tablets

14. POTENCY

25mg and 100mg

15. CHEMICAL NAME AND STRUCTURE



$C_{18}H_{19}ClN_4$ 326.83 *[5786-21-0]*
5*H*-Dibenzo[*b*,*e*][1,4]diazepine, 8-chloro-11-(4-methyl-1-piperazinyl)-.
Refer to USAN 1991, page 157.

16. RECORDS AND REPORTS

None

17. COMMENTS

This application was found to be approvable.
Labeling was reviewed and found to be satisfactory (11/3/97, reviewed by L. Golson).
The telephone amendment of November 5, 1997 was reviewed and found to be acceptable. The amendment was related to the specifications of other individual unknown impurities for the drug substance and the drug product at the time of release and on stability. The telephone amendment of November 21, 1997 was reviewed and found to be satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Liang-Lii Huang, Ph.D. November 25, 1997

cc:
ANDA 74-949
ANDA (DUP) 74-949
DIV FILE
Field Copy
Endorsements (Draft and Final with Dates):

/S/ 11/25/97

HFD-627 /Liang-Lii Huang, Ph.D./ 11/25/97
HFD-627 /Paul Schwartz, Ph.D./11/25/97
CHEMISTRY REVIEW - APPROVABLE

X:\NEW\FIRMSNZ\ZENITH\LTRS&REV\74949S00.RV2
Date: November 25, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74949

BIOEQUIVALENCE REVIEW(S)

ANDA 74-949

OCT 1 1997

Zenith Goldline Pharmaceuticals
Attention: Joan Janulis
140 Legrand Avenue
Northvale, NJ 07647

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Clozapine Tablets, 25 mg and 100 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs. The dissolution testing should be conducted in 1000 mL of pH 4.0 Acetate Buffer at 37°C using USP 23 Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than (b)(4) of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/ [redacted]

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Clozapine Tablets	Zenith Goldline
25 mg and 100 mg Tablets	Northvale, NJ
ANDA #74-949	Submission Date:
Reviewer: Moo Park	August 22, 1996
Filename: 74949sdw.896	

Review of an In Vivo Bioequivalence Study, Dissolution Data and a Waiver Request

I. Objectives

Review of:

- Two-way crossover *in vivo* bioequivalence study comparing Zenith's Clozapine Tablets, 25 mg strength, to Sandoz's Clozaril® Tablets, 25 mg strength, following administration of a 12.5 mg dose (one half tablet) under fasting conditions.
- Dissolution data for 25 mg and 100 mg tablets.
- A waiver request for 100 mg tablets.

Zenith has submitted *in vivo* bioequivalence data for clozapine and its metabolite, normethylclozapine. Agency's guidance requires *in vivo* data for clozapine only. Only clozapine data were evaluated in this review.

II. Background

Clozapine is a dibenzodiazepine derivative, with potent antipsychotic properties. It is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment.

Clozapine is rapidly and almost completely absorbed following oral administration. However, because of extensive hepatic first-pass metabolism, only about 27-50% of an orally administered dose reaches systemic circulation unchanged. Gastrointestinal absorption appears to occur principally in small intestine and is approximately 90-95% complete within 3.5 hours after an oral dose. Food does not appear to affect the systemic bioavailability of

clozapine. The relative oral bioavailability of commercially available 25 mg and 100 mg clozapine tablets reportedly is equivalent. Following oral administration of a single 25 mg or 100 mg oral dose of clozapine as tablets in healthy adults, the drug is detectable in plasma within 25 minutes, and peak plasma clozapine concentrations occur at about 1.5 hours. Peak plasma concentrations may be delayed with higher single doses and with multiple dosing of the drug.

Clozapine is approximately 95% bound to serum proteins. It is almost completely metabolized prior to excretion and only trace amounts (2-5%) 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; maximum fecal excretion has been estimated at 38%. The desmethylated, hydroxylated and N-oxide derivatives are the metabolized products seen in urine and feces. The desmethyl metabolite has only limited pharmacological activity, while the hydroxylated and N-oxide derivatives are inactive.

Currently, clozapine is marketed by Sandoz Pharmaceuticals Corporation under the name Clozaril^{R}, as 25 mg (scored) and 100 mg tablets.

III. Study Details

1. Protocol #ZEN-511 (December 6, 1995)

2. Applicant: Zenith Goldline, Northvale, NJ

3. Study sites:
   Clinical study: (b)(4)(CC)
   Analytical:
   Statistics & Report

4. Investigators:
   Principal investigator: (b)(4)(CC)

5. Clinical study dates:
   Group 1: 1/6/96-1/16/96
   Group 2: 1/20/96-1/30/96
   Group 3: 2/3/96-3/19/96

   Assay dates: 2/6/96-5/13/96

6. Study design: Open-label, randomized, two-way crossover

design.

7. Subjects: This study enrolled 24 male volunteers, 18-49 years of age. The candidates for enrollment were then subjected to a variety of examinations' to determine their health and suitability for enrollment. These included clinical laboratory examinations, including hematology (hemoglobin, hematocrit, platelet count, total and differential white cell count, red cell count, MCH, MCHC, and MCV), clinical chemistry (cholesterol, triglycerides, sodium, potassium, chloride, bicarbonate, anion gap, glucose, BUN, creatinine, BUN/creatinine ratio, CPK, calcium, phosphorus, uric acid, total protein, albumin, A/G ratio, SGOT, SGPT, alkaline phosphatase, LDH, GGT, and total, direct, and indirect bilirubin), HIV and hepatitis screens, routine urinalysis (specific gravity, pH, protein, bilirubin, urobilinogen, glucose, ketones, occult blood, red cells, white cells, bacteria, and casts), urine drug screen (for amphetamines, barbiturates, benzodiazepines, cocaine metabolites, marijuana metabolites, methaqualone, opiates, phencyclidine), electrocardiographic, and physical (body weight, height, vital signs, general appearance, HEENMT, chest/lungs, heart, abdomen, musculoskeletal, extremities, nervous system, skin, lymph nodes) examinations during the periods from January 3, 1996 to January 29, 1996. As subjects met the entry criteria, each was assigned a subject number in sequence, according to the order in which they began the enrollment process. The subjects selected to participate in the study were instructed to report to the dormitory, in groups of eight, by 7:00 PM on Friday January 5, 1996, Friday January 19, 1996, and Friday February 2, 1996.

Inclusion Criteria:

The investigator selected, from an appropriate subject population, forty subjects who met all of the following criteria:

1. The subject is a healthy male, 18-50 years of age. Subjects must be nonsmokers.

2. The subject has a normal EKG at screening as judged by the following parameters: PR interval of 120-200 msec, QRS interval of 40-100 msec, QTc less than 400 msec, and no evidence of any heart block.

3. Screening white blood cell count is within laboratory normal range, and blood pressure and pulse rate at check-in is at least 100/70 mmHg and 60 bpm, respectively.

4. The subject weighs within 10% of ideal body weight as determined by the 1983 Metropolitan Height and Weight Table (see Appendix D). Elbow breadth measurements must be taken to document body frame assignment.

5. The subjects has taken no Rx medications for 2 weeks prior and no OTC medications, vitamins or unusual **diet** from I week prior to drug administration and until after the study is completed.

6. The subjects must consume no alcohol- or xanthine-containing food or beverages from 48 hr prior to dosing and until after the last blood sample is collected.

7. The subject must sign an IRB-approved informed consent which adequately informs them of possible cardiovascular adverse effects.

Exclusion Criteria:

Subjects were not enrolled if any of the following criteria existed:

1. A clinically abnormal physical examination or EKG, suggesting an abnormality of any organ system.

2. The laboratory results show any clinically significant laboratory abnormalities or white blood cell count is outside the laboratory normal range.

3. The subject has numerous known allergies or is known to be allergic, hypersensitive or otherwise intolerant to a component of Zenith Clozapine Tablets, Clozaril^{R}, any other neuroleptics (chlorpromazine, thioridazine, haloperidol), benzodiazepines (diazepam, chlordiazepoxide, etc.), or diphenhydramines (Benadryl^{R}).

4. The subject has a history within the last year of alcohol or other drug dependence or abuse or any medical history of glaucoma, asthma, urinary retention, seizures, psychiatric disorders, serious cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal or ongoing infectious disease, drug-induced agranulocytosis or vasovagal syncope.

5. The subject smokes or has used tobacco in any form within four weeks prior to dosing.

6. The subject has received an investigational drug within

four weeks prior to study screening.

7. The subject has received any drug, vitamins, unusual diet, OTC products, or has been treated for a condition within four weeks prior to the study for a condition, which, in the investigator's opinion, should preclude enrollment into the study.

8. The subject has a blood loss of more than 200 mL within four weeks prior to study screening (e.g., donations or Injury) or has donated plasma within two weeks prior to study dosing. The 24 subjects who received at least one dose of study drug constitute the intent-to-treat sample for this study.

8. Product information:

(1) Test product: Zenith's Clozapine Tablets, 25 mg

Lot #ND-234
Batch size: (b)(4)(CC) tablets

(2) Reference product: Sandoz's Clozaril[R] Tablets, 25 mg

Lot #081U4750
Expiration date: Jan, '97

9. Dosing: A single one-half tablet (12.5 mg) of Clozapine Tablet or Clozaril[R] was administered to each subject with 240 mL of room temperature water. Subjects were instructed to lie in bed in prone position during the 12 hour periods following study drug administration. They were not to engage in any strenuous physical activity (e.g., that which would alter vital signs or splanchnic blood flow) at any time during the weekend.

10. Food and fluid intake: No food was permitted after 9:00 PM on Friday evenings, or during the approximately six hour periods following study drug administration. Standardized high protein, low-fat meals following a meal plan intended to provide about 2500 Kcal/day were served at approximately 1:00 PM and 5:00 PM each Saturday, and the subjects were instructed to consume all of each meal, and snacks were provided at 8:00 PM on Friday and Saturday evenings. No fluid intake was permitted during the one hour periods preceding and following test material administration, after which fluids were provided ad libitum. Subjects were

instructed to drink 240 mL of water 10.5 and one hours prior to and two, four, and six hours following study drug administration. No alcohol, caffeine or other xanthine-containing foods or beverages were permitted during the periods beginning 48 hours prior to test material administration and ending when the last blood sample was taken.

11. Housing: Subjects were instructed to report to the clinical facility previous evening of each dosing day and the subjects were released from confinement following collection of the 24 hour blood samples each period.

12. Washout period: Seven days for Groups #1 and 2 and 6 weeks for Group #3. The long washout period for Group #3 was due to FDA's action to stop the study temporarily due to adverse reactions.

13. Blood samples: Blood samples (10 mL) were collected in appropriately labeled, evacuated blood collection tubes containing heparin as the anticoagulant, just prior to and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 15, 18, 24, 36, 48, and 72 hours after study drug administration. Plasma was harvested without delay from the centrifuged samples using glass pipettes and transferred, in equally sized split samples, into two appropriately labeled polypropylene screw top transfer tubes. The plasma samples were frozen in the upright position and stored frozen at -20°C or colder until they were assayed.

14. IRB and informed consent: IRB approvals on the study protocol and informed consent forms were obtained.

15. Pharmacokinetic and statistical analysis: SAS-GLM procedures were used on AUCT, AUCI, CMAX, TMAX, KE, THALF and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for AUCT, AUCI, and CMAX.

IV. Validation of Assay Method for Plasma Samples

(b)(4)(CC)

[redacted]

A. Pre-study validation for clozapine assay

(b)(4)(CC)

[redacted]

(b)(4)(CC)

Table 1. (b)(4)(CC)

(b)(4)(CC)

[redacted]

Table 2. Stability Data

(b)(4)(CC)

[redacted]

B. **Within-study validation**

(b)(4)(CC)

[redacted]

V. In Vivo Results with Statistical Analysis

A total of 24 healthy male volunteers were enrolled in three groups and subjects in group were dosed at different time with 12.5 mg (= one half tablet) of either the test or reference product in two-way crossover design. There were 5 dropouts

throughcut the whole study period and final statistical analyses were done using only 19 subjects.

Details of dropouts:

Two subjects (#7 and #12) experienced severe adverse events following the first dose of study drug and were subsequently removed from the study by the Principal Investigator. Three subjects from group three (#19, #23 and #24) failed to return to the dormitory for the second study weekend, for scheduling reasons related to the long delay between the two study periods and the short notice preceding resumption of the study.

Missing samples:

Of the 860 blood samples scheduled to be taken from the 24 subjects who participated in the study, seven were missed: subject #1 failed to return for the 48 hour sample during period two, subject #12 failed to return for the 48 and 72 hour samples during period one, subject #15 failed to return for the 36 hour sample during period one, subject #18 failed to return for the 36 hour sample during period two, subject #23 failed to return for the 36 hour sample during period one, and the 12 hour sample was inadvertently not taken from subject #4 during period two.

Adverse events:

All 24 subjects experienced at least one adverse event. These included asystole in three, bradycardia in 24, hypotension in 11, headache in three, syncope in two, and shoulder pain and abdominal cramps in one each; asystole was treated by placing the subjects in the Trendelburg position and, in one case (subject #21), by the intravenous administration of physiological saline. In addition, most of the subjects appeared to be sedated or drowsy for four to six hours following study drug administration. This has been reported for clozapine in healthy human subjects, but was not separately recorded as an adverse event because the subjects supine position could naturally have resulted in sleepiness. A high incidence of bradycardia was observed in this study. A heart rate below 60 bpm was observed on 434 occasions, and on nine of those occasions the heart rate was below 40 bpm; 23 of those occasions occurred during baseline value measurement prior to study drug administration. Multiple occasions of bradycardia were observed for each subject following study drug administration totaling 410 observations.

With the exception of left shoulder pain, each of the adverse events reported by or observed in subjects have been reported as

adverse events associated with clozapine administration and therefore must be considered as possibly due to study drug administration.

1. **Mean plasma levels**

The mean plasma clozapine profiles for the test and reference products are comparable as shown in Table 4 and Fig P-1. Peak mean plasma levels were 21.5 ng/mL at 1.5 hours for the test product and 23.2 ng/mL at 1.5 hours for the reference product, respectively.

Table 4. MEAN PLASMA CLOZAPINE LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST; MEAN2=REF; RMEAN12=T/R RATIO
UNIT=NG/ML

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.5	0.95	1.39	1.97	3.21	0.48
1	18.80	15.66	18.17	14.44	1.03
1.5	21.49	10.83	23.21	12.17	0.93
2	18.79	8.43	19.05	9.54	0.99
2.5	16.16	7.92	16.50	8.28	0.98
3	16.05	7.88	16.37	6.99	0.98
3.5	14.93	7.40	14.30	6.91	1.04
4	13.58	6.20	13.81	6.20	0.98
5	12.73	5.93	12.10	4.33	1.05
6	11.97	5.37	11.84	4.48	1.01
8	8.72	4.28	8.60	3.72	1.01
10	7.32	3.45	6.70	2.39	1.09
12	5.36	2.59	5.59	2.34	0.96
15	4.52	2.37	4.78	2.67	0.94
18	3.57	2.18	3.43	1.67	1.04
24	2.84	1.78	2.78	1.41	1.02
36	1.84	1.36	1.74	1.04	1.05
48	1.12	0.88	1.04	0.70	1.08
72	0.45	0.49	0.37	0.39	1.23

2. Pharmacokinetic parameters

The test/reference ratios (RMEAN12) were within 0.97-1.03 range for the non-transformed and log-transformed AUCT, AUCI and CMAX as shown in Table 5. The 90% confidence intervals for log-transformed AUCT, AUCI and CMAX are all within 80-125% range as shown in Table 7. The SAS GLM model used for the study is as follows to reflect the experimental design:

```
MODEL Y=  GROUP SEQUENCE SEQUENCE*GROUP SUBJECT(SEQUENCE*GROUP)
          PERIOD(GROUP) TREATMENT
```

It was found that TREATMENT*GROUP interaction term was not significant and this term was not included in the above model. The sequence and group effects were tested using subject(sequence*group) as the error term.

There was no period(group), sequence, group or treatment effect for the non-transformed and log-transformed AUCT, AUCI and CMAX.

Table 5. ARITHMETIC MEANS AND RATIOS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
MEAN1=TEST; MEAN2=REF; RMEAN12=T/R RATIO

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	257.78	124.15	250.83	107.83	1.03
AUCT	241.36	112.02	234.77	100.88	1.03
CMAX	26.44	12.56	26.37	9.83	1.00
KE	0.04	0.01	0.05	0.01	0.94
LAUCI	229.19	0.52	224.12	0.55	1.02
LAUCT	215.66	0.51	209.26	0.56	1.03
LCMAX	23.55	0.51	24.26	0.46	0.97
THALF	17.41	4.91	16.46	4.55	1.06
TMAX	2.24	1.77	2.18	1.56	1.02

Table 6. LSMEANS AND RATIOS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
LSM1=TEST; LSM2=REF; RLSM12=T/R RATIO

PARAMETER	LSM1	LSM2	RLSM12
AUCI	264.21	256.23	1.03
AUCT	247.23	239.54	1.03
CMAX	26.64	26.73	1.00
LAUCI	235.53	231.02	1.02
LAUCT	221.66	215.52	1.03
LCMAX	23.86	24.85	0.96

Table 7. LSMEANS AND 90% CONFIDENCE INTERVALS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
LOWCI12=LOWER LIMIT; UPPCI12=UPPER LIMIT

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCI	264.21	256.23	95.98	110.26
AUCT	247.23	239.54	96.40	110.02
CMAX	26.64	26.73	80.96	118.32
LAUCI	235.53	231.02	93.73	110.90
LAUCT	221.66	215.52	94.87	111.50
LCMAX	23.86	24.85	80.17	115.05

3. Test/Reference Ratios for Individual Subjects

Test/Reference ratios for pharmacokinetic parameters for individual subjects are shown in Table 8 and their statistics are

summarized in Table 9.

Table 8. TEST PRODUCT/REFERENCE PRODUCT RATIOS FOR INDIVIDUAL SUBJECTS

OBS	SUB	SEQ	RAUCT12	RAUCI12	RCMAX12	RTMAX12	RKE12	RTHALF12
1	1	1	(b)(4)(CC)					
2	2	2						
3	3	2						
4	4	2						
5	5	2						
6	6	1						
7	8	1						
8	9	2						
9	10	1						
10	11	2						
11	13	2						
12	14	1						
13	15	1						
14	16	2						
15	17	2						
16	18	2						
17	20	1						
18	21	1						
19	22	2						

Table 9. STATISTICS ON THE TEST/REFERENCE RATIOS

Variable	N	Mean	Std Dev	Minimum	Maximum
RAUCT12	19	1.05	0.23	0.74	1.76
RAUCI12	19	1.04	0.23	0.73	1.70
RCMAX12	19	1.05	0.38	0.39	1.70
RTMAX12	19	1.23	1.06	0.33	5.00
RKE12	19	0.96	0.19	0.70	1.58
RTHALF12	19	1.08	0.18	0.63	1.44

4. AUCT/AUCI Ratios for Individual Subjects

AUCT/AUCI ratios are listed for individual subjects and treatments in Table 10.

Table 10. AUCT/AUCI RATIO FOR INDIVIDUAL SUBJECTS

OBS	SUB	TRT	AUCRATIO
1	1	1	(b)(4)(CC)
2	2	1	
3	3	1	
4	4	1	
5	5	1	
6	6	1	
7	8	1	
8	9	1	
9	10	1	
10	11	1	
11	13	1	
12	14	1	
13	15	1	
14	16	1	
15	17	1	
16	18	1	
17	20	1	
18	21	1	
19	22	1	
20	1	2	
21	2	2	
22	3	2	
23	4	2	
24	5	2	
25	6	2	
26	8	2	
27	9	2	
28	10	2	
29	11	2	
30	13	2	
31	14	2	
32	15	2	
33	16	2	
34	17	2	
35	18	2	
36	20	2	
37	21	2	
38	22	2	

VI. Drug Products Information

1. Formulation comparison

Test formulations for the 25 mg and 100 mg tablets are shown in Table 11. Two formulations are not exactly proportional but similar. The test formulations do not contain inactive ingredients which might adversely affect the oral bioavailability of clozapine. Inactive ingredients used for the reference products are: colloidal silicon dioxide, lactose, magnesium stearate, mineral oil, povidone, starch and talc.

Table 11. Formulation for Test Products

Ingredients	25 mg Tablets, mg	100 mg Tablets, mg
Clozapine	25	100
Lactose Monohydrate	(b)(4)(TS)	
Pregelatinized Starch		
Starch		
Povidone		
Colloidal Silicon Dioxide		
Talc		
Magnesium Stearate		
Total Weight	165	240

2. Assay and content uniformity

Assay, content uniformity, batch size and expiration date information are summarized in Table 12.

Table 12. Assay and Content Uniformity Data

Product	Assay, %	Content Uniformity,% (%CV)
Test, 25 mg Tablets, Lot#ND-234 Batch size: (b)(4)(CC) Tablets	98.3	98.2 (1.2)
Test, 100 mg Tablets, Lot#ND-322 Batch size: (b)(4)(CC) Tablets	98.7	100.9 (1.7)
Ref, 25 mg Tablets, Lot#081U4750 Exp: 1/97	99.5	100.4 (1.2)
Ref, 100 mg Tablets, Lot#351Y9985 Exp: 7/99	-	-

VII. Dissolution Testing Data

The following dissolution specifications shown in Table 13 was recommended in FDA's guidance for clozapine bioequivalence study (11/15/96 version). The firm, however, used different tolerances, i.e., NLT (b)(4)(C(Q) in 45 min. The firm is recommended to use FDA specifications.

The test and reference products met the FDA specifications as shown in Table 14.

Table 13. Dissolution Specifications

Medium and Volume	Acetate Buffer, pH 4.0; 1000 mL
Apparatus and rpm	1 (basket); 100 rpm
Tolerances	NLT 80% in 45 min
Assay Method	UV spectroscopy

VIII. Waiver Request

The applicant requested a waiver for the 100 mg tablets. Based on the acceptable *in vivo* and *in vitro* dissolution data and proportionality of formulations, the waiver for the 100 mg tablets will be granted upon approval of the study.

IX. Comments

1. The 2-way crossover study under fasting conditions was conducted in three groups. Twenty-four healthy male

volunteers participated in the study and 19 subjects completed the study.

2. The mean plasma clozapine profiles for the test and reference products are comparable as shown in Table 4 and Fig P-1. Peak mean plasma levels were 21.5 ng/mL at 1.5 hours for the test product and 23.2 ng/mL at 1.5 hours for the reference product, respectively.

3. The test/reference ratios (RMEAN12) were within 0.97-1.03 range for the non-transformed and log-transformed AUCT, AUCI and CMAX as shown in Table 5. The 90% confidence intervals for log-transformed AUCT, AUCI and CMAX are all within 80-125% range as shown in Table 7. The SAS GLM model used for the study is as follows to reflect the experimental design:

MODEL Y= GROUP SEQUENCE SEQUENCE*GROUP SUBJECT(SEQUENCE*GROUP) PERIOD(GROUP) TREATMENT

4. Assay method validation data are not acceptable. Stability data of internal standard and stability data of stock solutions of clozapine and the internal standard were not submitted. Stability study should be performed using samples of a wide concentration range such as the quality control samples. Some of the stability data were based on only one concentration.

5. Test products (25 mg and 100 mg strengths) met FDA dissolution specifications.

6. Assay and content uniformity data for the test products were acceptable.

7. The batch size of the bio-batch (25 mg strength; lot #ND-234) was (b)(4)(CC) tablets.

8. Two subjects (#7 and #12) experienced severe adverse events following the first dose of study drug and were subsequently removed from the study by the Principal Investigator. All 24 subjects experienced at least one adverse event. These included asystole in three, bradycardia in 24, hypotension in 11, headache in three, syncope in two, and shoulder pain and abdominal cramps in one each; asystole was treated by placing the subjects in the Trendelburg position and, in one case (subject #21), by the intravenous administration of physiological saline. In addition, most of the subjects appeared to be sedated or drowsy for four to six hours following study drug administration.

X. Deficiencies

1. Assay method validation: Submit assay method for review.

2. Assay method validation: Explain clearly why it is not possible to generate recovery data.

3. Assay method validation: Submit stability data of internal standard and stability data of stock solutions of clozapine and the internal standard.

4. Assay method validation: Stability study should be performed using samples of a wide concentration range such as the quality control samples. Some of the stability data were based on only one concentration.

5. Assay method validation: Clarify the meaning of assayed individual curve and assayed combined curve.

6. Assay method validation: Submit data showing intra- and inter-day variability for pre-study and within-study validation.

XI. Recommendation

The *in vivo* bioequivalence study conducted under fasting conditions by Zenith Goldline on its Clozapine Tablets, 25 mg strength, lot #ND-234, comparing it to Sandoz's Clozaril®, 25 mg tablets, lot #081U4750, has been found incomplete. The firm should respond to the deficiencies #1-6.

The firm should be informed of the recommendation and deficiencies.

/S/ [redacted]
Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE
/S/ [redacted] 6/27/97
Ramakant M. Mhatre, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

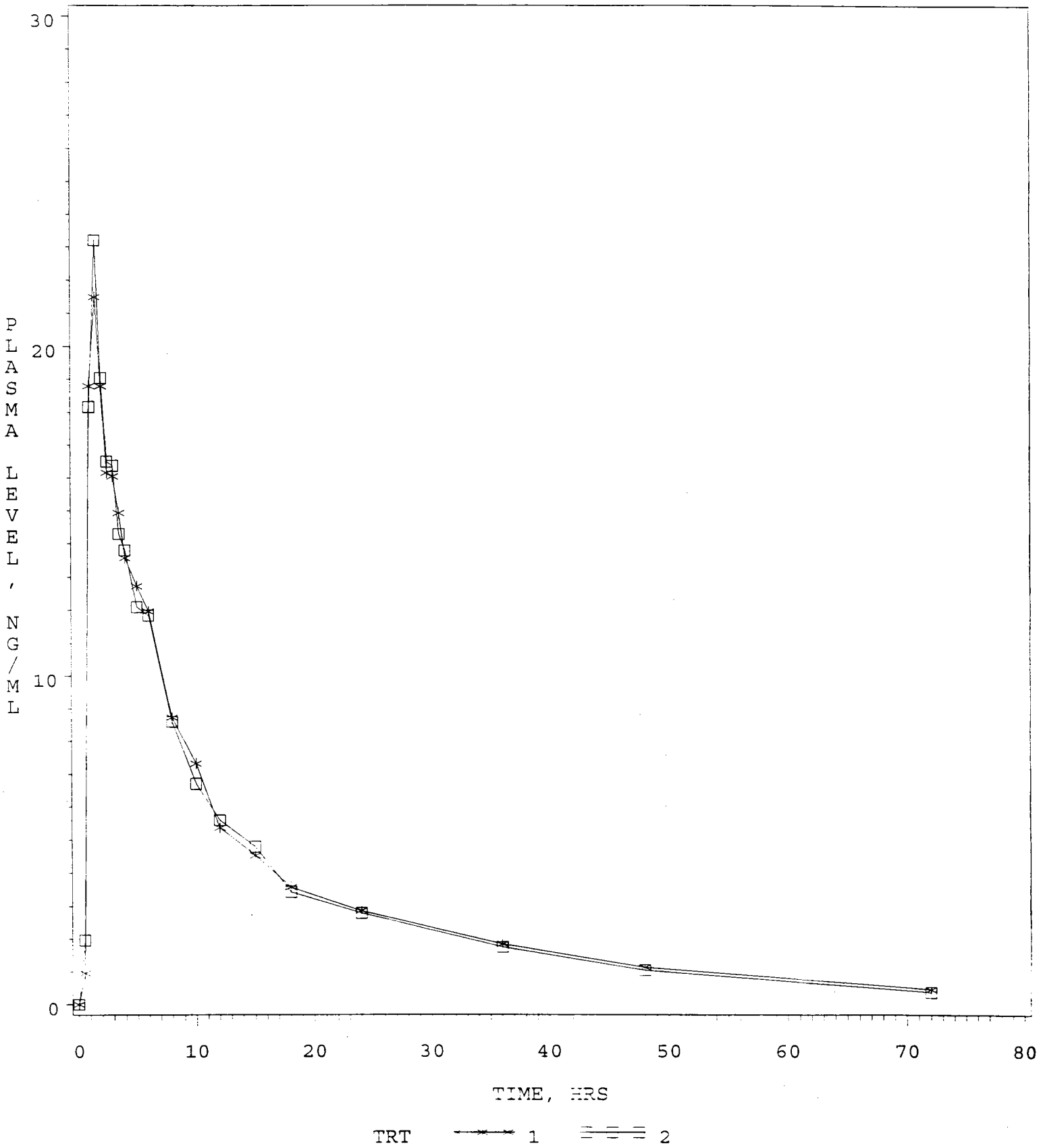
Concur: /S/ [redacted] Date: 2/3/97
Rabindra Patnaik, Ph.D.

Table 14. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Clozapine Tablets					
Strength	25 mg and 100 mg					
ANDA Number	74-949					
Applicant	Zenith Goldline					
Reference Drug Product	Sandoz's Clozaril					
II. FDA Method for Dissolution Testing						
Medium and Volume	Acetate Buffer, pH 4.0; 1000 mL					
Apparatus and rpm	1 (basket); 100 rpm					
Tolerances	NLT 80% in 45 min					
Assay Method	UV spectroscopy					
III. Dissolution Data (%)						
Time	Test Product Lot No: ND-234 Strength: 25 mg No of Units: 12			Reference Product Lot No: 081U4750 Strength: 25 mg No of Units: 12		
hrs	Mean	Range	%CV	Mean	Range	%CV
10	97.5	(b)(4)(CC)	1.1	101	(b)(4)(CC)	1.6
20	97.4		1.2	101		1.4
30	97.2		1.1	101		1.3
45	97.2		1.1	101		1.3
Time	Test Product Lot No: ND-322 Strength: 100 mg No of Units: 12			Reference Product Lot No: 351Y9985 Strength: 100 mg No of Units: 12		
hrs	Mean	Range	%CV	Mean	Range	%CV
10	54.8	(b)(4)(CC)	3.9	39.1	(b)(4)(CC)	8.2
20	93.3		3.9	68.8		7.0

30	102	(b)(4)(CC)	1.5	92.4	(b)(4)(CC)	6.9
45	102		1.5	102.8		1.5

FIG P-1. PLASMA CLOZAPINE LEVELS

CLOZAPINE TABLETS, 25 MG, ANDA #74-949
UNDER FASTING CONDITIONS
DOSE=12.5 MG(ONE HALF TABLET)



1=TEST PRODUCT(ZENITH) 2=REFERENCE PRODUCT(SANDOZ)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 74949

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 74-949

Date of Submission: October 17, 1997

Applicant's Name: Zenith-Goldline Pharmaceuticals, Inc.

Established Name: Clozapine Tablets, 25 mg and 100 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: (25 mg - 100s, 500s, 1000s, 5000s)
(100 mg - 200s, 500s, 1000s, 4000s)

Satisfactory as of June 2, 1997 submission

Professional Package Insert Labeling:

Satisfactory as of October 17, 1997 submission

Monitoring System:

Satisfactory as of October 17, 1997 submission

Clarifications needed post-approval on Monitoring System:

1. GENERAL COMMENTS

   a. A determination needs to be made and incorporated, where appropriate, who notifies Novartis when a patient is discontinued from clozapine.

   b. Clarify who contacts the Rechallenge Registry to determine the eligibility of a patient. The Step-by-Step Summary states that ZGP's registry staff will do this, but the Registration Form indicates that the physician and pharmacist do it.

2. Registration Form

   a. Revise to spell out "Oriental" rather than using just the letter "O" under race.

   b. For #9 of Part III, ZGP Clozapine ALERT Program™ should contact the internal QA contract person rather than the physician and pharmacist participants.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Clozaril® Tablets

NDA Number: 19-758

NDA Drug Name: Clozapine Tablets

NDA Firm: Novartis Pharmaceutical Corporation

Date of Approval of NDA Insert and supplement #035: September 19, 1997

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: 19-758

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?		x	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?			

Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		*	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?			x
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		x	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

1. Supplement S-015 involves reformulation of Clozaril to (b)(4)(TS) substance. Do these changes effect the formulation of Zenith's product?

3. The innovator packages its product in bottles of 100 and in unit dose packing. Zenith is proposing to package its products in bottles of 100, 500, 1000, and 5000 for the

25 mg tablet and bottles of 100, 500, 1000, 4000 for the 100 mg tablet. Do you concur with the proposed packaging configurations?

FOR THE RECORD:

1. Labeling review based on approved labeling for the listed drug (Clozapine - Sandoz Pharmaceuticals Corporation; revised June 1997; approved September 19, 1997.) This is new labeling.

2. Packaging
The innovator packages its products bottles of 100 and in unit dose packaging.

   The applicant proposes to package its products in white HDPE bottles of 100, 500, 1000, and 5000 for the 25 mg strength, and 100, 500, 1000, and 4000 of the 100 mg strength. The bottle of 100 will have a CRC.

3. In terms of safety, Jerry Phillips has contacted Novartis regarding their commitment to manage a national rechallenge registry. While awaiting their response, ZGP has opted to not propose any information or language regarding the notification of Novartis if and when a patient has to be discontinued from clozapine. They only mention recording data in their own rechallenge registry which, of course, will not include all those patients currently on Clozaril. Information from Novartis is critically needed at this point.

   Other issues of concern regarding ZGP's monitoring system are included in the Post-approval revision portion of this review.

4. To differentiate their products, Zenith has color coded their strength box, pink for the 25 mg tablet and blue for the 100 mg tablet.

5. In describing its tablets in the HOW SUPPLIED section of the insert labeling, Zenith has revised the description of their tablets which still does not include the "Z" preceding the "4359" and "4360" debossed on one side of their tablet as described on pages 119 and 123 of the Formulation Data. Perhaps the "Z" will not appear on the tablet.

6. Zenith has revised the scoring configuration of the 100 mg tablet. The change is reflected in the HOW SUPPLIED section of the labeling.

7. Inactive ingredients - The inactive ingredients listed in

the DESCRIPTION section of the insert agree with those listed on page 132 of Vol. 1.1.

Additionally, S-015 of the RLD indicates that a couple of changes have been made in its formulation. This has been brought to the attention of the chemist to ensure that these changes do not impact the formulation of the applicant's product.

8. Storage and Dispensing Issues
RLD - 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.

ANDA - PHARMACIST - Dispense in a tight container as defined in the USP. Use child-resistant closure (as required). It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
Store at CRT 15-30°C (59-86°F).

10. Bio is pending.

11. No patent/exclusivity issues pending.

Date of Review:
October 30, 1997

Date of Submission:
October 17, 1997

Primary Reviewer: Date:

Team Leader: Date:

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cc:
ANDA: 74-949
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
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Review