CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-758/S047

Trade Name: Clozaril

Generic Name: Clozapine

Sponsor: Novartis

Approval Date: December 18, 2002

Indications: For reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for reexperiencing suicidal behavior, based on history and recent clinical state.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-758 / S-047

Novartis Pharmaceuticals Corporation
Attention: James Rawls, Pharm.D.
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Rawls:

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

We acknowledge receipt of your submissions of October 11, 2002 and October 25, 2002.

Your submission of October 25, 2002 constituted a complete response to our action letter of August 30, 2002.

This supplemental new drug application provides for the use of Clozaril (clozapine) tablets to treat patients with schizophrenia or schizoaffective disorder at risk for emergent suicidal behavior.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-758/S-047." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Sincerely,

{See appended electronic signature page}

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

Enclosure (Labeling)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
12/18/02 02:13:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19758/S-047

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

Dear Dr. Rawls:

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

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

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

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

Issues for Study ABA 451that Need to be Addressed:

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

1. Change in Blinded Raters

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

2. SMB Performance

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

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

3. Unblinding of Blinded Psychiatrists

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

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

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

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

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

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

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

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

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

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

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

Sincerely,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
8/30/02 01:27:48 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

LABELING

T2002-XX
89004506

CLOZARIL®

(clozapine) Tablets

Rx only

Prescribing Information

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

WARNING

1. AGRANULOCYTOSIS

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

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

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

2. SEIZURES

SEIZURES HAVE BEEN ASSOCIATED WITH THE USE OF CLOZAPINE. DOSE APPEARS TO BE AN IMPORTANT PREDICTOR OF SEIZURE, WITH A GREATER LIKLIEHOOD AT HIGHER CLOZAPINE DOSES. CAUTION SHOULD BE USED WHEN ADMINISTERJNG CLOZAPINE TO PATIENTS HAVING A HISTORY OF SEIZURES OR OTHER PREDISPOSING FACTORS. PATIENTS SHOULD BE ADVISED NOT TO ENGAGE IN ANY ACTIVITY WHERE SUDDEN LOSS OF CONSCIOUSNESS COULD CAUSE SERIOUS RISK TO THEMSELVES OR OTHERS. (SEE WARNINGS)

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

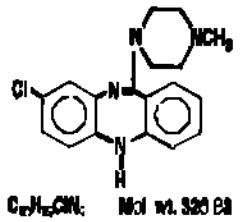
4. OTHER ADVERSE CARDIOVASCULAR AND RESPIRATORY EFFECTS
ORTHOSTATIC HYPOTENSION, WITH OR WITHOUT SYNCOPE, CAN OCCUR WITH CLOZAPINE TREATMENT. RARELY, COLLAPSE CAN BE PROFOUND AND BE ACCOMPANIED BY RESPIRATORY AND/OR CARDIAC ARREST. ORTHOSTATIC HYPOTENSION IS MORE LIKELY TO OCCUR DURING INITIAL TITRATION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

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

DESCRIPTION

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

The structural formula is:



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

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

25 mg and 100 mg Tablets

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

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

CLINICAL PHARMACOLOGY

Pharmacodynamics

CLOZARIL® (clozapine) is classified as an 'atypical' antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine mediated behaviors differ from those exhibited by more

typical antipsychotic drug products. In particular, although CLOZARIL® (clozapine) does interfere with the binding of dopamine at D_1, D_2, D_3 and D_5 receptors, and has a high affinity for the D_4 receptor, it does not induce catalepsy nor inhibit apomorphine-induced stereotypy. This evidence, consistent with the view that CLOZARIL® (clozapine) is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of CLOZARIL® (clozapine) from extrapyramidal side effects.

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

Absorption, Distribution, Metabolism and Excretion

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

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

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

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

Human Pharmacology

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

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

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

The effectiveness of CLOZARIL® (clozapine) in reducing the risk of recurrent suicidal behavior was assessed in the International Suicide Prevention Trial (InterSePT?), which was a prospective, randomized, international, parallel-group comparison of CLOZARIL vs. Zyprexa® (olanzapine) in patients with schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be at risk for reexperiencing suicidal behavior. Only about

one-fourth of these patients (27%) were considered resistant to standard antipsychotic drug treatment, and the remainder were not. Patients met one of the following criteria:

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

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

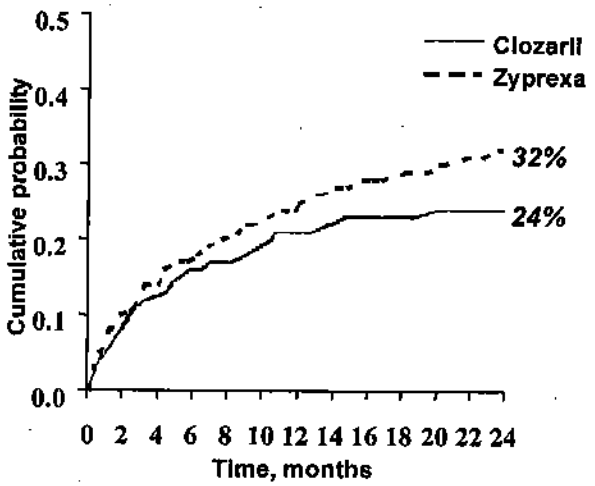
The primary efficacy measure was time to (1) a significant suicide attempt, including a completed suicide, (2) hospitalization due to imminent suicide risk (including increased level of surveillance for suicidality for patients already hospitalized), or (3) worsening of suicidality severity as demonstrated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

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

Data from this study indicate that Clozaril had a statistically significant longer delay in the time to recurrent suicidal behavior in comparison with Zyprexa. This result should be interpreted only as evidence of the effectiveness of Clozaril in delaying time to recurrent suicidal behavior, and not a demonstration of the superior efficacy of Clozaril over Zyprexa.

The probability of experiencing (1) a significant suicide attempt, including a completed suicide, or (2) hospitalization due to imminent suicide risk (including increased level of surveillance for suicidality for patients already hospitalized) was lower for Clozaril patients than for Zyprexa patients at Week 104: Clozaril 24% vs. Zyprexa 32%; 95% C.I. of the difference: 2%, 14% (Figure 1).

Figure 1 Kaplan-Meier Estimates of Cumulative Probability of a Significant Suicide Attempt or Hospitalization to Prevent Suicide



INDICATIONS AND USAGE

Treatment Resistant Schizophrenia

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

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

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

Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia and Schizoaffective Disorders

Clozaril is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for reexperiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that put him/herself at risk for death.

The effectiveness of Clozaril in reducing the risk of recurrent suicidal behavior was demonstrated over a 2 year treatment period in the InterSePT Trial (see Clinical Trials Data under Clinical Pharmacology). Therefore, Clozaril treatment to reduce the risk of suicidal behavior should be continued for at least 2 years (see DOSAGE AND ADMINISTRATION).

The prescriber should be aware that a majority of patients in both treatment groups in InterSePT received other treatments as well to reduce suicide risk, such as antidepressants and other medications, hospitalization, and/or psychotherapy. The contributions of these additional measures are unknown. .

CONTRAINDICATIONS

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

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

WARNINGS

General

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

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

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

Agranulocytosis

Agranulocytosis, defined as an absolute neutrophil count (ANC) of less than 500/mm^3, has been estimated to occur in association with CLOZARIL® (clozapine) use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 US cases out of 1743 patients exposed to CLOZARIL® (clozapine) during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and

therapy interrupted. Of the 149 cases of agranulocytosis reported worldwide in association with CLOZARIL® (clozapine) use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of CLOZARIL® (clozapine) induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for CLOZARIL® (clozapine) induced agranulocytosis, despite strict adherence to the required frequency of monitoring. In the U.S., under a weekly WBC monitoring system with CLOZARIL® (clozapine), there have been 585 cases of agranulocytosis as of August 21, 1997; 19 were fatal. During this period 150,409 patients received CLOZARIL® (clozapine). A hematologic risk analysis was conducted based upon the available information in the Clozaril® National Registry (CNR) for U.S. patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule, rose steeply during the first two months of therapy, peaking in the third month. Among Clozaril® (clozapine) patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree, so that by the sixth month the weekly incidence of agranulocytosis was reduced to 3 per 1000 person-years. After six months, the weekly incidence of agranulocytosis declines still further, however, never reaches zero. It should be noted that any type of reduction in the frequency of monitoring WBC counts may result in an increase incidence of agranulocytosis.

Because of the substantial risk for developing agranulocytosis in association with CLOZARIL® (clozapine) use, which may persist over an extended period of time, patients must have a blood sample drawn for a WBC count before initiation of treatment with CLOZARIL® (clozapine), and must have subsequent WBC counts done at least weekly for the first 6 months of continuous treatment. If WBC counts remain acceptable (WBC greater than or equal to 3000/mm^3, ANC ? 1500/mm^3) during this period, WBC counts may be monitored every other week thereafter. After the discontinuation of Clozaril® (clozapine), weekly WBC counts should be continued for an additional 4 weeks.

If a patient is on Clozaril® (clozapine) therapy for less than 6 months with no abnormal blood events and there is a break on therapy which is less than or equal to 1 month, then patients can continue where they left off with weekly WBC testing for 6 months. When this 6 month period has been completed, the frequency of WBC count monitoring can be reduced to every other week. If a patient is on Clozaril (clozapine) therapy for less than 6 months with no abnormal blood events and there is a break on therapy which is greater than 1 month, then patients should be tested weekly for an additional 6 month period before biweekly testing is initiated. If a patient is on Clozaril® (clozapine) therapy for less than 6 months and experiences an abnormal blood event as described below but remains a rechallengeable patient [patients cannot be reinitiated on Clozaril® (clozapine) therapy if WBC counts fall below 2000/mm^3, or the ANC falls below 1000/mm^3 during Clozaril® (clozapine) therapy], the patient must re-start the 6 month period of weekly WBC monitoring at day 0.

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

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

If the total WBC count falls below 3000/mm^3, or the ANC below 1500/mm^3, CLOZARIL® (clozapine) therapy should be interrupted, WBC count and differential should be performed daily, and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. CLOZARIL® (clozapine) therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3000/mm^3 and the ANC returns to levels above 1500/mm^3. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500/mm^3.

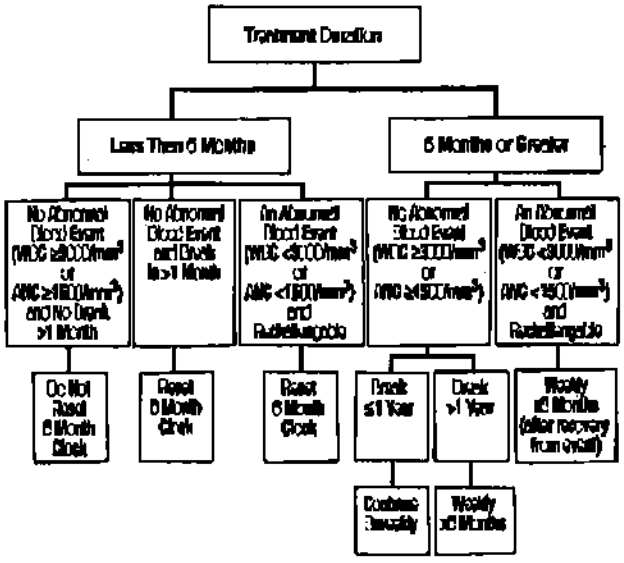
If the total WBC count falls below 2000/mm^3 or the ANC falls below 1000/mm^3, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000/mm^3, or ANCs below 1000/mm^3 during CLOZARIL® (clozapine) therapy should have daily WBC count and differential. These patients should not be re-challenged with CLOZARIL® (clozapine). Patients discontinued from CLOZARIL® (clozapine) therapy due to significant WBC suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on re-exposure. To reduce the chances of rechallenge occurring in patients who have experienced significant bone marrow suppression during CLOZARIL® (clozapine) therapy, a single, national master file will be maintained confidentially.

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

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

Interrupted Therapy (WBC < 3000/mm^3 ANC <1500/mm^3) for Bi-Weekly Monitoring



Eosinophilia

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

Seizures

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

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

Myocarditis

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

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

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

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

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

Other Adverse Cardiovascular and Respiratory Effects

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

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

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

A minority of CLOZARIL® (clozapine) treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of CLOZARIL® (clozapine). The clinical significance of these changes is unclear. However, in clinical trials with CLOZARIL® (clozapine), several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, arrhythmias and sudden death. In addition there have been postmarketing reports of congestive heart failure. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown.

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

Neuroleptic Malignant Syndrome (NMS)

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

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

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

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

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

Tardive Dyskinesia

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

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

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

Given these considerations, CLOZARIL® (clozapine) should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic CLOZARIL® (clozapine) use should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

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

PRECAUTIONS

General

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

Fever

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

Pulmonary Embolism

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

Hyperglycemia

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

Hepatitis

Caution is advised in patients using CLOZARIL® (clozapine) who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and pre-existing liver function abnormalities. In patients who develop nausea, vomiting, and/or anorexia during CLOZARIL® (clozapine) treatment, liver function tests should be performed immediately. If the elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with CLOZARIL® (clozapine) should be discontinued.

Anticholinergic Toxicity

Eye

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

Gastrointestinal

CLOZARIL® (clozapine) use has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction and paralytic ileus (*see ADVERSE REACTIONS*). On rare occasions, these cases have been fatal. Constipation should be initially treated by

ensuring adequate hydration, and use of ancillary therapy such as bulk laxatives. Consultation with a gastroenterologist is advisable in more serious cases.

Prostate

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

Interference with Cognitive and Motor Performance

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

Use in Patients with Concomitant Illness

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

Use in Patients Undergoing General Anesthesia

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

Information for Patients

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

- Patients who are to receive CLOZARIL® (clozapine) should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required for the first 6 months, if acceptable WBC counts (WBC greater than or equal to 3000/mm^3, ANC ? 1500/mm^3) have been maintained during the first 6 months of continuous therapy, then WBC counts can be monitored every other week in order to monitor for the occurrence of agranulocytosis, and that CLOZARIL® (clozapine) tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.
- Patients should be informed of the significant risk of seizure during CLOZARIL® (clozapine) treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking CLOZARIL® (clozapine).
- Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.
- Patients should be informed that if they stop taking CLOZARIL® (clozapine) for more than 2 days, they should not restart their medication at the same dosage, but should contact their physician for dosing instructions.
- Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol.
- Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should not breast feed an infant if they are taking CLOZARIL® (clozapine).

Drug Interactions

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

Pharmacodynamic-related interactions

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

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

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

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

Pharmacokinetic-related interactions

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

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

Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine. Cimetidine, caffeine, and erythromycin may increase plasma levels of CLOZARIL® (clozapine), potentially resulting in adverse effects. Although concomitant use of CLOZARIL® (clozapine) and carbamazepine is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in CLOZARIL® (clozapine) plasma levels.

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

A subset (3%-10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isozyme P450 2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, the tricyclic antidepressants, and clozapine. These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. In addition, certain drugs that are metabolized by this isozyme, including many antidepressants (clozapine, selective serotonin reuptake

inhibitors, and others), may inhibit the activity of this isozyme, and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy Category B

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

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

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

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

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Sixteen percent of 1080 patients who received CLOZARIL® (clozapine) in premarketing clinical trials discontinued treatment due to an adverse event, including both those that could be reasonably attributed to CLOZARIL®

(clozapine) treatment and those that might more appropriately be considered intercurrent illness. The more common events considered to be causes of discontinuation included: CNS, primarily drowsiness/sedation, seizures, dizziness/syncope; cardiovascular, primarily tachycardia, hypotension and ECG changes; gastrointestinal, primarily nausea/vomiting; hematologic, primarily leukopenia/ granulocytopenia/agranulocytosis; and fever. None of the events enumerated accounts for more than 1.7% of all discontinuations attributed to adverse clinical events.

Commonly Observed

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

Incidence in Clinical Trials

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

Treatment-Emergent Adverse Experience Incidence

Among Patients Taking CLOZARIL® (clozapine) in Clinical Trials (excluding the InterSePT Study)

(N = 842)

(Percentage of Patients Reporting)

Body System **Adverse Event**[a]	**Percent**
Central Nervous System	
Drowsiness/Sedation	39
Dizziness/Vertigo	19
Headache	7
Tremor	6
Syncope	6
Disturbed sleep/Nightmares	4
Restlessness	4
Hypokinesia/Akinesia	4
Agitation	4
Seizures (convulsions)	3[b]
Rigidity	3
Akathisia	3
Confusion	3
Fatigue	2
Insomnia	2
Hyperkinesia	1
Weakness	1
Lethargy	1
Ataxia	1

Slurred speech	1
Depression	1
Epileptiform movements/Myoclonic jerks	1
Anxiety	1
Cardiovascular	
Tachycardia	25[b]
Hypotension	9
Hypertension	4
Chest pain/Angina	1
ECG change/Cardiac abnormality	1
Gastrointestinal	
Constipation	14
Nausea	5
Abdominal discomfort/Heartburn	4
Nausea/Vomiting	3
Vomiting	3
Diarrhea	2
Liver test abnormality	1
Anorexia	1
Urogenital	
Urinary abnormalities	2
Incontinence	1
Abnormal ejaculation	1
Urinary urgency/frequency	1
Urinary retention	1
Autonomic Nervous System	
Salivation	31
Sweating	6
Dry mouth	6
Visual disturbances	5
Integumentary (Skin)	
Rash	2
Musculoskeletal	
Muscle weakness	1
Pain (back, neck, legs)	1
Muscle spasm	1
Muscle pain, ache	1
Respiratory	
Throat discomfort	1
Dyspnea, shortness of breath	1
Nasal congestion	1
Hemic/Lymphatic	

Leukopenia/Decreased WBC/Neutropenia	3
Agranulocytosis	1[b]
Eosinophilia	1
Miscellaneous	
Fever	5
Weight gain	4
Tongue numb/sore	1

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

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

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

Treatment-Emergent Adverse Experience Incidence[1]

Among Patients Taking CLOZARIL® (clozapine) or Zyprexa® (olanzapine) in the InterSePT study

(Percentage of Patients Reporting)

	Clozaril N=479 % Reporting	Zyprexa N=477 % Reporting
Adverse Events		
Salivary hypersecretion	48%	6%
Somnolence	46%	25%
Weight increased	31%	56%
Dizziness (excluding vertigo)	27%	12%
Constipation	25%	10%
Insomnia NEC	20%	33%
Nausea	17%	10%
Vomiting NOS	17%	9%
Dyspepsia	14%	8%

[1]AEs are listed by frequency in Clozaril group, and included in the table are those for which the risk ratio of Clozaril over Zyprexa or of Zyprexa over Clozaril was greater than 1.5.

-

NEC – not elsewhere classified

NOS – not otherwise classified

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

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

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

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

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

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

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

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

Musculoskeletal System: twitching and joint pain.

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

Hemic and Lymphatic System: anemia and leukocytosis.

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

Postmarketing Clinical Experience

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

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

Cardiovascular System: atrial or ventricular fibrillation and periorbital edema.

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

Hepatobiliary System: cholestasis; hepatitis; jaundice.

Hepatic System: cholestasis.

Urogenital System: acute interstitial nephritis and priapism.

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

Musculoskeletal System: myasthenic syndrome and rhabdomyolysis.

Respiratory System: aspiration and pleural effusion.

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

Vision Disorders: narrow angle glaucoma

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

DRUG ABUSE AND DEPENDENCE

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

OVERDOSAGE

Human Experience

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

Management of Overdose

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

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

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

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

DOSAGE AND ADMINISTRATION

Treatment Resistant Schizophrenia

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

Initial Treatment

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

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

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary

support for the superiority of CLOZARIL® (clozapine) in treatment resistant patients, the mean and median CLOZARIL® (clozapine) doses were both approximately 600 mg/day.]

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

Dosing should not exceed 900 mg/day.

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

Maintenance Treatment

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

Discontinuation of Treatment

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

Reinitiation of Treatment In Patients Previously Discontinued

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

Certain additional precautions seem prudent when reinitiating treatment. The mechanisms underlying CLOZARIL® (clozapine) induced adverse reactions are unknown. It is conceivable, however, that re-exposure of a patient might enhance the risk of an untoward event's occurrence and increase its severity. Such phenomena, for example, occur when immune mediated mechanisms are responsible. Consequently, during the reinitiation of treatment, additional caution is advised. Patients discontinued for WBC counts below 2000/mm^3 or an ANC below 1000/mm^3 must *not* be restarted on CLOZARIL® (clozapine). (*See WARNINGS*)

Reducing the Risk of Recurrent Suicidal Behavior in patients with Schizophrenia or Schizoaffective Disorder

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

The InterSePT study demonstrated the efficacy of CLOZARIL in the treatment of patients with schizophrenia or schizoaffective disorder at risk for recurrent suicidal behavior where the mean daily dose was about 300 mg (range 12.5 to 900 mg).

Patients previously treated with other antipsychotics were cross-titrated to Clozaril over a one month interval; the dose of the previous antipsychotic was gradually decreased simultaneous with a gradual increase in Clozaril dose over the first month of the study. Patients on depot antipsychotic medication began Clozaril after one full dosing interval since the last injection.

Recommendations to reduce the risk of recurrent suicidal behavior in patients who otherwise previously responded to treatment of schizophrenia or schizoaffective disorder with another antipsychotic medication

The results of the InterSePT study demonstrated that, for a 2-year treatment period, the probability of a suicide attempt or a hospitalization due to imminent suicide risk is stable at approximately 24% after one year of treatment with Clozaril (Figure 1, Clinical Trial Data Section). A course of treatment with Clozaril of at least 2 years is therefore recommended in order to maintain the reduction of risk for suicidal behavior. After 2 years, it is recommended that the patient's risk of suicidal behavior be assessed. If the physician's assessment indicates that a significant risk for suicidal behavior is still present, treatment with Clozaril should be continued. Thereafter, the decision to continue treatment with Clozaril should be re-visited in regular intervals, based on thorough assessments of the patient's risk for suicidal behavior during treatment. If the physician determines that the patient is no longer at risk for suicidal behavior, treatment with Clozaril may be discontinued (see recommendations above regarding discontinuation of treatment) and treatment of the underlying disorder with an antipsychotic medication to which the patient has previously responded may be resumed.

HOW SUPPLIED

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

CLOZARIL® (clozapine) Tablets

25 mg

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

Bottle of 100.....NDC 0078-0126-05

Bottle of 500.....NDC 0078-0126-08

Unit dose packages of 100: 2 x 5 strips, 10 blisters per strip .....NDC 0078-0126-06

100 mg

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

Bottle of 100..... NDC 0078-0127-05

Bottle of 500.....NDC 0078-0127-08

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

Store and Dispense

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

*Trademark of Medical Economics Company, Inc.

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

OFFICE DIRECTOR MEMO

MEMORANDUM

DATE: August 29, 2002

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 19-758/S-047

SUBJECT: Action Memo for NDA 19-758/S-047, for the new indication of Treatment of Suicide with Clozaril (clozapine) Tablets

NDA 19-758/S-047, for the new indication of Treatment of Suicide with Clozaril (clozapine) Tablets was submitted by Novartis Pharmaceuticals Corporation on 2/28/02. The submission contains the results of a single controlled trial that the sponsor believes demonstrates the capacity of clozapine to treat suicidality in patients with schizophrenia or schizoaffective disorder. Clozapine is currently marketed for treatment-resistant schizophrenia. This indication was supported by a trial in which clozapine demonstrated superiority to an active agent in patients who had not responded to previous anti-psychotic treatment. This showing was required because of the high incidence of agranulocytosis associated with clozapine use. Because of this incidence, patients being treated with clozapine are required to enter a registry, and obtain a blood count before receiving continued treatment every week for the first 6 months of treatment, and every 2 weeks thereafter.

The results of a cohort mortality study, reported in May, 1995, based on data from the registry, suggested that patients currently receiving clozapine had a marked reduction in the risk of suicide compared to past users. The sponsor submitted a labeling supplement proposing a claim for the treatment of suicidality in 1995, based on the results of this study. While the application was turned down (based on the observational nature of the data), the sponsor was encouraged to perform a prospective controlled trial designed to address this question.

The current application has been reviewed by Dr. Greg Dubitsky, medical officer (review dated 8/22/02), Dr. Kun He, statistician (review dated 8/21/02), Dr. Gurpreet Gill-Sangha, chemist (review dated 8/1/02), and Dr. Thomas Laughren, psychiatric drugs team leader (memo dated 8/23/02). In this memo, I will briefly review the critical findings in the controlled trial, and offer the basis for the division's action.

STUDY ABA 451

This was a randomized, unblinded study in patients with schizophrenia or schizoaffective disorder with a history of suicide attempts or recent suicidal

ideation. Patients in 67 centers worldwide (31 US sites) were randomized to receive clozapine 200-900 mg/day or olanzapine 5-20 mg/day, and were to be followed for up to 24 months. It was felt impossible to practically blind the trial because clozapine patients had to have blood drawn every week, and it was felt to be unacceptable to draw blood every week from patients who do not require such blood draws. In order to control for the fact that clozapine patients had contact with the health care system every week, olanzapine treated patients were seen weekly for vital sign measurements.

Patients were to be evaluated every month by an unblinded investigator who would administer the Intersept Suicidal Thinking Scale (ISST) and the CGI Severity of Suicidality Scale (CGI-SS; this scale comes in 2 versions-a 5 question and a 7 question form). In addition, detailed information about major events (suicide attempts, suicides, hospitalization for suicidality, and increased surveillance for suicidality in in-patients) was collected by the investigators and/or their staff. These events were referred to as Type 1 events. In addition to these ratings, blinded investigators at each site rated the patients on the ISST and CGI-SS every 8 weeks.

When the unblinded investigators felt that a Type 1 event had occurred, they forwarded the relevant data to Ingenix Pharmaceutical Services, which prepared a package of blinded information to be reviewed by a 3 person Suicide Monitoring Board, which was to determine if, in fact, a Type 1 event had occurred. In addition, the blinded investigators at each site received the same package of blinded data, and made their own determination of whether or not the event in question was a Type 1 event.

Ingenix Pharmaceutical Services also received a great deal of other data, including information on all hospitalizations, adverse events, etc. They were to perform a "blinded" review of this data, to determine if there were additional cases, not identified by the unblinded investigators, that could have constituted a Type 1 event. If so, they were to prepare a package as described above. However, it appears that the unblinded investigator had the ultimate authority to decide if such a blinded package should be prepared by Ingenix to be sent for adjudication. Also, and critically, as Dr. Laughren notes, we have no confidence that the "blinded" reviews presumably performed by Ingenix were, in fact, blinded. Indeed, it is likely that they were unblinded, given the staff's access to the unblinded data.

The original statistical plan called for 2 primary outcome measures: 1) time to significant suicide attempt, and 2) change from baseline in CGI-SS (performed by the blinded investigator), with no provision for correction of the alpha level due to multiple comparisons.

However, based on an interim (blinded) review, the sponsor noted that there were very few events of the first kind, and a considerable number of early

discontinuations. Because of this, they proposed that there be a new primary analysis, the time to either of 2 endpoints: Type 1 events, as described above, or Type 2 events, defined as worsening of suicidality, as determined by a score of 6 (much worse) or 7 (very much worse) on the CGI-SS, or the occurrence of a Type 1 event. These endpoints were to be assessed whether or not patients were still receiving treatment; indeed, an effort was to be made to observe patients for the full 24 months, whether or not they continued on treatment (an amendment to the protocol also permitted patients to be re-enrolled if they had previously stopped treatment). The revised primary outcomes, as well as the revised statistical methodology (described in detail by Dr. He in his review, pages 7-8), were agreed to with the Division.

A total of 490 patients were randomized to each treatment group. The following table presents the disposition of patients in the trial:

	Clozapine	Olanzapine
Randomized	490	490
Received Treatment	479	477
Completed	298	303
Discontinued	192	187
Retreived Dropouts	61	60
Patients with Type 1 event	102	141
Patients with Type 2 event	120	161
Lost to Follow-up	25	26

(Recall that Type 1 events are a subset of Type 2 events; therefore, the number of patients who met the CGI-SS criteria for Type 2 events was 18 clozapine and 20 olanzapine patients. Recall also that Retreived Dropouts could either have had, or not had, either type of event).

The results of the primary analysis yielded a p-value of 0.031, in favor of the clozapine treated patients (see Dr. Dubitsky's review, page 68, for Kaplan-Meier curves [although not the primary analysis] for the cumulative probability at the end of the study for Type 1 and Type 2 events). The p-values for the between-treatment contrasts for the individual types of events were 0.03 and 0.04 for Type 1 and Type 2 events, respectively, in favor of clozapine.

Patients who experienced either Type 1 or Type 2 events could continue in the study; indeed, the 102 clozapine patients who met the endpoint of Type 1 event experienced a total of 217 Type 1 events, and the 141 olanzapine patients who met the endpoint of Type 1 events experienced a total of 266 such events.

Recall that the events analyzed were those determined by the blinded SMB to be true events of either kind. In actuality, a total of 577 potential Type 1 events

(representing 122 clozaril and 157 olanzapine patients) were referred for adjudication, 261 clozapine and 316 olanzapine (we do not know the distribution of sources of identification of these potential events, the unblinded investigators or Ingenix staff, although the US monitor suggests that only about 20 of the referrals originated with Ingenix staff). Therefore, the rate of confirmation of Type 1 events was essentially identical between the treatment groups; 217/261, or 83% for clozapine, and 266/316, or 84% for olanzapine.

There was reasonable agreement between the SMB and the blinded investigators on what constituted a Type 1 event: there was agreement for 86% of the referred cases for clozapine (both called 82% of the referred cases events, and both called 4% of the referred cases Not an Event), and 78% for olanzapine (both called 73% of the referred cases an Event, and both called 5% of the referred cases Not an Event).

Dr. Dubitsky has identified a number of issues that he believes call into question the results of the trial as presented by the sponsor. Dr. Laughren has addressed these issues. Briefly, Dr. Dubitsky identifies the fact that 1) retrieved dropouts were included in the analysis, 2) patients were permitted to re-enter after having discontinued drug, 3) there were a number of patients for whom follow-up was not obtained, 4) blinded raters changed during the trial in about 50% of the cases, 5) there was a relatively high rate of psychotropic drug use, 6) there were discrepancies in the adjudication of cases between the blinded investigators and the SMB, 7) and there were cases in which the blinded investigators were unblinded, as factors that make the results as presented potentially unreliable.

Dr. He expresses additional concerns. He notes that the p-values from the analyses of the CGI-SS (5 and 7 point versions) are consistently lower (though not significant) using the ratings performed by the unblinded investigators compared to those utilizing the ratings from the blinded investigators. In addition, he is concerned that there may have been a bias in the referral of potential cases to the SMB. Specifically, he notes that the number of referrals determines the number of cases ultimately classified as true events, and he implies that, since the study is blinded, there might have been fewer referrals for the clozapine patients than perhaps there should have been; this would result in fewer cases classified as true events by the SMB, introducing a bias in favor of clozapine.

Dr. Laughren has addressed these concerns, and I generally agree with his views. I have no particular concern that retrieved dropouts and re-entered patients were included. There is no evidence that these inclusions introduced a bias, and including them keeps faith with the intent-to-treat principle. I further agree with Dr. Laughren that the change in blinded raters is not unexpected in a long trial; even the same rater over this period of time is not likely to recall the patient's baseline status very well, and the ratings on the CGI-SS did not make a major contribution to the outcome of the trial. The number of patients lost to follow-up was not insignificant, but was relatively small, and, as Dr. Laughren

suggests, we can ask the sponsor to obtain additional data on these patients, but it is unlikely that they will get much more information than they have (further, as Dr. Laughren points out, Dr. He did an analysis in which he considered all patients lost to follow-up as having had a Type 1 event; this revealed no bias).

I am also in agreement that the degree of use of psychotropic medications (more in the olanzapine patients) is not unexpected, could not have been prevented, and would appear, if anything, to bias the analysis in favor of olanzapine (by making these patients better clinically; indeed, the increased use of psychotropics by olanzapine patients could be taken as a measure of the effectiveness of clozapine). In addition, the number of cases of unblinding of the blinded investigators was small, and their ratings were not the source of the primary analysis in any event.

The discrepancy between the classification of cases by the blinded investigators and the SMB is of some concern. However, disagreements are expected, in my view, the general overall agreement was reasonably good, as noted earlier, and the discrepancies went generally equally in both directions (the blinded investigators calling a case an Event when the SMB didn't, and vice versa-see Dr. Laughren's memo, page 8-9). In any event, as Dr. Laughren notes, Dr. Dubitsky will inspect additional records of those cases in which there was a disagreement, to ensure that the SMB made the correct decision (most of the time). Ultimately, I am not quite sure what to make of these disagreements, in any case. The SMB (the source of the classifications used in the primary analysis) was blinded as to treatment assignment, and there is no reason (even if disagreements are found) to discount their assessments as being invalid. Nonetheless, we will inspect additional records.

Dr. He's concerns are of greater importance, in my view.

The fact that the p-values for the contrasts using the unblinded investigators' ratings on the 2 versions of the CGI-SS are consistently lower than those using the blinded investigators' ratings is intriguing. Of course, the 2 scales are undoubtedly highly correlated, and so this "finding" does not represent multiple independent lines of evidence that knowing the treatment assignments introduced an important bias.

However, of more concern is the possibility that there was a bias in the referral pattern of potential cases to the SMB. It is easy to contemplate that such a bias could have occurred, given that the treatment assignments were obviously known by the referrers. Dr. Laughren points out that Dr. He considers that the unblinded investigators were the only source of referrals; however, as Dr. Laughren notes, the Ingenix staff could also refer cases. He feels that any bias in the referral pattern related to the unblinded investigators would be overcome by the Ingenix staff's assessment of a larger number of potential cases. Dr. Laughren does note, however, that, given that the unblinded investigators'

apparently had the final authority to refer cases (even those identified by Ingenix), the bias could still exist.

I agree, but would add that, given that we are under the impression that the Ingenix staff did not, in reality, perform blinded assessments, the same bias could have existed in their identification of potential cases for referral.

For these reasons, I agree completely with Dr. Laughren that the only way we can be reassured that important biases did not affect the referral pattern is to perform an independent review of clozapine patients who were not referred, to see if this was the appropriate decision in (essentially) all of these patients.

To get a sense of how significant misclassification of the sort described would need,to be in order to meaningfully affect the outcome of the study, I asked Dr. He to perform an analysis to determine how many more clozapine patients would need to have had Type 1 events in order for statistical significance to be lost. The analysis he performed (though not the primary analysis) was a chi-square test; he determined that if there were 13 more clozapine patients classified as having a Type 1 event (115 compared to the 102 reported), the p-value for that between-treatment comparison would be 0.06. An additional patient (14) would raise the p-value to 0.07.

I believe that this issue (potential bias in the referral pattern) is the critical issue that must be resolved before the application can be approved. Of course, one could argue that, even if an independent review confirms that the appropriate cases were referred, the fact that the treatment assignments were known poses a more fundamental (and perhaps intractable) problem; namely, that the primary data on which the decision to refer was based were biased. Knowledge of the treatment assignments could conceivably have affected how the unblinded investigator interpreted and recorded the patient's symptoms in the first place. If the patient's symptoms were misinterpreted (unconsciously) by the unblinded investigator, that patient would not be a candidate for referral. An independent audit of the records of such a patient would not, and could not, detect such a bias, given that the audit depends entirely on an interpretation of the primary records, which, in the scenario I am painting, would not accurately reflect the patient's symptomatology.

While these concerns related to the recording of the primary data are real, they are likely not of major importance, in my view. Determinations about potential Type 1 events are not likely highly susceptible to the sort of unconscious bias I have described and would, if present, probably only apply in unusual cases. Many of the criteria for Type 1 events are clear and unambiguous; hospitalization, increased surveillance, significant suicide attempt, etc. In addition, the patient's complete experience is to be taken into account, including assessments made by staff other than the unblinded investigator. While all relevant staff were also unblinded, it is unlikely that they all would frequently

minimize a (clozapine) patient's symptoms. Nonetheless, in some cases, the investigator's knowledge of the patient's treatment could result in inaccurate recording of the patient's symptoms with a resultant bias, and we will need to explore this issue further.

There are other issues raised in this application.

First, although a previous observational study was performed and submitted, there is only one prospective, randomized, controlled trial submitted. Typically, of course, at least 2 such trials are required to establish substantial evidence of effectiveness for a claim. In this case, however, the outcome measure (decreased suicidality) could be presumed to be sufficiently important that the current package of data might be sufficient to establish effectiveness. One could argue, in this case, that the submitted data meet the alternative definition of substantial evidence introduced in the FDA Modernization Act (FDAMA): namely, one adequate and well-controlled trial and confirmatory evidence. Indeed, it might be considered unethical to replicate the findings of a single trial with a robust finding of decreasing mortality.

Of course, in this trial, there is no effect on mortality. There were only 8 completed suicides; 5 on clozapine, 3 on olanzapine. Nonetheless, decreasing the risk of suicidality as defined in this trial could be considered sufficiently important (and perhaps predictive of a decrease in actual suicides with time) to justify approval on the basis of a single adequate and well-controlled trial.

In this context, the question of whether or not this study is sufficiently robust to stand on its own must be asked.

As Dr. Laughren points out, if the results as presented persist after an examination of the questions raised above, the treatment difference seen here might be expected to have an important public health benefit. If, on the other hand, we cannot obtain assurances about some of the important concerns raised above (in particular, the question of the introduction of bias in the referral process), the result presented may not be seen as sufficiently robust to justify approval at this time.

My view is that the questions raised here are, for the most part, answerable. Again, in particular, my main concern relates to the potential for the referral process to have introduced a bias in favor of clozapine. As noted above, and as discussed by Dr. Laughren, the only clear way to address this question is for us to perform an independent assessment of the clozapine cases that were not referred, to see if some portion should have been (as I stated earlier, the fact that Ingenix also could have referred cases does not, in my view, adequately address our concerns, because I believe that their review was also based on unblinded data, and, critically, in any case, it appears that the unblinded investigator had

the final authority to decide if a case should be referred, even if Ingenix staff identified the case).

I believe that if a full and complete investigation of the questions discussed above supports the results of the study as presented, and the outcome measure can be taken as sufficiently reflective of an effect on preventing suicide, the application could ultimately be approved. However, in addition to these questions (the answers to which are critical to a decision to approve the application), a number of additional questions will need to be addressed.

For example, most (about 75%) of patients in this trial were not refractory patients, and about 35-40% of patients had schizoaffective disorder. Currently, clozapine is not approved for any indication for either of these populations. Although the data seem to support an effect on suicidality in both of these populations (although the study was not designed to assess traditional anti-psychotic effectiveness in schizoaffective disorder), we will need to consider in whom the drug should be indicated.

Further, the sponsor proposes that the drug be indicated for the treatment of suicidality. As Dr. Dubitsky notes, the study was not designed to assess this effect; it was designed to examine clozapine's capacity to decrease the risk of suicidality. If it is to be approved, the exact language in labeling will need to describe this latter effect, in my view, and in the view of the review team.

As described, the controlled trial compared clozapine to olanzapine. We will need to consider whether the trial can be interpreted to mean that clozapine is, in fact, superior to olanzapine in decreasing the risk of suicidality, whether, if it is truly superior, this would support a global superiority claim for clozapine or only one in comparison to olanzapine, or whether the data simply support a statement that clozapine decreases suicidality.

In summary, while I believe the application is approvable, there are many questions left unanswered. Some fall into the category of critical questions that must be adequately answered (for example, a full examination of the possibility of bias in the referral process, whether the data provide substantial evidence of effectiveness, including the question of the meaningfulness of the outcome assessed as a measure of a clinical importance, etc). Other questions relate to, among other things, the appropriate language to be included in labeling (for example, to which population should the results be described as applying, should the claim be global, or a specific comparative claim to olanzapine, etc.). My conclusion that the application is approvable is based on the view that the study, as presented, would support approval if the former questions are adequately answered, with the latter questions relating more to the details of the approval. In any event, while I believe the application is approvable, I believe that all of these questions should be brought to the Psychiatric Drugs Advisory Committee (PDAC) for broad discussion (as Dr. Laughren has noted, we are scheduled to

take this application to the PDAC on 11/4/02). While I recognize that it is unusual to present an application to the Committee after an approvable action has been taken, especially when fundamental questions about the approvability of the application remain, I believe it is appropriate to take this action because:1) as I have discussed, if these questions can be satisfactorily answered, I believe the application could be approved, 2) the application has no significant lesion that is not correctable that would warrant a Not Approvable action, and 3) if a full discussion of these issues with the Committee results in a recommendation that the application should not be approved, and we agree, the current action does not preclude such a subsequent action.

For the reasons stated above, then, I have issued an Approvable letter with draft labeling on 8/30/02.

Russell Katz, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
9/4/02 12:15:43 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

CROSS DISCIPLINE TEAM LEADER REVIEW

M E M O R A N D U M

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

DATE: August 23, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Clozaril (clozapine) for the treatment of suicidality in schizophrenia and schizoaffective disorder

TO: File NDA 19-758/S-047
[**Note:** This overview should be filed with the 2-28-02 original submission.]

1.0 BACKGROUND

Clozapine (Clozaril) is an atypical antipsychotic drug that has a limited indication, i.e., for treatment-resistant schizophrenia, and was first marketed in 1990. Because of its potential to cause agranulocytosis, the sponsor was required to show a benefit in treatment-resistant schizophrenia, and they were able to conduct a study that supported this claim. Clozaril is currently marketed under a registry to ensure that the required WBC monitoring is conducted. This supplement is intended to support a new claim for clozapine, i.e., for "use in the treatment of suicidality in patients with schizophrenia or schizoaffective disorder." There are, at present, no drugs approved for such a claim, and if clozapine does have a benefit in suicidality, this would represent a major advance, since suicidality is a frequent problem in this population, with an estimated 10% lifetime prevalence of suicide in these patients. Our own meta-analysis, and those of others, for the existing clinical clinical trials database of available atypical antipsychotics (risperidone, olanzapine, quetiapine, and ziprasidone) suggest that these currently available drugs are essentially neutral with regard to suicide. There is no risk of excess suicide resulting from assignment to placebo and, thus, no benefit regarding suicide risk for those assigned to active drug.

Several years after the marketing of Clozaril, we became concerned about what appeared to be excess mortality in association with this drug, and we encouraged the sponsor to conduct a study to examine this question (March, 1993). They contracted with Epidemiology Resources, Inc (ERI) to conduct a cohort mortality study (referred to in this document as the "ERI Study"), using data from the registry along with publically available death data. The most remarkable finding that emerged from this study

(reported May, 1995) was a dramatically reduced risk of suicide in current clozapine users compared to past users. Based on this finding, and other reports in the literature, the sponsor (August, 1995) sought a labeling change to include a new claim for suicidality in schizophrenia. We rejected this claim, since it was based entirely on observational data, and we encouraged the sponsor to conduct a randomized trial.

Our discussions regarding the design of such a trial began in January, 1997, and a complete protocol was submitted in January, 1998. We had already reached agreement with the sponsor that one such study would be adequate to establish a claim regarding suicidality, and although we did not formally respond to the sponsor's protocol, we in essence agreed by our silence. Thus, the study began in March, 1998 (under IND 8,333). There were two important amendments to the protocol (see later under Efficacy), and the study was completed as of 2-13-01. We held a preNDA meeting with the sponsor on 9-5-01, and they submitted a draft study report on 12-21-01. We requested several additional datasets in a 1-29-02 letter, and the NDA was submitted 2-28-02. A decision to file this supplement as a priority review was made on 4-4-02.

Since the proposal is to use the currently approved Clozaril formulations for this additional claim, there was no need for chemistry, pharmacology, or biopharmaceutics reviews of this supplement. Consequently, the focus was on clinical data. The primary review of the efficacy and safety data was done by Greg Dubitsky, M.D., from the clinical group. Kun He, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The original supplement for this additional claim (S-047) was submitted 2-28-02.

It was not possible to take this supplement to the Psychopharmacological Drugs Advisory Committee before the action date, however, I feel there are issues in this application that need input from this committee.

2.0 CHEMISTRY

As Clozaril is a marketed product, there were no CMC issues requiring review for this supplement.

3.0 PHARMACOLOGY

As Clozaril is a marketed product, there were no pharmacology/toxicology issues requiring review for this supplement.

4.0 BIOPHARMACEUTICS

As Clozaril is a marketed product, there were no biopharmaceutics issues requiring review for this supplement.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Studies Pertinent to Efficacy

Our review of efficacy was focused on the results of study ABA 451. However, I will also comment briefly on the ERI study, since this study was critical to the evolution of study ABA 451 and is a key part of the evidence base upon which my recommendation for approvability is based.

5.1.2 Summary of ERI Study

This was a retrospective cohort mortality study designed to address our concern about possible excess mortality for clozapine. The study was possible since clozapine is marketed under a registry. The study covered a period in the registry from 4-1-91 to 12-31-93. The sample included n=57,681 patients in the primary cohort of interest (ages 10-54), and these patients represented 85,399 person-years of exposure. This exposure time was divided into current use, recent use (up to 3 mo since last use), and past use (more than 3 mo since last use). Deaths were ascertained using the National Death Index and the Social Security Administration Death Master Files. Death certificates were obtained from the states to determine cause of death. The primary comparison of interest was for standardized mortality rates, i.e., current vs past users. There were a total of 396 deaths, and the overall mortality was in fact dramatically lower for current users compared to past users. The all cause mortality rate ratio for current exposure to past exposure, adjusted for age, race, and sex, was 0.46, i.e., current users had a mortality rate roughly ½ that of past users. An analysis of cause specific mortality revealed that this overall finding was driven largely by a dramatic reduction in suicides in current users compared to past users. The rate ratio for suicides was highly in favor of clozapine, i.e., 0.17. While there were findings suggesting higher rates of mortality from pulmonary embolism and respiratory disorders for current users, these results were clearly overshadowed by the effect on suicides.
-Comment: Of course, this was not a randomized study, and there was a potential for bias. On the other hand, the results are entirely consistent with the results of the randomized trial (ABA 451), and I feel this study adds substantial support to the conclusion that clozapine may reduce the emergence of suicidal behavior in schizophrenic patients.

5.1.3 Study ABA 451

5.1.3.1 Summary of Study ABA 451

Design and Conduct

-This was a prospective, randomized, multicenter (67 centers, worldwide, including 31 US centers), open-label, 24-month comparison of clozapine and olanzapine in patients with schizophrenia or schizoaffective disorder (DSM-IV) who were judged to be at risk for suicide (by history of suicide attempts or suicidal ideation within 1 week of baseline evaluation). Importantly, patients did not have to be considered treatment-resistant.

-The total sample randomized was n=980, with n=490 randomized to each treatment arm.

-Clozapine was dosed in a range of 200-900 mg/day (mean dose achieved overall was 309 mg/day).

-Olanzapine was dosed in a range of 5-20 mg/day (mean dose achieved overall was 17 mg/day).

-Patients were dosed to their most effective dose, as tolerated.

-Patients were cross-titrated from their previous antipsychotic to study drug over a 3-day period. However, concomitant medications, including antidepressants and other antipsychotic drugs, were permitted as needed (and widely used), in keeping with community practice.

-An attempt was made (with patient consent) to continue to collect information, even after dropout, until the 2-year nominal endpoint (retrieved dropouts, or RDOs).

-Amendment #10 (3-14-00) allowed patients who had dropped out to resume study participation (on the same drug as previously assigned). We had recommended against this change in a 5-1-00 letter; nevertheless, the sponsor implemented this change.

-In order to balance the frequent contact clozapine patients were receiving, for WBC monitoring, olanzapine patients were required to have the same visit frequency, for VS monitoring.

-There was an independent Steering Committee for general oversight of the trial.

-Patient Assessments: Patients were assessed monthly by investigators, who were unblinded, with the Intersept Suicidal Thinking (ISST) scale and the CGI Severity of Suicidality (CGI-SS) scale. In addition, detailed information was collected by the investigators and other staff at times of major events regarding suicidality (suicide, suicide attempt, hospitalization for suicidality, and need for increased surveillance due to suicidality for inpatients = potential Type 1 event). This information was recorded on the suicide attempt form (SAF), for suicides or suicide attempts, or the Imminent Risk of Suicide Requiring Hospitalization form (IRH), for hospitalizations for suicidality, and need for increased surveillance due to suicidality for inpatients. There were also blinded psychiatrists (BP) at each site who blindly rated patients every 8 weeks on the ISST and the CGI-SS. There were two versions of the CGI-SS, a 5-point version focused on severity, and a 7-point version focused on change from baseline in suicidality. [Since only the 7-point change version for the BP's was used in the primary analysis, I will refer to these data as the CGI-SS-BP throughout this memo.]

-Suicide Monitoring Board: In order to maintain the integrity of information pertinent to Type 1 events, information judged by the unblinded investigators to possibly represent a Type 1 event was forwarded to Ingenix Pharmaceutical Services, who prepared the information for blinded evaluation by the Suicide Monitoring Board (SMB), consisting of three experts who made a determination of whether or not any particular clinical situation considered to possibly represent a Type 1 event in fact met the criteria for such a determination. The same information was seen and evaluated by the BP's at each site, who then also made a determination of whether or not these events could be considered Type 1 events. However, only the Type 1 events identified by the SMB were used in the primary analysis. In addition, Ingenix staff , according to the study report (pp.38-39).did "blinded reviews" of the clinical datebase to search for other possible major events that may have been overlooked by the unblinded investigators, and prepared and forwarded information on these cases as well to the SMB. It is unclear how these Ingenix reviews could have been blind, since they would have had access to

the complete patient record. On the other hand, the protocol for these reviews suggested that any event that might even remotely be considered to be a Type 1 event would be prepared for blinded review by the SMB. Thus, it seems unlikely that potential events could have been missed, and not sent on to the SMB. On the other hand, the unblinded investigators apparently had the final say on whether or not an endpoint package would be prepared for any particular event (item #5, p. 39).

Analysis Plan

-The original analysis plan was to look at two outcomes: (1) time to significant suicide attempt or hospitalization for suicidality (Cox proportional hazards model); and (2) change from baseline in CGI-SS-BP (rated on 5-point scale), ANCOVA.

-During the course of the study, the sponsor discovered that (1) the number of suicide attempts and hospitalizations for suicidality was lower than anticipated; (2) there were more losses-to-followup than anticipated; and (3) they had not taken into consideration the need to adjust for the two primary outcomes. They convened an expert group to propose an alternative plan, which was submitted 1-2-01 (amendment #6).

-The new analysis plan was as follows:

-2 types of events were defined:

-Type 1 Event: as already defined above (suicide, suicide attempt, hospitalization for suicidality, and need for increased surveillance due to suicidality for inpatients), regardless of whether or not patient was still on assigned treatment (i.e., included RDOs)

-Type 2 Event: (1) worsening of suicidality, as evidenced by a score of 6 (much worse) or 7(very much worse) on the 7-point CGI-SS-BP, or (2) the occurrence of a Type 1 event, again, regardless of whether or not patient was still on assigned treatment (i.e., included RDOs)

-The analysis model now proposed was the Wei, Lin, and Weissfeld (WLW) method, which provided a single test for time to both endpoints, with equal weighting for both types of events.

Results

-Patients were 61% male, about 70% Caucasian, and the mean age was 37 years.

-About 3/5 of patients were schizophrenic, and 2/5 schizoaffective; only 1/4 were considered treatment-resistant

-The 2-year completion rates were as follows:

-Clozapine: 61% (298/490)

-Olanzapine: 62% (303/490)

-Note: These rates do not include the RDOs

-There were a total of 121 RDOs:

-Clozapine 61

-Olanzapine 60

-A sizeable number of patients were lost-to-followup:

-Clozapine: 33

-Olanzapine: 39

-While the overall completion rates to study endpoint were very similar for the two drugs, clozapine patients tended to drop out earlier than olanzapine patients; in fact, the proportions remaining were somewhat lower for clozapine vs olanzapine at every 4-week interval throughout the 2-year study, and

the differences were most pronounced early in the study, but even at these early time, the differences were rather minor, in my view (see Appendix VI-4 of Dr. Dubitsky's review).
-Several patients randomized never received any medication, so that the actual samples for patients receiving assigned treatment were as follows:

-Clozapine: 479
-Olanzapine: 477

-Concomitant Psychotropic Use: There was extensive use of other psychotropic medications concomitantly with the assigned treatment, including drugs from all the major classes (antidepressants, antipsychotics, anxiolytics, and mood stabilizers). The sponsor developed an approach to converting doses for drugs in each class to a standard reference drug, and calculating AUCs for each 6-month interval and mean dose per patient for each class as well. Overall, there was less concomitant psychotropic use for patients assigned to clozapine than to olanzapine, suggesting that if there was any bias introduced by concomitant drug use, it would have favored olanzapine, and not clozapine.
-Change in Raters: One potential problem with study conduct was the fact that almost half of the patients had a change in the blind psychiatrist (BP) rater during the course of the study. This is potentially important since the CGI-SS-BP was one component of the Type 2 events, and this was supposed to be a rating of how much a patient had improved or worsened since baseline. Having different raters at baseline and subsequent visits raises a question about the reliability and validity of this rating.

-<u>SMB Referrals and Type 1 Designations</u>:
-There were a total of n=577 events referred to the SMB for a decision about Type 1 event status:

-Clozapine n=261 (coming from n=122 patients)
-Olanzapine n=316 (coming from n=157patients)

-Of these n=577 events, n=483 were judged to represent Type 1 events

-Clozapine n=217 (coming from n=102 patients)
-Olanzapine n=266 (coming from n=141patients)

-These results indicate that the rate of confirmation of potential events as true Type 1 events by the SMB was comparable for both drug groups and quite high:

-Clozapine: 217/261 = 0.83
-Olanzapine: 266/316 = 0.84

-Note: As is clear from these data, patients may have had more than one Type 1 event (and, in fact, they may also have had more than one Type 2 event)

-An alternative approach to presenting the data is to enumerate patients on the basis of their having $\geq$ 1 Type 1 events:

-Clozapine n=102 (out of n=122 referred as possibly having $\geq$ 1 Type 1 events)
-Olanzapine n=141 (out of n=157 referred as possibly having $\geq$ 1 Type 1 events)

-<u>The crude risks for Type 1 and Type 2 events by treatment group were as follows</u>:

<u>Event Type</u>	<u>Clozapine</u>	<u>Olanzapine</u>
Type 1	102/490 (21%)	141/490 (29%)
Type 2	120/490 (25%)	161/490 (33%)

Note: (1) As noted above, the numerator is the number of patients who had 1 or more of each type of event, and the denominator is the total number of patients randomized to each group.

(2) Clearly, the majority of the events were Type 1 events.
(3) There were a total of only 8 completed suicides, 5 for clozapine and 3 for olanzapine.

-WLW Analysis:

-As noted, this was a composite analysis of time to Type 1 events and Type 2 events, with equal weighting
-The p-value significantly favored clozapine over olanzapine (p=0.03) overall.
-The p-values also significantly favored clozapine over olanzapine when looking at the Type 1 and Type 2 events separately, i.e., p=0.03 for Type 1 events and p=0.04 for Type 2 events.

-Kaplan-Meier Analysis (cumulative probability at week 104):

Event Type	Clozapine	Olanzapine	Log-Rank P-Value
Type 1	0.24	0.32	0.0195
Type 2	0.28	0.37	0.0270

5.1.3.2 Comment on Dr. Dubitsky's Reasons for Considering this Supplement Non-Approvable
-While Dr. Dubitsky found that the results of this study on the primary outcome favored clozapine over olanzapine on reduction in the risk of emergent suicidality, he had sufficient concerns about the conduct of the trial and analysis of the data that he is recommending a nonapproval action at this time. His concerns, and my comments, are as follows:

-RDOs: The WLW analysis included data for retreived dropouts (RDOs), and Dr. Dubitsky feels this is an unacceptable practice since it makes it difficult to confidently attribute any observed effect to assigned drug. Thus, he feels these patients should be censored (see Dubitsky review, p.29).

-Comment: It seems to me that the important question is what happens to patients who are assigned to one treatment arm or the other, regardless of whether or not all patients continue to the nominal endpoint on their assigned treatment, i.e., a more pragmatic view. I think including the RDOs actually enhances the validity of the trial, rather than detracting. This is an approach that has been encouraged by Phil Lavori and others for years in this field, even though it is rarely applied. Consequently, I am not troubled by this feature of the analysis. Furthermore, Dr. He conducted a sensitivity analysis to determine whether or not inclusion of the RDOs represented a bias, and he concluded that there was no indication of a bias being introduced by this practice (see Dr. He review, pp.16-18).

-Re-Entered Patients: Dr. Dubitsky objects to the sponsors inclusion in the analysis of patients who had dropped out at one point in the trial, and then were re-entered, and he notes that the sponsor was encouraged not to adopt this practice (see Dubitsky review, p.29).

-Comment: It's true that we did recommend, early in the trial (5-1-00), that the sponsor not re-enter patients; however, it's not clear to me at this point what is objectionable about this practice. I don't see how this could bias the trial in favor of clozapine (any added noise would affect both arms equally), and I think it enhances the validity of the trial, since this is very consistent with patient care in the real world.

-Loss-to-Followup: Dr. Dubitsky notes the substantial number of patients lost to followup (72 overall), and wonders whether or not any of these patients experienced Type 1 events. He

recommends that we ask the sponsor to try harder to obtain followup information (see Dubitsky review, pp.29-30).

-Comment: We could ask the sponsor to try to obtain information, but in reality, especially for this population of often transient patients, it is unlikely they will be able to accomplish this task. We could ask the PDAC whether or not it is reasonable to expect more, and if this is a fatal flaw. Furthermore, Dr. He conducted a sensitivity analysis to determine whether or not this loss-to-followup represented a bias. He assumed that all of the censored patients among those lost-to-followup had Type 1 events, and the WLW analysis still favored clozapine over olanzapine (see Dr. He review, p.16).

-Change in Blinded Rater: Dr. Dubitsky questions the reliability of the 7-point CGI-SS-BP change from baseline ratings, given the almost 50% change in raters for this instrument (see Dubitsky review, p.30).

-Comment: We can ask the sponsor to comment on this issue. However, I think that, in a study of this length, it is unlikely that even raters who assessed patients throughout the 2 years are able to clearly remember the state of the patients at baseline. In reality, I think it is likely this instrument is used more in practice like an absolute severity rating than a change rating, but we can also ask experts to comment on this question. In addition, as noted earlier, the contribution of the CGI-SS-BP ratings to the identification of Type 2 events was essentially trivial, and had almost no effect on the outcome overall. So, I don't consider this a serious problem.

-Concomitant Medications: Dr. Dubitsky expresses concern about the large amount of concomitant psychotropic drug use and worries that this is a potential confounder (see Dubitsky review, p.30).

-Comment: I am less troubled by this finding, in part because the intent of this trial was to test the hypothesis in a real world situation, and in the real world, there is often extensive concomitant psychotropic use. So, again, from a pragmatic standpoint, this is a more useful trial. Furthermore, I don't see how this practice could help the clozapine arm. If the concomitant use were equal across treatment groups, it should only add noise that would diminish the ability of the trial to detect a difference. In fact, the use was greater for the olanzapine arm, for all drug classes, and if there is any bias, it seems to me it would have to favor olanzapine.

-SMB Performance: Dr. Dubitsky audited the information that would have been seen by the SMB, and focused on 3 cases where there was a discrepancy between the BP designation and the final determination by the SMB. In all 3 cases, the BP's did not consider the cases to warrant a Type 1 designation, but were overruled by the SMB. Dr. Dubitsky reviewed the available information and found the support lacking for a Type 1 designation, in agreement with the BP's. He recommended a series of steps to try to better understand and explore this finding (see Dubitsky review, pp.43-44).

-Comment: I agree that this is worrisome, and needs to be further explored. In an 8-14-02 telcon with Novartis staff, I asked for more complete information on the extent of agreement/disagreement between BP's and the SMB in classification of potential Type 1 events. On 8-20-02, they provided the following table:

	Clozapine		Olanzapine	
	BP Event	BP No Event	BP Event	BP No Event
SMB Event	208 (82%)	9 (4%)	227 (73%)	37 (12%)
SMB No Event	28 (11%)	9 (4%)	29 (9%)	16 (5%)

-Thus, overall, there was quite good agreement: 86% for clozapine events and 78% for olanzapine events. Furthermore, disagreements went in both directions:

-In 46 instances, the BP ruled no event, but the SMB ruled event.

-In 57 instances, the BP ruled event, but the SMB ruled no event.

-Thus, I am satisfied that there was no indication of bias in the actual process of classification of cases. Nevertheless, Dr. Dubitsky will randomly sample 25 of the 103 events for which the BP and SMB did not agree, to reassure himself that the correct classification was made by the SMB (We initiated this request as of 8-23-02).

-Unblinding of BP's: Apparently the CRFs provided a place for BP's to indicate if they became unblinded at any particular patient visit. A search of the entire database for such notations revealed a total of 6 BP's who indicated that they had become unblinded to 6 patients. No details were provided, and Dr. Dubitsky is asking that this information be provided (see Dubitsky review, pp.44-45).

-Comment: If the treatment assignments were inadvertantly revealed (e.g., by recognizing unique side effects) for only 6 patients in a trial of 980 patients, that would be remarkable, and not at all worrisome to me. Nevertheless, we can ask the question to see if we can at least better understand these specific cases.

5.1.3.3 Comment on Dr. He's Concern of Bias in the Referral of Information to the SMB

-While Dr. He has found that the results of this study on the primary outcome favor clozapine over olanzapine on reduction in the risk of emergent suicidality, he had sufficient concerns about the conduct of the trial that he recommended interpreting the positive outcome with caution. His primary concern was with the possibility of bias in the referral of information to the SMB. He makes several points in support of his concern (see Dr. He review, pp.13-15):

-As noted, both the unblinded investigators and the BP's rated patients on the CGI-SS (both the 5-point and 7-point versions). Dr. He reviewed the data for these ratings and found that, for both versions of the CGI-SS, the p-values for the unblinded psychiatrists were lower (in favor of clozapine) than those for the blinded psychiatrists. [**Note**: This is true, but it should also be noted that none of the p-values reach the usual 0.05 level of significance, so it isn't clear what value there is in comparing nonsignificant p-values.]

-Dr. He had the impression that it was solely the unblinded investigators who made the decision of which events to forward on to the SMB for determination of Type 1 status, and he summarized the numbers of referrals (of patients with 1 or more events that might possibly represent Type 1 events) and the proportions of those referred who were judged to have 1 or more events that in fact were Type 1 events, as follows:

	Clozapine	Olanzapine	Difference

# referred	122	157	35
# with ≥ 1 Type 1	84% (102/122)	90% (141/157)	39

-Dr.He argues that the CGI-SS data suggest that the unblinded investigators might have been biased in favor of judging olanzapine patients to be more suicidal than clozapine patients. Then, since they had primary responsibility for deciding which events would be forwarded to the SMB, he argues that they may have, due to this bias, forwarded more olanzapine patients with events than clozapine patients with events. Dr. He argues that there is a high correlation between the number of referrals and the ultimate number of events judged to be Type 1, and so, the bias in deciding which events to refer might have biased the overall results of this study.

-Comment: I agree this is an issue that bears close examination. However, I have several comments on Dr. He's argument:

-I am somewhat less impressed than he is by the CGI-SS data, since none of the p-values are statistically significant. Nevertheless, bias in the referral of events by investigators who knew the treatment assignment is clearly a concern.

-However, Dr. He fails to mention an important point, i.e., that the unblinded investigators were presumably not the only source of referrels to the SMB. Staff from Ingenix were supposed to have also reviewed all events that might possibly have been considered to have represented Type 1 events in order to identify any additional major events that might have been overlooked by the unblinded investigators, and they prepared information on these events similar to that prepared for the events referred by the investigators. These additional events were presumably then referred to the SMB for blinded evaluation (see pp. 38-39 of study report).

-Thus, if there was a bias on the part of unblinded investigators, it should have been overcome by the detection of overlooked major events by Ingenix staff.

-In a 8-14-02 telcon with the sponsor, I asked for more information on what proportion of events referred originated with the unblinded investigators and what proportion from Ingenix staff. They indicated that this information would be difficult to retrieve. In an 8-20-02 response to this question, they noted that Dr. Kevin Cox, the US medical monitor, estimated that about 20 of the 577 events referred to the SMB resulted from independent review by Ingenix staff. He also estimated that more than half of the hospitalizations due to suicide risk were initiated by someone other than the unblinded investigators.

-While this new information provides some reassurance, there is still concern that bias may have been a factor, since, as noted in the study report (p.39), the unblinded investigators apparently had the final say regarding whether or not a particular event would be referred to the SMB.

-We discussed this important matter internally 8-21-02, and decided that the only way to adequately resolve this concern would be to have an independent audit of the entire clinical record for a sample of clozapine patients for whom events were not referred, in order to determine definitively whether or not potential events were differentially ignored for patients assigned to clozapine (n=368). At the time of completion of this memo, we are attempting to arrange for this complicated audit.

5.1.3.4 Summary Comments Regarding Study ABA 451

I feel that, on face, the results of this trial are positive in favor of clozapine and suggest an important benefit, i.e., a reduction in the risk of emergent suicidal behavior in patients with schizophrenia and schizoaffective disorder. However, it will be critical to address several concerns, but in particular, a concern about potential bias in the referral of events to the SMB. In addition, I think one other issue needs to be further explored, i.e., the high percentage of referred events that were judged to represent true Type 1 events (84%). If the identification of potential Type 1 events for referral was a broad screen to avoid missing any events, as it should have been, it might have been expected that the rate of confirmation would be lower than 84%. So I think it would be useful to sample from the n=577 referred events to get a better sense of whether or not broad screening was the actual practice, and to get a better impression of the severity of events judged to be Type 1 events by the SMB. Dr. Dubitsky did in fact audit 21 CRFs to verify the correctness of the classification of events. He agreed with the classifications of all but 3 of the events he examined; those 3 were the events already noted, where there was disagreement between the classifications by the BP and the SMB. I think it might be useful to audit an additional sample. In fact, as noted, we have asked for an additional 25 endpoint packages where there was a disagreement between the BP and SMB on classification, and evaluation of the decisions made for these events should also help in addressing the question of whether or not the Type 1 events included in the analysis represented significant suicidality.

5.1.4 Comment on Other Important Clinical Issues Regarding Clozaril in Suicidality

Evidence Bearing on the Question of Dose/Response for Efficacy: This was a flexible dose study that, for clozapine, involved dosing patients in a range of 200 to 900 mg/day, based on tolerability and antipsychotic efficacy. Thus, if this claim is approved, labeling would need to recommend the dosing strategy employed in this study.

Clinical Predictors of Response: Separate analyses for patients with schizophrenia and schizoaffective disorder still revealed numerical superiority for clozapine over olanzapine in the WLW analysis. However, the results were statistically significant only for the schizophrenia subgroup. While the effect size was slightly lower for the schizoaffective disorder subgroup compared to the schizophrenia subgroup, it appears that the failure to achieve statistical significance was more related to insufficient power than any real difference in efficacy.

Size of Treatment Effect: The cumulative probabilities for Type 1 events for the clozapine and olanzapine groups were 0.24 and 0.32, respectively. While we have no prior experience evaluating claims for suicidality, this seems to me to represent a substantial benefit from a public health perspective. There may be close to 3 million patients in the US with one of the two diagnoses in question, and probably at a minimum 20% of these patients would meet criteria for having a substantial risk for suicidal behavior, i.e., 600,000. If the estimated effect size of 8% is accurate, then it may be estimated that 48,000 fewer patients would have Type1 events over a two year period of treatment with clozapine than if they took olanzapine. Further, if only 10% of these events represented completed suicides, that would represent roughly 5000 fewer suicides. Of course, the actual decision regarding the switching of a patient who is not treatment resistant to clozapine to reduce the risk of suicidal behavior is a complex one, involving many considerations. In any case, I feel that this demonstrated benefit is sufficient to justify the approvability of this supplement.

Duration of Treatment: It's difficult to reach any conclusions about the duration of this benefit based on the results of this single study. I think labeling should simply describe the study and let clinicians decide how long to treat patients with clozapine for this purpose, based on the complex set of circumstances that would bear on any such decision. However, I think we should ask the sponsor and the PDAC whether or not they have any thoughts on how to advise prescribers on what to do with non-refractory patients who were placed on Clozaril because of suicidal risk but who have responded and no longer can be considered suicidal.

Indication Sought by Sponsor: The sponsor seeks an indication "for the treatment of suicidality..." Dr. Dubitsky correctly points out that for study ABA 451 patients with only a history of suicidality may have been enrolled, and thus, a minority were likely currently suicidal, and "highly suicidal" patients were specifically excluded. He feels that an indication focusing on a reduction in the risk of emergent suicidality in patients judged to be at risk would be more appropriate. He also prefers to limit the new claim to a description of the trial results in the Clinical Trials section, rather than adding it in Indications.

> -Comment: I agree that clozapine has not been shown to be a treatment for actively suicidal patients, and that the focus should be on what was shown. My only disagreement is with placement of the claim in labeling. The new claim is distinctively different than the current claim, both in the nature of the claim and also in the population targeted. Thus, I think it is important to add this information to Indications as well as to Clinical Trials.

5.1.4 Conclusions Regarding Efficacy Data

The sponsor has, in my view, provided evidence to support the claim of the effectiveness of clozapine in reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at particular risk of having such behavior. This evidence comes primarily from study ABA 451, however, I feel that the results from the ERI Study provide very substantial support for this conclusion. Nevertheless, I think there are several questions about study ABA 451 that need to be answered before we can take any final action on this NDA, and I feel it will be very important to bring this application to the PDAC for their consideration.

5.2 Safety Data

Clozapine's safety profile is well known, so Dr. Dubitsky's safety review focused on SAEs and adverse dropouts from study ABA 451; this included data arising from a clozapine-exposed cohort of n=479. His review detected the following events, all of which are well known for this drug: leukopenia; bowel obstruction; hyperglycemia; dizziness; and somnolence. Thus, there were no new safety findings that impact on labeling for this drug.

5.3 Clinical Sections of Labeling

We have modified the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

The sponsor provided a literature review that identified 34 published papers, of which 11 described studies regarding the topic of reduction of suicidality with clozapine treatment in schizophrenia. Dr. Dubitsky focused his review of the literature on these 11 papers, and concluded that, overall, they were suggestive of a reduced risk of suicide in schizophrenia for clozapine treatment, compared to other antipsychotic drugs. However, he also noted that all 11 studies had important flaws that would preclude their consideration as primary sources of support for the intended claim. I agree, and I will not comment further on these studies, beyond the comments I have already made for one of these 11 studies, i.e., the ERI Study.

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Clozaril is not approved for the treatment of suicidality in schizophrenia anywhere at this time. We will ask for an update on the regulatory status of Clozaril in the treatment of suicidality in schizophrenia in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted earlier, it was not possible to take this supplement to the PDAC before taking an action. However, I think it would be useful to bring this supplement to the PDAC, even after taking an approvable action. Following are some of the issues that I think would benefit from PDAC feedback:
-Does study ABA 451, along with the findings from the ERI study, support an indication focused on suicidality in schizophrenia and schizoaffective disorder?
-What claim is supported?
-Should the claim apply to both schizophrenia and schizoaffective disorder?
-What labeling language should be included to advise prescribers about this new claim and how to use Clozaril in treating this population?
-Ask for comment on the various problems with study ABA 451raised by Drs. Dubitsky and He:

- -The inclusion of RDOs in the analysis
- -The use of data from re-entered patients
- -The extent of loss-to-followup
- -The validity of the CGI-SS-BP ratings, given that many raters changed over the course of the study
- -The extensive use of concomitant medications
- -Concerns about SMB performance
- -Unblinding of some of BP's
- -Potential bias in the referral of events to the SMB by unblinded investigators

9.0 DSI INSPECTIONS

Four sites were inspected and judged to be acceptable.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made changes to the sponsor's draft dated 2-28-02.

10.2 Foreign Labeling

Clozaril is not approved for the treatment of suicidality in schizophrenia anywhere at this time.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a literature update and a regulatory status update.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Novartis has submitted sufficient data to support the conclusion that Clozaril is effective and acceptably safe in reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for such behavior. Thus, I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates. As noted, however, I feel there are several important issues that must be addressed before we can take a final action on this NDA, and I think it is critical that we plan on bringing this application to the PDAC, before taking any final action.

cc:
Orig NDA 19-758
HFD-120
HFD-120/TLaughren/RKatz/GDubitsky/SHardeman
HFD-101/RTemple

DOC: MEMCLZSC.AE1

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/s/

Thomas Laughren
8/23/02 10:53:31 AM
MEDICAL OFFICER

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

DATE: December 12, 2002

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for
Clozaril (clozapine) for the treatment of suicidality in schizophrenia and schizoaffective disorder

TO: File NDA 19-758/S-047
[**Note:** This overview should be filed with the 10-25-02 response to the 8-30-02 approvable letter.]

In our 8-30-02 approvable letter, we identified 4 issues that needed to be addressed for study ABA 451. We also included draft labeling, and we notified Novartis of our plans to bring this application to a Nov 4, 2002 meeting of the PDAC.

Novartis responded to the 4th issue for study ABA 451 in a 10-11-02 submission, and to the remaining 3 issues for that study in the 10-25-02 submission. They also responded to our labeling proposal with a labeling counter-proposal in the 10-25-02 response. In addition, this application was discussed at an 11-04-02 meeting of the PDAC. The Novartis responses and labeling counter-proposal were reviewed by Greg Dubitsky, M.D., from the clinical group [see reviews dated: (1) 8-30-02; (2) 10-24-02; (3) 11-7-02; and (4) 12-3-02.

Issues for Study ABA 451

1. Change in Blinded Raters
-Blinded raters completed the CGI-SS-BP ratings, and this was intended to be an improvement rating relative to baseline. Since almost half of raters changed during the course of the 2 year study, we asked the sponsor to comment on this potential problem.

-Comment: I never considered this to be a problem (see my 8-23-02 memo), since it seems unlikely that, even if all the raters remained the same throughout the 2 years, they would be able to recall the patient's state at the initial visit. Thus, the rating is more likely either an absolute severity rating, or a rating relative to the documented severity at baseline. Furthermore, these ratings contributed essentially nothing to the Type 2 events, since Type 2 events were overwhelmingly driven by Type 1 events. In their 10-25-02 response, Novartis

also made these arguments, and Dr. Dubitsky now agrees that this concern has been adequately addressed.

2. SMB Performance

-There was an initial concern about SMB performance based on Dr. Dubitsky's audit of 3 cases for which there was not agreement between the SMB and the blinded psychiatrists on classification of the events. In response to an 8-14-02 telcon with me, Novartis provided more complete information on the extent of agreement between the SMB and the blinded psychiatrists on classification of cases. In fact, there was overall quite good agreement (see my 8-23-02 memo). Nevertheless, we asked for and received (in an 8-26-02 submission) a random sample of 25 of the 103 events for which the BP and SMB did not agree.

-Comment: Dr. Dubitsky reviewed these event packages and concluded that the classifications of these cases provided reassurance about the performance of the SMB, and I agree (see Dubitsky review, 8-30-02).

3. Unblinding of Blinded Psychiatrists

-We asked for clarification regarding the unblinding of 6 of the blinded psychiatrists, and Novartis provided what information they had.

-Comment: Given the small number of instances of unblinding, and the fact that Type 2 events were of essentially no importance to this study, I never considered this to be a problem (see my 8-23-02 memo). Dr. Dubitsky has also now concluded that this minimal unblinding was unlikely to have had any impact on the outcome of this study.

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

-The major concern about study ABA 451 was the potential for bias in the referral of information to the SMB. Most events referred to the SMB came from the unblinded investigators, and for those that did not, the unblinded investigators had the final say regarding whether or not these events could be referred. Given the very high correlation between the number of events referred and the number of events classified as Type 1 events, the possibility of bias in favor of clozapine with regard to events referred needed to be definitively addressed. As noted, Novartis provided a response to this concern in a 10-11-02 submission which Dr. Dubitsky reviewed (see 10-24-02 review). Novartis conducted a search of the electronic database for the n=701 patients for whom events were not referred, using predefined search terms, and identified n=279 patients matching on 1 or more of these terms. They then conducted an unblinded review of these 279 cases to determine whether or not there were events that should have been referred. They concluded that there were only 2 events that should have been referred, but were not. Dr. Dubitsky found this assessment flawed, since it was unblinded, and I agree. Alternatively, we had DSI audit a sample of the n=368 clozapine-treated patients for whom events had not been referred. Their audit involved a visit to the selected sites and an examination of all available clinical records for these patients. At the time of the PDAC meeting (11-4-02), they had completed the audit at 2 sites, involving n=22 patients for whom events had not been referred, and found no instances of events that should have been referred. A final report from DSI (11-27-02) included findings from an additional 2 sites (n=11 patients). Again, they found no instances of events that should have been referred.

-Comment: I think the combined audits of Novartis and FDA are reassuring regarding the issue of bias in referral of events, and I feel that this issue has been adequately addressed.

11-4-02 Meeting of the PDAC

We asked the committee to discuss several specific topics, and also anything else they felt might be relevant to this new claim. The discussion was wide-ranging, but several key topics emerged:
-Potential bias in referral of events to SMB: The committee seemed inclined to accept the findings from the sponsor's and FDA's audits of cases as evidence against bias.
-Support for a claim in schizoaffective disorder: There was some concern about the approach to diagnosing patients with this illness, in particular since there was not a structured interview in this large and somewhat simple trial. Ultimately, only roughly half of the committee voted in favor of the findings supporting a claim in schizoaffective disorder.

-Comment: I feel that the diagnostic method used was acceptable, and likely to be the same as that used in clinical practice, and thus valid.

-Appropriateness of a new claim focusing on suicidality in these 2 conditions: The committee did not seem to be troubled with the concept of a drug being approved in support of such a narrow indication, or with an expansion of the target population to include non-treatment resistant patients and schizoaffective patients.
-Interpretation of study with regard to olanzapine: The committee accepted our view that olanzapine should be considered only as a representative comparator drug, useful in providing a benchmark to demonstrate the activity of clozapine in this narrow indication, and not as evidence in support of a claim of superiority to either this atypical or all atypicals.
-Adequacy of single randomized trial: There was much discussion of this issue, especially given the unblinded nature of the InterSePT study (and despite the fact that the committee, for the most part, seemed quite comfortable with the blindedness of the SMB in classifying cases and in the lack of bias in referral of cases to the SMB).
-Ultimately, we asked the committee to vote on the question of whether or not the InterSePT study provided sufficient support to support the agreed upon claim. Of the 9 members who were able to vote, 8 voted in favor of the data supporting this claim, despite all the reservations expressed during the discussion.

Labeling Issues

We reached agreement on final labeling with the sponsor as of 12-12-02.

Conclusions/Recommendations

I believe that Novartis has submitted sufficient data to support the conclusion that Clozaril is effective and acceptably safe in reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk for such behavior. All remaining issues have been resolved, including obtaining an endorsement of this new claim from the PDAC. Thus, I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

cc:
Orig NDA 19-758
HFD-120
HFD-120/TLaughren/RKatz/GDubitsky/SHardeman
HFD-101/RTemple

DOC: MEMCLZSC.AP1

APPEARS THIS WAY ON ORIGINAL

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/s/

Thomas Laughren
12/12/02 01:56:48 PM
MEDICAL OFFICER

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

SUMMARY REVIEW

REVIEW AND EVALUATION OF CLINICAL DATA

Application Information

NDA#:	19-758/S-047
Sponsor:	Novartis
Due Date:	September 1, 2002

Drug Name:

Generic Name:	Clozapine
Trade Name:	Clozaril

Drug Categorization:

Pharmacological Class:	D_4/5-HT receptor antagonist
Proposed Indication:	Suicidality
Dosage Forms:	25mg and 100mg tablets
Route:	Oral

Review Information

Clinical Reviewer:	Gregory M. Dubitsky, M.D.
Completion Date:	August 1, 2002

NDA 19-758/S-047
CLOZARIL FOR SUICIDALITY
TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on Approvability

The sponsor is requesting an indication for the use of Clozaril in the treatment of suicidality in patients with schizophrenia and schizoaffective disorder. It is recommended that this indication not be approved.

B. Recommendations for Phase 4 Studies

At this time, there are no recommendations for Phase 4 studies.

II. Summary of Clinical Findings

A. Brief Overview of the Clinical Program

Support for the requested indication derives solely from one clinical trial, study ABA 451. This was a multicenter, randomized, open-label comparison of Clozaril and Zyprexa with respect to suicidality risk over a treatment period of 2 years in 980 patients with schizophrenia or schizoaffective disorder. Raters of suicidality outcome measures were to be blinded to the patient's treatment.

B. Efficacy

On face, study ABA 451 provides evidence to suggest a reduced risk of suicidality over two years among patients treated with Clozaril versus Zyprexa. However, there were a number of irregularities in the conduct and analysis of this study that preclude a definitive interpretation of the study results at this time. These problems are further discussed in section VI.B.12 below.

Moreover, the indication sought by the sponsor, treatment of suicidality, is distinctly different from the indication which may be supported by ABA 451, a reduction in suicide risk with long-term therapy. This issue is discussed in more detail in section VI.C.1 below.

C. Safety

A limited review of the safety data from study ABA 451 revealed a number of clinically significant adverse experiences associated with Clozaril: white blood cell count decreases, bowel obstruction, hyperglycemia, non-vertiginous dizziness, and somnolence.

None of these represented previously unrecognized toxicities which would preclude the approval of this supplement or require amendment of Clozaril labeling.

CLINICAL REVIEW

I. Introduction and Background

A. Role in the Treatment Armamentarium

Suicide is an important contributor to the shorter life expectancy among patients with schizophrenia compared to the general population. It has been estimated that approximately 10% of patients with schizophrenia commit suicide; this fraction may be even higher in patients with treatment-refractory schizophrenia. Risk factors for suicide in this population appear to be male gender, age under 30 years, depressive symptoms, unemployment, and recent hospital discharge.[1]

Currently, there are no drugs approved for the treatment of suicidal patients with schizophrenia or schizoaffective disorder. If this supplement is approved, Clozaril will be the only agent approved for this indication.

B. Administrative History

Clozapine is an atypical antipsychotic that has been marketed in the U.S. since 1990 as Clozaril for the treatment of neuroleptic-resistant schizophrenia. Since clozapine had demonstrated the potential to cause agranulocytosis, Clozaril has been distributed under a controlled system to ensure regular monitoring of WBC counts in all patients receiving this drug. All Clozaril-

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[1] American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC, American Psychiatric Association, 1994.

treated patients in this country must be registered in the Clozaril National Registry (CNR).

A few years after the launch of Clozaril in the U.S., data from the FDA Spontaneous Reporting System database suggested an increased all-cause mortality, increased mortality due to acute cardiovascular events, and an increased incidence of pulmonary embolism associated with clozapine.[2] To more formally investigate these safety findings, the innovator company (then Sandoz Pharmaceuticals Corporation) contracted with Epidemiology Resources, Inc. (ERI) to perform a retrospective study of overall and cause-specific mortality in current and former users of Clozaril from CNR data.

One finding that emerged from this study was a markedly reduced risk of death due to suicide (approximately seven-fold) in current compared to past users of Clozaril.[3] Based on this finding as well as a published study by Meltzer and Okayli that purported to show a reduced risk of suicidal behavior during Clozaril treatment compared to pre-Clozaril, Sandoz submitted a supplement (S-028) to describe this finding in Clozaril labeling. They further requested that the Agency consider expanding the indication for Clozaril (i.e., for any schizophrenic patient, regardless of neuroleptic-responsiveness, who exhibits suicidality or hopelessness).[4]

Upon review, we found these findings to be difficult to interpret for various reasons, in particular the fact that the neither study compared randomized samples.[5] Thus, we felt that it would be premature to place this information in labeling at that time.

The sponsor elected to conduct a prospective study to more definitively demonstrate that Clozaril treatment was associated with a reduced risk of suicide. Representatives of Sandoz as well as two consultants to Sandoz (Dr. Herbert Meltzer and Dr. Alexander Walker) met with the Division on 1-13-97 to discuss a proposed protocol for such a study.

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[2] See a clinical review by Dr. James Knudsen dated 2-10-93.
[3] Please see my Review and Evaluation of Clinical Data dated 10-27-95 for a complete description of the ERI study design and findings.
[4] Meltzer HY and Okayli G. Reduction of Suicidality During Clozapine Treatment of Neuroleptic-Resistant Schizophrenia: Impact on Risk-Benefit Assessment. Am J Psychiatry 1995;152:183-190.
[5] See a Memorandum by Dr. Thomas Laughren dated 11-3-95.

Important points conveyed to the sponsor at this meeting included the following:

- there was a concern on the part of the Division that suicidality in patients with schizophrenia may be a pseudospecific phenomenon, i.e., a clinical symptom common to many disorders that is "specific" to schizophrenia in name only as opposed to a distinct clinical entity unique to schizophrenia; if that is the case, a new indication would not be allowed.
- there was a high standard to gain a comparative claim; we would have to be reassured that any between-drug differences were not due to an unfair comparison.
- inclusion of non-treatment resistant patients would be acceptable but results should be presented by subgroup to assess for any interaction with this factor.
- open-label drug administration with a blinded rater of suicidality could be problematic since unblinding of this rater might occur by virtue of medication side effects or hallway conversations.
- labeling of the study results under Indications mandates a higher level of evidence compared to a description of the results under Clinical Trials.
- suicide attempts could be used as a surrogate for completed suicides.
- measures should be taken to minimize the number of patients lost to follow-up.

On 1-16-98, the sponsor (Novartis Pharmaceuticals Corporation at this point) submitted the protocol for a 24-month, prospective, randomized comparison of Clozaril vs. Zyprexa with respect to suicidality in 900 patients with schizophrenia or schizoaffective disorder (study ABA 451). I reviewed this protocol on 1-28-98. Supervisory comments were appended by Dr. Thomas Laughren on 1-29-98, and biometrics comments were provided by Dr. David Hoberman in a 2-10-98 E-Mail. The results from this study form the basis for this sNDA.

Study ABA 451 was initiated on 3-19-98.

A number of protocol amendments to ABA 451 were subsequently submitted by the Novartis. Two important amendments are summarized below:

• Amendment #6 was submitted on 1-2-01. This amendment provided for changes in the primary outcome variable and the primary statistical analysis. The Division met with the sponsor on 5-16-01 to discuss this amendment and reach agreement on its acceptability. This amendment will be discussed in detail in the review of study ABA 451 below.
• Amendment #9, dated on 3-14-00, allowed patients who had dropped out of the study to later re-enter if certain conditions were met. I reviewed this change on 3-24-00 and found it to be unacceptable due to potential confounding of the efficacy analysis. The sponsor was advised to not implement this change in a 5-1-00 letter from the Division.

The last patient in study ABA 451 completed participation on 2-13-01.

A pre-sNDA meeting was held with the sponsor on 9-5-01. The following issues were discussed at this meeting:

• we suggested that the primary analysis should be based on the WLW method with c fixed at 0.5 and the expanded definition for Type 2 Events (see the review of ABA 451 below for details). Other analyses would be considered supplementary.
• we indicated that the sNDA would likely be granted priority status and be taken to the Psychopharmacological Drugs Advisory Committee (PDAC).
• an ISS and ISE would not be needed for this sNDA.
• safety data from only study ABA 451 was required but all relevant information pertaining to suicidality, including published literature, should be submitted.
• after our review of an advance listing of all serious adverse events, we would inform them of which patients warranted submission of a full complement of clinical data (e.g., Case Report Forms).
• we requested a listing of all patients with Type 1 or Type 2 Events, from which we would select a random sample for auditing.
• we stated that if a new indication is granted, it would encompass both refractory and non-refractory patients since both types of patients were studied.

Novartis submitted a draft copy of the study report for ABA 451 on 12-21-01 and requested our feedback. A request for further information was E-Mailed to the sponsor by the

FDA Project Manager, Steve Hardeman, on 1-29-02 and included the following items:

- a in-depth analysis of concomitant psychotropic drug use during the study.
- a listing of the median dose and dose range for each treatment arm by visit.
- primary efficacy analyses for the schizophrenia and schizoaffective disorder subgroups separately.

Novartis submitted this sNDA on 2-28-02.

At a meeting of the review team on 4-4-02, it was decided to file this sNDA with Priority review status.

C. Proposed Instructions for Use

The proposed instructions for use in patients with schizophrenia or schizoaffective disorder with suicidality are essentially identical to those recommended in current labeling for patients with treatment-resistant schizophrenia.

II. Clinically Relevant Findings from Other Disciplines and from Consultants

A. Statistical Review and Evaluation

The Statistical Review and Evaluation is pending completion at this time.

B. DSI Clinical Site Inspections

The following four centers from study ABA 451 were inspected by the Division of Scientific Investigations (DSI): 107, 114, 302, and 956. The report of the DSI site inspections is not yet complete.

III. Human Pharmacokinetics and Pharmacodynamics

No new data regarding human pharmacokinetics or pharmacodynamics have been submitted for review in this supplement.

IV. Description of Clinical Data Sources

The primary source of clinical data for this supplement is study ABA 451, also known as the International Suicide Prevention Trial or InterSePT. Efficacy data from this trial is discussed in section VI and safety data is discussed in section VII of this review.

A. Study ABA 451

1. Study Design/Enumeration of Patients

Study ABA 451 was a prospective, randomized, open-label, 24-month trial in patients with DSM-IV schizophrenia and schizoaffective disorder who were deemed to be at high risk for suicide.

A total of 980 patients were randomized to either Clozaril or Zyprexa in a 1:1 ratio (490 patients per arm).

2. Demographic Characteristics

The baseline demographic characteristics of the patients in study ABA 451 are displayed in **Appendix IV-1**.

The Clozaril and Zyprexa treatment groups were almost identical in terms of age, gender, and racial composition. Among patients with baseline body weight information, the two groups were very comparable in terms of weight when stratified by gender.

3. Extent of Exposure

The suggested dosage range for Clozaril in study ABA 451 was 200-900 mg/day and, for Zyprexa, 5-20 mg/day. In the Clozaril group, the overall mean daily dose was 308.7 mg (SD= 555 mg). Among Zyprexa-treated patients, the overall mean daily dose was 17.0 (SD= 25.5 mg).[6]

The overall exposure in terms of treatment duration is summarized in **Appendix IV-2**. In all, 304 Clozaril patients and 312 Zyprexa patients received study drug for at least 631 days. Patient-years of exposure were not provided.

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[6] These figures are based on corrected data submitted to the Agency on 5-17-02.

B. Published Literature

The sponsor performed a literature search of the following databases: Medline (1966-date), Biosis (1993-date), Embase (1974-date), Psycinfo (1887-October 3, 2001), Derwent Drug File (1983-2001), and Sandoz Medical Document (1966-date). These databases were searched using the following string: "(clozapine or Clozaril or Leponex) and (suicide)."

Additionally, an independent internet search using PubMed was conducted utilizing the search terms "clozapine and suicide" and "clozaril and suicide."

Finally, the sponsor located an additional eight papers in the review of the reference lists of identified articles.

Altogether, 70 articles were identified by these searches and were reviewed by the sponsor. Among these, 34 were deemed to be relevant to the effects of Clozaril on suicidality. Of the pertinent articles, 11 described studies, 6 consisted of case reports and observational data, and 17 were review articles of previously published data on suicidality and clozapine.

Case reports cannot provide persuasive evidence of efficacy in suicidality and the review articles contained no data or references not presented in the other papers. Thus, this review will summarize findings of the 11 investigations describing studies of clozapine and suicidality.

V. Clinical Review Methods

A. Items Utilized in the Review

Appendix V-1 lists the items that were utilized in this review. Also, relevant information from the Division File for IND 8,333 was examined.

Case Report Forms and Narrative Summaries were not submitted for all patients who experienced a serious adverse event (SAE). There were about 1500 adverse experiences classified by the sponsor as "serious" in study ABA 451. Many of these were classified as serious solely by virtue of hospitalization for exacerbation of the primary psychiatric illness. Thus, a listing of all serious adverse events (SAE's) was examined by the undersigned prior to the sNDA submission to identify those

events which warranted submission of a Case Report Form and Narrative Summary. This determination was based on a consideration of the expected clinical seriousness of the events and knowledge of those events already known to be associated with clozapine treatment. The selected adverse events are listed in **Appendix V-2**.

B. Methods Used to Evaluate Data Quality

The quality of data pertaining to efficacy (suicidality risk) in this supplement was evaluated by examination of randomly selected Case Report Forms. Additionally, a search was conducted for any blinded psychiatrist who had become unblinded during study ABA 451. These two assessments are further described in **section VI.E** below.

The quality of safety data was assessed by an audit of randomly selected Case Report Forms submitted for patients in study ABA 451 who died or experienced other designated serious adverse events. Also, the appropriateness of the coding of reported adverse event terms to MedDRA preferred terminology for patients in study ABA 451 was evaluated by the undersigned. These assessments are further described in **section VII.D** below.

Data quality was also assessed by the Division of Scientific Investigations via on-site inspections of four centers from Study ABA 451 (107, 114, 302, and 956). That inspection report is pending completion at this time.

C. Adherence to Accepted Ethical Standards

According to the study report (page 19), study ABA 451 was performed in accordance with Good Clinical Practice (GCP) standards.

Additionally, Novartis certifies that it did not and will not use in any capacity the services of any individual debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

D. Evaluation of Financial Disclosure

Financial disclosure information was requested by the sponsor from principal investigators, blinded raters, and members of the Suicide Monitoring Board (SMB) and Steering Committee (SC).

The following proportions of these individuals responded to the requests by the time this supplement was completed:

- 74% (60/81) of the principal investigators.
- 46% (80/174) of the blinded raters.
- 100% (3/3) of the SMB members.
- 84% (5/6) of the SC representatives.

Novartis states that due diligence is continuing to be exercised to collect financial disclosure information for all principal investigators and blinded raters.

Four principal investigators reported disclosable financial arrangements and interests:

- Vinod Kumar, M.D., of center 115, received consulting fees from the sponsor and began full-time employment with Novartis on 3-26-01. Involvement in study ABA 451 ended on 8-23-00. This center enrolled 4 patients (2 treated with Clozaril and 2 with Zyprexa).

- Alan I. Green, M.D., of center 116, has received support from Novartis as the principal investigator in other ongoing clinical trials as well as grants for other research. This center enrolled 12 patients (6 treated with Clozaril and 6 with Zyprexa).

- George T. Grossberg, M.D., of center 120, has received grants for ongoing research and honorarium from Novartis. This center enrolled 14 patients (7 treated with Clozaril and 7 with Zyprexa).

- Herbert Meltzer, M.D., of center 129, has received research grants from Novartis for a number of projects. This center enrolled 13 patients (7 treated with Clozaril and 6 with Zyprexa).

It is unlikely that these arrangements biased the study results since none of these individuals were raters of suicidality and each of these sites contributed a small fraction of the total patient sample.

VI. Integrated Review of Efficacy

A. Overview of Data Relevant to Efficacy

The demonstration of the efficacy of Clozaril in reducing suicide risk in schizophrenic patients at high risk for suicidality rests on the results of a single, prospective clinical trial, study ABA 451. This study is reviewed in detail below.

As mentioned above, the sponsor's literature search revealed 11 published investigations that produced clinical data relevant to a purported anti-suicide effect of Clozaril. These studies are summarized below. Based on my review of each investigation, they all suffer from significant flaws that render them incapable of providing convincing evidence of an anti-suicide effect.

B. Study ABA 451

1. Investigators/Sites

In all, 67 centers worldwide enrolled patients in study ABA 451 (31 U.S. centers and 36 foreign centers). The location, number of randomized patients by treatment group, and principal investigator(s) for each of these centers are listed in **Appendix VI-1**.

No principal investigator (PI) was listed as disqualified by the Agency as of 7-16-02.

2. Objectives

The primary efficacy objective was to demonstrate a decreased risk for suicide among schizophrenic patients treated with Clozaril compared to the risk among patients treated with Zyprexa.

3. Study Population

A total of 980 patients were randomized to treatment with either Clozaril or Zyprexa in study ABA 451: 396 patients were randomized in the U.S. centers (198 each to Clozaril and Zyprexa) and 584 were randomized in foreign studies (292 each to Clozaril and Zyprexa).

Important inclusion criteria were:

• male or female patients, age 18-65, meeting DSM-IV criteria for schizophrenia or schizoaffective disorder.
• at high risk for suicidality as indicated by one of the following:

- attempted suicide within 3 years of study baseline assessments.
- hospitalized to prevent a suicide attempt within 3 years of baseline assessments.
- moderate to severe suicidal ideation with a depressive component within one week of baseline assessments.
- moderate to severe suicidal ideation with command hallucinations to do self-harm within one week of baseline evaluation.

Although Clozaril is approved only for treatment-resistant schizophrenia in the U.S., patients were enrolled in this trial irrespective of treatment-responsiveness.

Important exclusion criteria were:

• judged to be incompetent to make treatment decisions or refusal to agree to participation.
• no previous exposure to antipsychotic medication.
• extreme psychosis requiring immediate treatment.
• pregnancy or nursing a child.
• highly suicidal patients were not randomized until their condition was stabilized.

Additionally, enrollment of the following patients was discouraged:

• previous inadequate response to adequate doses of Clozaril (≥600 mg/day) or Zyprexa (≥10 mg/day) for at least 4 weeks.
• good clinical response to either Clozaril or Zyprexa, since they could be randomized to less effective medication.
• requiring complicated regimens of multiple medications.
• history of poor compliance with treatment plans.

4. Study Description

Design

This was a prospective, randomized, open-label, 24-month trial with two active treatment arms, clozapine (Clozaril) and olanzapine (Zyprexa). Eligible patients were randomized in a 1:1 ratio to Clozaril or Zyprexa within each study center. Patients and PI's were not blinded during this study but each site did include blinded raters for efficacy and suicidality assessments.

Dosing and Concomitant Medications

All study medication was dispensed at the investigational site. The recommended starting dose for Clozaril was 12.5mg bid with a suggested target dose range of 200-900 mg/day. The recommended starting dose for Zyprexa was 5 mg/day with a recommended target dose range of 5-20 mg/day. All patients were titrated to their most effective dose as tolerated. The doses used were to reflect the community norm.

Patients who entered the trial while receiving other antipsychotics were to be cross-titrated. The prior medication was to be weaned as the dose of study medication was titrated to therapeutic levels. Cross-titration was to be completed within 30 days of randomization if possible. Patients who had received depot medication were to be randomized once a full dosing interval had passed.

Randomized patients were allowed to take any medication deemed medically necessary and appropriate by the PI, to include the judicious use of antidepressants to treat worsening suicidal ideation or depression during the trial.

Assessments

The PI conducted scheduled assessments of suicidality (i.e., completion of the InterSePT Suicidal Thinking and the CGI Severity of Suicidality scales) on a frequent basis.[7] However, information pertaining to a completed suicide, suicide attempt, hospitalization due to imminent suicide risk, or (for inpatients) an increased level of surveillance due to suicidality was collected throughout the 104 week treatment period and recorded in the CRF by the PI. Data relevant to suicides and suicide attempts

[7] These assessments were conducted at baseline and at the following weeks: 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 60, 68, 80, 92, and 104.

were documented on the Suicide Attempt Form (SAF). Data relevant to hospitalization or increased surveillance due to imminent suicide risk were documented on the Imminent Risk of Suicide Requiring Hospitalization (IRH) form.

Psychiatrists at each site who were blinded to the patient's treatment (Blinded Psychiatrists or BP's) conducted the same assessments of suicidality on a less frequents basis.[8]

Additional efficacy measures (PANSS, CGI for Change in Psychosis, CGI for Severity of Psychosis, Calgary Depression Scale) were performed by blinded raters who could also have acted as the blinded psychiatrists.

Dropouts

If a patient discontinued participation in the study for any reason, the PI was to attempt to follow the patient by regular contact with the patient or the patient's family to determine if the patient completed or attempted suicide or was hospitalized for imminent risk of suicide. This follow-up period was to extend to what would have been Week 104 of the patient's treatment. Patients could elect not to be contacted during this period. Patients who consented to this follow-up were considered Retrieved Dropouts (RDO's) and assessments of suicidality by the unblinded PI were done every 12 weeks. Assessments on RDO's included the ISST-PI (InterSePT Scale for Suicidal Thinking-Principal Investigator) and the CGI-SS-PI (Clinical Global Impression of Severity of Suicidality-Principal Investigator); as indicated, the SAF (Suicide Attempt Form) and the IRH (Imminent Risk Requiring Hospitalization) form were also completed. All RDO assessments were completed by unblinded study staff.

Amendment #10 to the study protocol, submitted on 3-14-00, permitted the return of patients who had dropped out due to mild adverse events, loss to follow-up, transportation difficulties, and exacerbation of illness due to noncompliance, among other reasons, to resume study participation on the drug to which they were originally randomized at the study timepoint at which they had dropped out. Such patients had to request to resume study participation and continue to meet all eligibility criteria. Also, the treating physician must have deemed

[8] Blinded assessments were done at baseline and at the following weeks: 8, 16, 24, 32, 40, 48, 52, 60, 68, 80, 92, and 104.

resumption of study treatment in the best interest of the patient.

Novartis was advised by the Division in a 5-1-00 letter that this amendment was considered likely to confound the assessment of suicidality in this study for several reasons, such as the introduction of a variable (a break in treatment that may include other interim therapy) which could influence the occurrence of suicidality later in the trial. Therefore, the Division recommended that this amendment not be implemented. Despite this advice, it appears that the sponsor implemented this protocol change.

Maintenance of Blinding

It was considered possible that any decrease in suicidality observed in Clozaril patients might be due to the frequent contact with healthcare professionals consequent to the mandatory WBC monitoring with Clozaril. WBC monitoring was performed weekly for the first 26 weeks then every 2 weeks thereafter. To balance this potential source of bias between the two groups, Zyprexa patients were also seen on this same schedule for vital sign measurements. Also at these visits, an unblinded healthcare professional assessed the patient's overall psychiatric condition, to include suicidality, and referred the patient to the investigator or other professional for further evaluation and possible intervention when deemed appropriate.

As noted above, patients and PI's were not blinded. To address the possibility of biased assessments of primary outcome occurrences (Type 1 and Type 2 Events), the following measures were instituted.

First, as mentioned above, each site included a psychiatrist who was blinded to the patient's treatment. Ratings on the CGI-SS-BP, to detect a possible Type 2 Event, were performed by the blinded psychiatrist. These individuals affirmed their blinded status or indicated unblinding at each assessment.

Second, the flow of data pertaining to a possible Type 1 event was designed to help assure unbiased detection and confirmation of these events. The relevant personnel and study features are described in detail below.

PI's collected and forwarded all relevant information on any potential Type 1 event to Ingenix Pharmaceutical

Services, Inc., a contract research organization. This included information on all deaths, suicide attempts, psychiatric hospitalizations, discontinuations of study drug, and increased surveillance due to imminent suicide risk. Blinded reviews of the study clinical database were also performed by Ingenix to identify any potential Type 1 events that might have been missed.

Ingenix reviewed the data from the study site and censored any information that was likely to unblind the reader to the patient's treatment, to include signs or symptoms that might unwittingly reveal the patient's treatment. The data were then forwarded to the BP's and to the Suicide Monitoring Board (SMB).

The SMB was a blinded body comprised of three clinicians who are experts in the study of suicide with experience in schizophrenia. The SMB Chairman was Ranga Krishnan, M.D., Duke University Medical Center, Durham, NC; SMB members were Hannele Heila, M.D., National Public Health Institute, Helsinki, Finland, and Isaac Sakinofsky, M.D., University of Toronto, Toronto, Canada.

Under no circumstances was the SMB to be unblinded to the treatment of any study patient. If any member of the SMB became unblinded, the SMB Chairman was to be notified who, in turn, would notify Novartis.

The primary purpose of the SMB was to make determinations regarding the blinded data received from Ingenix as follows:

- for all deaths, to judge whether the death represented a suicide.
- for all self-damaging acts, regardless of intention, to determine if the act represented a serious suicide attempt as opposed to a suicide gesture or non-attempt.
- for all hospitalizations and increases in the level of surveillance for suicide, to ascertain whether these represented interventions to prevent an imminent suicide attempt.
- for all discontinuations from study drug treatment due to increasing suicidality, to determine whether discontinuation occurred because of imminent suicide risk.

The SMB conducted regular teleconferences to discuss blinded data from Ingenix and to reach consensus on each

event. If there was disagreement on a determination, a vote was to be taken and the final determination was defined as that of the majority of the SMB members.

Although blinded data from Ingenix for all potential Type 1 events were also reviewed by the BP's, the determination of the SMB regarding the presence or absence of a Type 1 event was considered primary for purposes of efficacy analysis.

Steering Committee

Oversight and guidance for study ABA 451, with the purpose of minimizing risk to study participants and maintaining the scientific integrity of the trial, was provided by the study Steering Committee (SC). Although the SC interacted with a liaison from Novartis (Ravi Anand, M.D.), this committee was considered to be an independent body. The SC was comprised of the Chairman, John Kane, M.D., and members Daniel Casey, M.D., Prof. Frederic Rouillon, Prof. Giovanni Cassano, Prof. Shon Lewis, Prof. Istvan Bitter (resigned November 2000), and Nancy Temkin, Ph.D.

5. Efficacy Analysis Plan

The efficacy analysis plan for this study has been amended from that specified in the original protocol. In the original protocol, two primary variables were specified:

- time from baseline to the first significant suicide attempt or hospitalization due to imminent risk of suicide confirmed by the SMB.[9] This analysis was to be performed using a Cox proportional hazards regression model. Explanatory variables were treatment and the following baseline measures: number of lifetime suicide attempts, active substance/alcohol abuse, pooled country, sex, and age (18-32 years, 33-44 years, and 45 years and older).
- change from baseline in the CGI-SS-BP severity score as rated on a 5-point scale. These data were to be analyzed using an ANCOVA model with the same explanatory variables listed above as well as the baseline CGI-SS-BP severity score.

During the course of study ABA 451, Novartis found that the rate of suicides and suicide attempts was lower than predicted and the rate of loss to follow-up was higher than

[9] Amendment #1 to the protocol added an increased level of surveillance for suicide risk as a primary outcome.

predicted when the sample size for the trial was computed. Additionally, the sample size calculation did not account for the need to adjust the significance level for multiple comparisons, given that there were two primary efficacy variables. As a result of these factors, Novartis felt that 80% power to detect a intergroup difference would not be achieved and, therefore, it would be more likely that this trial would fail to demonstrate the superiority of Clozaril over Zyprexa in reducing suicidality.

To address this concern, the sponsor convened a group of clinical and statistical experts in August 2000. It was recommended that specific revisions to the primary study objectives and statistical analysis plan be implemented as described below. These changes comprised Amendment #6 to the protocol, which was submitted to the Agency on 1-2-01.

The revised study objective was to demonstrate a decreased risk for suicide among schizophrenic patients treated with Clozaril compared to patients treated with Zyprexa as measured by the time (in days after randomization) to the following two types of events:

Type 1 Event - a significant suicide attempt or completed suicide, hospitalization due to imminent suicide risk, or increased surveillance due to suicide risk, whichever came first and regardless of whether the subject was still on randomized treatment. If none of these events occurred during the entire study period, time was censored on the date of study drug discontinuation or on the last date of retrieved data, whichever was later.[10]

Type 2 Event - 1) worsening of the severity of suicidality as manifested by a score of 6 or 7 (worse or very much worse) on the 7-point change score of the Clinical Global Impression for Severity of Suicidality as rated by a blinded psychiatrist (CGI-SS-BP) or 2) the occurrence of a Type 1 Event, whichever came first and regardless of whether the subject was still on randomized treatment. If neither event occurred throughout the entire study period, time was censored on the date of study drug discontinuation or on the last date of retrieved data, whichever was later.

[10] Amendment #6 did not specify that time to either type of event or censoring would include time subsequent to premature termination for dropouts.

The revised primary analysis was based on the approach of Wei, Lin, and Weissfeld, known as the WLW method.[11] Using this multiple events analysis technique, the time to the first occurrence of a Type 1 event and time to the first occurrence of a Type 2 event were modeled using a proportional hazards approach to derive treatment effect estimators for each event type, with country pool as strata and treatment group as the only covariate.[12] The WLW method provided a single test for treatment effect based on two time to event endpoints, with the two event types given equal weighting in this case. Then, a two-sided test was performed at the 0.05 level of significance to compare the combined treatment estimators between the two treatment groups.

A number of supplemental analyses were also performed, to include the following:

- the original primary efficacy analyses, as described above.
- analysis of time to Type 1 events using a full Cox proportional hazards regression model adjusted for a number of baseline factors, which permitted assessment of the effect of these factors on time to event.
- analyses for diagnostic subgroups, i.e., patients with schizophrenia versus patients with schizoaffective disorder.
- analyses for geographic subgroups, i.e., North America versus the rest of the world.

6. Baseline Patient Characteristics

At baseline, the Clozaril and Zyprexa treatment groups were comparable in terms of mean PANSS total scores (84.8 vs. 82.6, respectively).

With respect to suicidality, the two treatment arms had almost identical distributions of CGI-Severity of Suicidality scores as rated by the blinded psychiatrists (**Appendix VI-2**). On average, Clozaril patients had a

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[11] Please see the statistical review for further discussion of the WLW methodology.

[12] Countries with small numbers of patients were pooled with other countries to form a "pooled country" factor that was used as a stratum in the statistical analyses. Pooled countries were grouped as follows: U.S. and Canada, S. Africa and the U.K., France and Italy, Argentina and Chile, Croatia and the Czech Republic, and Hungary.

lifetime history of 3.6 suicide attempts compared to 3.2 suicide attempts among Zyprexa patients. About 15% of each group had no history of previous suicide attempts and another 15% of each group had a history of more than 5 suicide attempts. The median number of lifetime hospitalizations to prevent a suicide attempt was 2 in each treatment arm.

Baseline demographic characteristics are displayed in **Appendix IV-1**. The treatment groups were almost identical in terms of age, gender, and racial composition.

Diagnostically, 61% (300/490) of Clozaril and 63% (309/490) of Zyprexa patients were diagnosed with schizophrenia; 39% (190/490) of Clozaril and 37% (181/490) of Zyprexa patients were diagnosed with schizoaffective disorder. About one-fourth of each group was considered treatment-resistant by clinical assessment.

About one-half of each treatment group had a history of alcohol or other substance abuse (48% of Clozaril and 51% of Zyprexa patients). At baseline, 11% of each group had current alcohol or other substance abuse.

The baseline mean total scores for the Calgary Depression Scale (CDS) were very similar between groups: Clozaril= 9.8 (SD=5.9), Zyprexa= 9.9 (SD=5.9). The percentages of patients with each score on the Hopelessness item (item #2) of the CDS were also similar between the two groups at baseline.

7. Patient Disposition

A total of 1,065 patients were screened for study ABA 451. Of these, 980 were randomized to Clozaril (N=490) or Zyprexa (N=490) and comprised the intent-to-treat (ITT) population.

In all, 61% (298/490) of the Clozaril and 62% (303/490) of the Zyprexa patients completed the entire 2 year study. Including retrieved dropouts, 39% (192/490) of the Clozaril and 38% (187/490) of the Zyprexa patients discontinued from the study. These dropouts are enumerated by reason for discontinuation in **Appendix VI-3**. It is notable that 33 Clozaril and 39 Zyprexa patients were lost to follow-up. It is not known if any of these patients were lost due to suicide attempts or completed suicide.

The numbers of patients in the study by visit are displayed in **Appendix VI-4**. At least 70% (344/490) of Clozaril patients were still in-study at the week 40 visit, with 76% (370/490) of the Zyprexa patients still participating at that timepoint.

8. Dosing Information

Ten of the Clozaril patients and 11 of the Zyprexa patients in the ITT population were not dispensed study drug. Also, one of the Clozaril patients and 2 of the Zyprexa patients who were dispensed drug did not take study medication.

Among the 479 Clozaril patients who took study drug, the overall mean daily dose was 308.7 mg (SD= 555 mg). The mean prescribed doses of Clozaril gradually increased from 150 mg/day at week 1 to just under 300 mg/day at week 12; thereafter, mean prescribed doses were in the range of 300 to 334 mg/day, with a maximum of 800 or 900mg/day.

Among the 477 Zyprexa patients who took study drug, the overall mean daily dose was 17.0 mg(SD= 25.5 mg). Mean prescribed doses of Zyprexa gradually increased from 12 mg/day at week 1 to about 17 mg/day after week 10; mean doses remained in the range of 17 to 18 mg/day for the remainder of the trial, with maximum doses of generally 50 mg/day.

Median prescribed doses by visit are presented in **Appendix VI-5**. From week 10 onward, the median doses of Clozaril and Zyprexa were 300 and 20 mg/day, respectively.

9. Concomitant Medications

Patients who entered the study while taking other antipsychotic medication were to be cross-titrated within 30 days of randomization. Also, after randomization, concomitant psychotropic medications were permitted by protocol if deemed necessary and appropriate by the investigator. Psychopharmacologic agents were used by a substantial proportion of patients during the study. For example, among the 479 Clozaril and 477 Zyprexa patients who took study medication, concurrent selective serotonin reuptake inhibitors were used by 39% of Clozaril and 46% of Zyprexa patients. Also, it is notable that 5 patients randomized to Zyprexa received Clozaril concomitantly and

16 patients randomized to Clozaril received Zyprexa concomitantly.

The concomitant use of psychopharmacologic agents during this trial could confound the assessment of an anti-suicide effect. To better appreciate the extent of this potential source of bias, the Division requested that Novartis devise a method to demonstrate that the use of concomitant psychotropic medication is unlikely to have biased the results of study ABA 451. The plan devised by the sponsor and the results of this analysis are described below.[13]

Analysis Plan

The sponsor grouped concomitant psychotropic medication used in study ABA 451 into the following groups: antidepressants, antipsychotics, sedatives/anxiolytics, and mood stabilizers. Stimulants and anti-dementia drugs were excluded. Once a medication was assigned to one of the above classes, all uses were included in the analysis (both psychiatric and non-psychiatric indications). However, medication usage based on a PRN schedule was excluded as were antidepressants and mood stabilizers taken for less than 14 days.

To pool the use of medications of different potencies within a class, the dosage of each drug was converted to dosage equivalents within each class based on conversion data and average doses reported in current literature. Antidepressants were converted to fluoxetine equivalents, sedatives/anxiolytics to diazepam equivalents, antipsychotics to haloperidol equivalents, and mood stabilizers to carbamazepine equivalents.

Then, the total AUC (sum of the areas under the converted dosage versus time curves for all drugs within a class) over successive 6 month intervals was calculated for each patient for each concomitant drug class.

Next, the mean dose per patient for each class was calculated by dividing the total AUC by the number of days in-study for that patient during each 6 month interval. For dropouts, no mean dose was computed after the end of the 6 month interval in which the patient dropped out.

[13] This information was submitted to the NDA on 6-24-02.

Finally, for each drug class and each interval, the average mean dose was determined over all patients. ANCOVA, with terms for treatment, pooled country, and concomitant medication dose at baseline, was performed to compare the least squares mean dosage (LSMD) between treatment groups for each 6 month interval, with statistical significance defined as a p-value ≤ 0.05.

Analysis Results

Of all patients who took study drug (N=956), a large proportion took psychopharmacologic drugs concomitantly and were included in the analysis: 84% took antipsychotics, 65% took sedative/anxiolytics, 53% took antidepressants, and 28% took mood stabilizers. **Appendix VI-6** enumerates these patients by treatment group.

Pooling data across all 6 month intervals, the LSMD's for Clozaril were significantly less than for Zyprexa for all four drug classes (**Appendix VI-7**).

A breakdown of the LSMD's by 6 month intervals is provided in **Appendix VI-8** (for antipsychotics), **Appendix VI-9** (antidepressants), **Appendix VI-10** (sedatives/anxiolytics), and **Appendix VI-11** (mood stabilizers). For most comparisons, the LSMD for Clozaril was less than for Zyprexa to a statistically significant degree. For the remainder of the comparisons (i.e., antidepressants during months 13-18 and 19-24 and mood stabilizers during months 19-24), the LSMD's was numerically less for Clozaril than for Zyprexa.

In sum, the sponsor's analysis revealed no evidence to suggest a bias due to concomitant medication usage that favored Clozaril over Zyprexa. These results should be interpreted with a large grain of salt since this analysis is based on an imperfect surrogate measure for the confounding influence of concomitant psychotropic medication on suicidality.

10. Protocol Deviations

A common protocol deviation was a change in clinical raters during the study. In particular, it was noted that 42% of the Clozaril patients and 44% of Zyprexa patients had a change in the rater for the CGI-SS-BP during their trial participation, which included an assessment by a blinded psychiatrist of the change in suicidality compared to the

patient's condition at baseline. The reliability of this specific rating, which was one of the key outcome variables, may have been compromised by the changes in raters for this scale. The extent to which this was true is very difficult to gauge.

11. Study Results

Psychotic Symptomatology

Both treatment groups experienced improvement in psychotic symptomatology as measured by changes from baseline to end of study (LOCF) in the PANSS total score (-23.6 for Clozaril and -22.4 for Zyprexa; p-value= 0.3591). The PANSS positive and negative subscales and the CGI for severity of psychosis (CGI-SP) provided further evidence of improvement for both Clozaril and Zyprexa patients.

Enumeration of Patients with Type 1 & Type 2 Events

The numbers and percentages of patients with Type 1 events, as determined by the SMB, and Type 2 events, as determined by the BP's, are displayed in **Table VI-1** below. In the primary analysis, any Type 1 event was taken to imply a Type 2 event; thus, patients with a Type 1 event are a subset of the patients with a Type 2 event. Clearly, the predominant event type was Type 1. For both event types, the proportion of patients with the event was significantly lower in the Clozaril compared to the Zyprexa group.

TABLE VI-1
NUMBER (%) OF ITT PATIENTS WITH TYPE 1 AND TYPE 2 EVENTS

Event Type	Clozaril (N=490)	Zyprexa (N=490)	p-value[14]
Type 1	102 (20.8%)	141 (28.8%)	0.0049
-Completed Suicide	5 (1.0%)	3 (0.6%)	0.7254
-Suicide Attempt	34 (6.9%)	55 (11.2%)	0.0257
-Hospitalization	82 (16.7%)	107 (21.8%)	0.0518
Type 2	120 (24.5%)	161 (32.9%)	0.0047

WLW Analysis

The amended primary analysis was a single composite analysis of time to the first occurrence of a Type 1 event and time to the first occurrence to a Type 2 event using WLW methodology, as described above, with equal weighting given to each event type in the model. The analysis was

[14] Based on Fisher's exact test.

based on all randomized patients (490 Clozaril and 490 Zyprexa patients).

The results are summarized in **Appendix VI-12**. The coefficient of combined treatment effect from the primary model was -0.265, with a p-value for the Clozaril/Zyprexa comparison of 0.0309.[15] Examining the WLW treatment effect estimators for Type 1 and Type 2 events separately, there was a significantly lower risk of each event with Clozaril versus Zyprexa: the respective hazard ratios (95% CI) were 0.76 (0.58, 0.98) and 0.78 (0.61, 0.99).[16]

Original Primary Analysis

As a supplemental analysis, the sponsor also analyzed the results of this trial utilizing the methods proposed in the original protocol (and Amendment #1). This entailed examination of two variables: 1) the time from baseline to the first significant suicide attempt, hospitalization due to imminent risk of suicide, or an increased level of surveillance for suicide risk (Type 1 event), using a Cox proportional hazards regression model; and 2) change from baseline in the CGI-SS-BP severity of suicidality score as rated on a 5-point scale, analyzed using an ANCOVA model.

The Type 1 event results were similar to those in the amended primary analysis: there was a statistically significant lower risk of a Type 1 event among Clozaril versus Zyprexa patients (regression coefficient for treatment= -0.304, p=0.0211; hazard ratio= 0.74 (95% CI= 0.57, 0.96)). However, results for the change from baseline in the CGI-SS-BP severity score were not statistically significant (regression coefficient= +0.007, p-value= 0.8884).

Kaplan-Meier Analysis

A secondary analysis was a Kaplan-Meier survival analysis of the cumulative probabilities of Type 1 events and Type 2 events. Kaplan-Meier survival curves are displayed in **Appendix VI-13** (Type 1 events) and **Appendix VI-14** (Type 2 events). Survival data by visit are displayed in **Appendix VI-15**. The cumulative probabilities of experiencing an event were numerically lower for Clozaril patients than for Zyprexa patients at all visits for each event type.[17] At

[15] A coefficient <0 indicates that Clozaril was superior to Zyprexa.
[16] A hazard ratio <1 indicates superiority of Clozaril over Zyprexa.
[17] The 95% CI's for the treatment group differences contained zero (implying no difference) up to and including the week 80 visit.

week 104, the cumulative probabilities were significantly lower for Clozaril (**Table VI-2** below).

TABLE VI-2
KAPLAN-MEIER ESTIMATES OF THE CUMULATIVE PROBABILITIES OF A TYPE 1 OR TYPE 2 EVENT AT WEEK 104

Event Type	Clozaril	Zyprexa	p-value[18]
Type 1	0.24	0.32	0.020
Type 2	0.28	0.37	0.027

12. Conclusions from Study ABA 451

The results of study ABA 451 appear, on face, to support the hypothesis that Clozaril treatment is associated with a reduced risk of suicidality compared to Zyprexa therapy. However, the validity of this finding is questionable for several reasons:

1) the primary efficacy analysis (WLW methodology) included patients who had dropped out and discontinued study drug but were being followed as retrieved dropouts. In my opinion, to assess the effect of ongoing drug exposure on event occurrence, patients included in the analysis should be receiving drug and patients who drop out of drug treatment should be right-censored at the time of dropout. Otherwise, and particularly in a long-term study like ABA 451, it is very tenuous to ascribe the occurrence or non-occurrence of events to study drug. Censoring dropouts may significantly change the study outcome.

2) Amendment #9 to the study protocol allowed patients who had dropped out of the study to re-enter the trial as full participants at a later date and continue the originally assigned medication on the study day of dropout. This change introduced a variable (a break in treatment that may have included interim interventions) that could have influenced the risk of suicidality after re-entry of these patients, thus confounding the efficacy results. It is not known how many patients actually returned to the study under this amendment.

3) a number of patients (33 Clozaril and 39 Zyprexa patients) were lost to follow-up at some point during this trial. It is not known if any of these patients experienced a suicidality-related event (such as suicide or

[18] Log rank test.

a serious suicide attempt) that led to study discontinuation. The possibility remains that information about the circumstances of discontinuation in these patients might appreciably change the study results.

4) for a sizeable proportion of patients in each group (42% of Clozaril and 44% of Zyprexa patients), there was a change in the blinded rater who completed the CGI for severity of suicidality (CGI-SS-BP). A key outcome variable was the rating of the change in the patient's suicidality compared to the baseline condition using this scale. The reliability of a new rater in assessing change from the baseline condition is very questionable.

5) a substantial number of patients took concomitant psychiatric medication during this study. While it would be expected to see a large number of such patients taking antipsychotics early in the trial (due to the cross-titration procedure for patients on antipsychotics at study entry), it is noted that 273 Clozaril and 279 Zyprexa patients took concomitant antipsychotics during the last 6 month interval of the study (months 19-24). During this same interval, antidepressants were taken by 169 Clozaril and 201 Zyprexa patients. It is unknown how many of these patients were simply continuing pre-study medication versus the number who were deemed to require the institution of psychotropics for emergent conditions, such as suicidal ideation, during the study. It is acknowledged that the sponsor's analysis of concomitant psychotropic drug use represents a good-faith effort to address this issue and that a complete understanding of the impact of this usage is likely impossible. Nonetheless, the inability to fully quantify this potential confounding influence does not render it ignorable.

6) as is discussed in detail in section VI.E (Assessment of Efficacy Data Quality), an audit of the suicidality data from this trial revealed two potential findings (possible biased SMB determinations and unblinding) that could impact on the reliability of the data from study ABA 451.

The above factors raise a considerable question about the validity of the study findings. At this point in time, the stated findings from study ABA 451 are best considered inconclusive.

C. Important Clinical Issues Pertinent to Efficacy

1. Suicidality Indication

According to the proposed INDICATIONS AND USAGE section of Clozaril labeling, Novartis is seeking approval for the treatment of suicidality in patients with schizophrenia or schizoaffective disorder. Suicidality is defined as actions by a patient committed either with willful intent or as a response to internal compulsions or disordered thinking that put him/herself at high risk for death.

Evidence for this claim is derived from study ABA 451. This trial utilized the following inclusion criteria to identify patients at high risk of suicidality:

- attempted suicide within 3 years of baseline.
- hospitalized to prevent a suicide attempt within 3 years of baseline.
- moderate to severe suicidal ideation with a depressive component within one week of baseline.
- moderate to severe suicidal ideation with command hallucinations to do self-harm within one week of baseline.

To be included in this study, a patient had to meet one of the above criteria. Thus, the study population was likely quite heterogeneous at baseline in terms of imminent suicide risk, ranging from patients with active suicidal ideation and a plan to harm themselves to patients who were hospitalized 3 years before study participation for suicidal ideation which has long since resolved. Clearly, patients were not required to be actively suicidal at the time of study entry. In fact, according to the study report, patients who were "highly suicidal" were not randomized until their condition stabilized.

Critical to the approval of a claim for the treatment of any given condition is the requirement that the effect of the intervention be demonstrated in patients with that condition. Therefore, to the extent that study ABA 451 included patients who were not suicidal at baseline, this trial is not capable of providing evidence of the efficacy of Clozaril in treating suicidality.

Furthermore, the design of ABA 451, which examined the risk of suicidality-related events over a two year period, would not be appropriate to demonstrate efficacy in treating

acute suicidality. A claim for the latter would imply an intervention that reduces the risk of self-harm or death in the short-term (days to a few weeks), not over a period of years.

In summary, an acceptable study for evaluating a treatment for suicidality would enroll actively suicidal patients only and anticipate a response over a relatively brief period of time. ABA 451 is not such a trial.

On the other hand, the results of ABA 451 may be useful in demonstrating a reduced risk of suicidality associated with long term Clozaril versus Zyprexa treatment. The use of Clozaril as a preventive measure in this regard would be a feasible indication for the sponsor to seek. In that case, a critical and difficult clinical issue to be addressed is the identification of patients for whom Clozaril is indicated for the purpose of suicidality prevention. Since it is anticipated that the sponsor will amend this application to seek approval of this use, this issue will be explored further at this point.

The emergence of suicidality is frequently precipitated by external events (e.g., loss of a significant other person or a financial crisis) superimposed on various underlying cofactors (such as substance abuse, depression, or health problems). Unfortunately, due to the unpredictable nature of these precipitants, there is no reliable way of identifying those patients who will become suicidal.

As a conservative practice, any patients with a history of any suicidality might be treated with Clozaril. However, the wisdom of switching large numbers of patients to Clozaril from otherwise effective and well-tolerated antipsychotic therapy or choosing to initiate Clozaril over other drugs that might be better tolerated and perhaps more effective is debatable. Not to be ignored are the cost, inconvenience, and discomfort associated with the white blood cell monitoring required for patients treated with Clozaril.

A better approach would be the use of Clozaril in a more discriminating fashion, such as in patients with a pattern of chronic suicidal behavior or suicidal ideation who are deemed to be at some continuing risk of suicide. It would be difficult to formulate specific criteria for such use for labeling and, ultimately, this decision should depend

on the judgement of the treating physician, who is capable of considering the clinical nuances of the patient's history and presentation and weighing the risks versus potential benefits for the individual patient. But, in this case, it may be more appropriate to simply describe the results of study ABA 451 in labeling and allow prescribers to decide, on a patient-by-patient basis, whether Clozaril is indicated. A potential downside is that some managed healthcare organizations may refuse to subsidize the cost of Clozaril and WBC monitoring for these patients without a formal, labeled indication for such use.

The best solution to this problem is not clear at this time.

2. Predictors of Response

Covariate Analyses

A covariate analysis was performed on data from study ABA 451 to identify prognostic factors for suicidality using a full Cox proportional hazards regression model for time to a Type 1 event. Covariates included the following: treatment, gender, age group (≤32, 33-44, ≥45 years), number of lifetime suicide attempts, diagnosis, alcohol or other substance abuse, and a number of baseline ratings, to include the CGI-SS-BP severity score, Calgary Depression Scale score, and the Covi Anxiety Score.

Results are depicted in **Appendix VI-16.** These analyses revealed that treatment, the number of lifetime suicide attempts, and the presence of substance or alcohol abuse were statistically significant prognostic factors for Type 1 events.

Adjusting for risk factors demonstrated a treatment effect favoring Clozaril on SMB-confirmed Type 1 events (hazard ratio= 0.73, p-value= 0.0172). Interestingly, when this analysis is applied to the time to Type 1 events as confirmed by the blinded psychiatrist, Clozaril has a somewhat larger hazard ratio (0.84) and treatment is no longer a statistically significant predictor (p=0.1839).[19]

With respect to the number of lifetime attempts, the hazard ratio was 1.03 (p=0.0001), indicating that an increased

[19] See Appendix 5.3.1, Table 9.1-5, of the study report.

number of attempts was associated with a very slightly increased risk of a Type 1 event.

Regarding substance or alcohol abuse, the hazard ratio was 1.48 (p=0.0081), indicating an association between alcohol or substance abuse and an increased risk of a Type 1 event.

A similar covariate analysis of time to a Type 2 event revealed analogous findings.

Diagnostic Subgroup Analysis

Although the above analysis did not reveal an significant effect of diagnosis on the time to a Type 1 or Type 2 event, a subgroup analysis was specifically requested by the Division. The numbers and percentages of Clozaril and Zyprexa patients with Type 1 and Type 2 events as well as the Kaplan-Meier cumulative probabilities of events are displayed by diagnostic subgroup (schizophrenia vs. schizoaffective disorder) in **Table VI-3** below. For all treatment group comparisons, Clozaril was numerically superior to Zyprexa in terms of event risk regardless of diagnosis (formal statistical testing was not performed).

TABLE VI-3
NUMBER (%) OF ITT PATIENTS WITH TYPE 1 AND TYPE 2 EVENTS BY DIAGNOSTIC SUBGROUP[20]

	Clozaril (N=490)			Zyprexa (N=490)		
	n/N	%	KM %	n/N	%	KM %
Schizophrenia						
Type 1	51/300	17.0%	19.5%	82/309	26.5%	29.3%
Type 2	67/300	22.3%	25.9%	98/309	31.7%	35.1%
Schizoaffective Disorder						
Type 1	51/190	26.8%	31.0%	59/181	32.6%	37.2%
Type 2	53/190	27.8%	32.1%	63/181	34.8%	39.5%

The sponsor repeated the WLW analysis for each of the two diagnostic subgroups. The results are presented in **Appendix VI-17**.

For patients with schizophrenia, the results were consistent with those for the entire study population. The combined estimate of treatment effect favored Clozaril over

[20] N= total number of patients in subgroup, n= number of patients with event in subgroup, %= (n/N)×100%, KM %= Kaplan-Meier estimate of the cumulative probability of the event at week 104.

Zyprexa to a statistically significant degree (p=0.0298). For Type 1 events, the Clozaril effect was superior (p=0.0251) and, for Type 2 events, borderline superior (p=0.0516). The hazard ratios (95% CI's) were 0.67 (0.47, 0.95) and 0.73 (0.54, 1.00), respectively.

For patients with schizoaffective disorder, the estimates of treatment effect using the WLW analysis and for Type 1 and Type 2 events separately favored Clozaril but were smaller than in the schizophrenia subgroup; none approached statistical significance. The hazard ratios (95% CI's) for Type 1 and Type 2 events were 0.87 (0.60, 1.27) and 0.85 (0.59, 1.23), respectively.

These data suggest that Clozaril may be less effective in reducing suicide risk in patients with schizoaffective disorder compared to patients with schizophrenia.

Geographic Subgroup Analysis

The sponsor repeated the WLW analysis of time to Type 1 and Type 2 events based on geographic subgroups (U.S. and Canada (N. America) vs. the rest of the world). The results are summarized in **Appendix VI-18**. In both subgroups, Clozaril was numerically superior to Zyprexa in the combined estimate of treatment effect as well as for Type 1 and Type 2 events separately. However, statistical superiority was not demonstrated for any comparison in either subgroup. Hazard ratios (95% CI's) were not substantially different between North America and the rest of the world (for Type 1 events, 0.78 (0.56, 1.08) and 0.72 (0.48, 1.08), respectively; for Type 2 events, 0.75 (0.55, 1.04) and 0.81 (0.57, 1.16), respectively).

3. Size of Treatment Effect

In terms of the anti-suicide effect size in study ABA 451, it is useful to consider the cumulative probability of a Type 1 event from the Kaplan-Meier survival analysis.

At week 104, there was a substantial cumulative probability of suicide, attempted suicide, or hospitalization or increased surveillance due to imminent suicide risk in both the Clozaril and Zyprexa treatment groups (0.24 and 0.32, respectively). The 95% CI for the difference between the two groups is (0.02, 0.15). Thus, the point estimate for the difference in cumulative probabilities is not large (0.08) and the true difference may be quite small (0.02).

4. Choice of Dose

The sponsor is recommending that the dosage of Clozaril for the treatment of schizophrenic and schizoaffective disorder patients at risk for suicide be the same as for patients with treatment-resistant schizophrenia.

Presumably, in study ABA 451, doses were titrated primarily on the basis of tolerability and antipsychotic efficacy, as opposed to antisuicidal efficacy, since most patients did not manifest imminent suicidality most of the time. Based on this assumption, the sponsor's dosing recommendations seem appropriate.

5. Duration of Treatment

This application seeks an indication for suicidal antipsychotic-naive patients to initiate continuous antipsychotic treatment with Clozaril or for suicidal patients currently treated with another antipsychotic to begin continuous Clozaril therapy either in place of or in addition to their existing treatment.

In this context, the duration of treatment with Clozaril would be dictated by its use as an antipsychotic agent and currently labeled advice would apply.

D. Summary of Pertinent Published Literature

1. Botsis AJ, et al. Clozapine efficacy on suicidal behavior across two main psychiatric disorders. Eur Neuropsychopharmacol 1997;7:S202.

This was a prospective study of 10 patients with severe suicidal behavior, 6 diagnosed with schizophrenia and 4 with psychotic depression. These patients had received high doses of typical neuroleptics (and high doses of antidepressants in the depressed patients) for at least 4 weeks, followed by treatment with clozapine (up to 450 mg/day) for 4 weeks. Suicidal behavior and general psychopathology was found to be decreased after 3 weeks of clozapine therapy.

This study was a small, historical control trial. Details of suicidality assessments and findings were not provided.

2. Ciapparelli A, et al. Clozapine for treatment-refractory schizophrenia, schizoaffective disorder and psychotic bipolar disorder: a 24-month naturalistic study. J Clin Psychiatry 2000;61:329-334.

This was a prospective study in adult patients with schizophrenia (N=31), schizoaffective disorder (N=26), and psychotic bipolar disorder (N=34). About 25% had suicidal ideation or a history of suicide attempt at baseline. Patients were treated for 24 months with flexible dose clozapine; many patients also received other neuroleptics as well as typical neuroleptics, antidepressants, anticonvulsants, lithium, benzodiazepines, and other medications. An analysis restricted to those with suicidal ideation at baseline revealed a significant reduction in the BPRS-Expanded suicide item at 24 months.

This trial was a historical control trial with efficacy findings confounded by substantial use of concomitant psychotropic medication.

3. Littrell KH, et al. The experience of hope in adults with schizophrenia. Psychiatric Rehabilitation Journal 1996;19:61-65.

This was a prospective study of the combined effect of psychosocial treatment and clozapine in 44 adult patients with refractory schizophrenia. The primary study focus was on 14 patients with previous suicide attempts. Patients were assessed after 6 and 12 months of clozapine at a mean dose of 550 mg/day. None of the patients attempted suicide during the 12 month trial period. The authors suggest that combined intervention is associated with decreased suicidality.

This was a historical control trial in a small number of patients with past suicide attempts. Clozapine effects may have been confounded by psychosocial treatment. The methodology for assessing a reduction in suicide potential was not described in detail.

4. Meltzer HY and Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995;152:183-190.

This was a retrospective study that included an evaluation of the effect of clozapine on suicidality in 183 patients with neuroleptic-resistant schizophrenia or schizoaffective disorder. Clozapine was begun during an index hospitalization and 88 neuroleptic-resistant patients received clozapine for at least 6 months for a period up to 2 years. Data reflecting suicidal thoughts and suicide attempts prior to clozapine were compared with corresponding measures during clozapine treatment. Results indicated a reduction in suicide attempts from 25% (22/88) pre-clozapine to 3.5% (3/88) after clozapine treatment.

This was a historical control study. Also, although the reduction in the proportion of patients attempting suicide was remarkable, it was not clear that the authors had adequately controlled for the durations of observation during the pre-clozapine and clozapine treatment periods in analyzing the suicidality results, rendering the findings difficult to interpret.

5. Modaj I, et al. Sudden death in patients receiving clozapine treatment: a preliminary investigation. J Clin Psychopharmacology 2000;20:325-327.

This retrospective study examined rates of sudden death, suicide, and deaths secondary to known diseases in schizophrenic patients from a mental health center database over a period of 6 years, 8 months. This encompassed 561 patients treated with clozapine and 4918 patients treated with other drugs. Among clozapine patients, 1.07% experienced sudden death compared to 0.28% of non-clozapine patients ($p<0.01$). A greater proportion of non-clozapine patients died secondary to known diseases (1.75% vs. 0.35%, $p<0.05$). The fractions of patients who suicided were not significantly different between clozapine and non-clozapine patients (0.36% vs. 0.10%, respectively).

The two treatment groups were not randomized and it does not appear that the authors controlled for duration of exposure or other potentially confounding variables.

6. Munro J, et al. Active monitoring of 12,760 clozapine recipients in the U.K. and Ireland. Br J Psychiatry 1999;175:576-580.

Data from 12,760 patients who were registered to receive clozapine in the U.K. and Ireland (Clozaril Patient Monitoring Service or CPMS) were retrospectively analyzed to identify risk factors for agranulocytosis. Of 144 deaths, 13 were noted to be confirmed suicides. Based on a review of the literature, the suicide rate among schizophrenic patients in various cited studies was consistently about 20 times greater than that in the general population. However, the suicide rate in this CPMS cohort was only about 5 times higher than that expected for the U.K. population, suggesting that clozapine may have an anti-suicide effect.

This was an observational study that used literature-reported estimates of suicide risk as a comparator. This trial did not control for the possible effects of regular clinical contact for WBC monitoring on suicide risk. Also, the adequacy of ascertainment of deaths due to suicide is difficult to gauge.

7. Reid WH, et al. Suicide prevention effects associated with clozapine therapy in schizophrenia and schizoaffective disorder. Psychiatric Services 1998;49:1029-1033.

This was a retrospective analysis of annual suicide rates among patients who received services from the Texas Department of Mental Health and Mental Retardation. A total of 30,130 patients with schizophrenia and schizoaffective disorder were treated over a two year period (1993-1995). In this population, the average annual suicide rate was 63.1 per 100,000 patients. During a 6 year interval (1991-1996), 1,367 patients received clozapine with only one suicide in this group, yielding an annual rate of 12.74 per 100,000 patients (95% CI 0-53 per 100,000).

This study did not compare randomized groups. Also, it did not control for regular contact associated with WBC monitoring and did not adjust for duration of drug exposure.

8. Sajatovic M, et al. An assessment of clinical practice of clozapine therapy for veterans. Psychiatric Services 2000;51:669-671.

This was a retrospective study of 2,996 patients with schizophrenia treated with clozapine in the U.S. Department of Veterans Affairs healthcare system over a 5 year period (1991-1996). Prior to treatment, 42.3% of patients has a history of suicide attempts. Also, 5% attempted suicide and 17.5% had suicidal ideation in the month prior to starting clozapine. During the study observation period, 2 patients (0.1%) died due to suicide.

This study suffers several weaknesses, to include lack of an adequately defined control group, no adjustment for duration of drug exposure, apparent comparison of disparate measures of suicidality (attempts and ideation pre-clozapine versus suicide deaths on clozapine), lack of control for the potential effect of regular patient contact, and possibly inadequate ascertainment of suicide deaths.

9. Sernyak MJ, et al. Impact of clozapine on completed suicide. Am J Psychiatry 2001;158:931-937.

This study examined the discharge summaries of 45,917 unique patients with Veterans Affairs (VA) psychiatric hospitalizations of at least one day for the fiscal years 1992 through 1995 in which the primary discharge diagnosis was schizophrenia. From this group, 1,415 patients were identified who started clozapine treatment for the first time during an "index" hospitalization. Then, using a matching process, a two-fold larger (N=2,830) group of control subjects who had not received clozapine during the study period were identified from the remaining discharged patients. Utilizing the National Death Index (NDI), searches were conducted for any study patients who died beginning with the year of discharge and continuing through every subsequent year through the end of 1998. Then, a coding algorithm from the National Center for Health Statistics was used to determine the most probable primary cause of death. The primary clozapine group comprised patients who received clozapine for any length of time. Follow-up time for each individual was calculated as the time between hospital discharge until either the date of death or December 31, 1998. The total follow-up time in each group was used to compute all-cause mortality and

cause-specific mortality rates. The duration of clozapine treatment for each patient was determined using data from the VA's National Clozapine Coordinating Center database. In total, 345 deaths were identified, 250 in the control group and 95 in the clozapine group. Among the deaths that were ruled suicide, 10 occurred in the clozapine group and 23 occurred in the control group. The rate of suicide in the total clozapine group was slightly less than that in the control group but not significantly so (1.50 versus 1.75 per 1,000 person-years; p=0.76).

Although this study is more rigorously designed than most previously published studies in this area, it too has flaws. Most importantly, the matching process did not include some factors that might contribute substantially to suicide risk, such as previous suicide attempts and depressive symptomatology. Thus, it is difficult to feel assured that the clozapine and control groups were balanced on important risk factors for suicidality. In addition, it appears that the calculation of follow-up time for clozapine patients may have included time during which the patient did not receive clozapine treatment. If true, this means that the patient exposure time counted under the clozapine group may in fact be inflated and the true rate of suicide in the clozapine group may be considerably higher than computed. This is a potential major confounding factor that does not seem to be addressed in the paper.

10. Spivak B, et al. Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine. Clin Neuropharmacol 1998;21:245-250.

This study evaluated the effects of clozapine on multiple variables, including a retrospective analysis of suicidality, in a group of 30 neuroleptic-resistant chronic schizophrenic patients who were treated with clozapine and a control group of 20 chronic schizophrenic patients maintained on a typical antipsychotic for a one year study period. Past suicide attempts were reported in 7/30 clozapine patients and in 11/20 control patients. None of the clozapine patients attempted suicide during the study period compared to 5 patients in the control group; this difference was statistically significant ($p<0.05$).

This is a small study comparing non-randomized groups. There was a numerical difference in the fraction of patients with past suicide attempts between the two groups (7/30 or 23% of clozapine patients versus 11/20 or 55% of the control group), a possible indicator that the control group may have been more prone to suicide attempts. This study also did not control for the possible effects of regular clinical contact associated with WBC monitoring in clozapine patients.

11. Walker AM, et al. Mortality in current and former users of clozapine. Epidemiology 8;1997:671-677.

This retrospective study of mortality among clozapine-treated patients was based on a cohort of patients in the U.S. Clozaril National Registry (CNR) during the period of April 1, 1991 to December 31, 1993. For each patient, the observation period started with April 1, 1991 or the earliest WBC record in the CNR for patients who began Clozaril after that date. The observation period ended with December 31, 1993, the date on which the patient reached age 101, or the date of death, whichever came first. Then, for each patient, each day during the observation period was classified as current use, recent use (up to and including 3 months after stopping Clozaril), or past use (more than 3 months after stopping Clozaril).

Deaths among this cohort were ascertained using the National Death Index (NDI) and the Social Security Administration Death Master Files using certain matching criteria. Death certificates were then requested from the states and the underlying causes of death were coded in accordance with ICD-9, along with recording of autopsy data. Mortality rates (standardized for age, race, and gender) in current and recent use were compared with rates in past use. The primary analysis focused on patients in the age range 10 to 54 years.

A total of 57,681 patients were eligible for the primary study cohort, representing a total of 85,399 person-years (PY) of observation. There were 396 deaths in this cohort. With respect to deaths due to suicide, the standardized mortality ratios (95% CI), using past use for comparison, were 0.17 (95% CI = 0.10-0.30) for current use and 1.11 (0.62-1.99) for recent use. These data suggest that active clozapine treatment is associated with a reduced risk of suicide.

The finding of a reduced suicide rate during the current use period is difficult to interpret with confidence. These were not randomized samples and it is unknown whether the use periods were balanced for various factors that might contribute to suicide risk. Also, as suggested by the authors, discontinuation of Clozaril due to poor response may select out a subset of patients particularly vulnerable to suicide, shifting these patients to the recent and past use categories. And, as with other studies, the WBC monitoring program may itself produce a bias by reducing the risk of suicidality through regular contact with healthcare staff or by earlier detection of the emergence of suicidality compared to patients in the recent and past use categories.

E. Assessment of Efficacy Data Quality

A total of 21 CRF's were randomly selected by the undersigned to audit the quality of data pertinent to suicidality from study ABA 451. Of these, 7 were for patients who were identified by the sponsor as not having experienced a Type 1 or Type 2 Event and 14 were identified as having experienced one of these events. The selected samples represent about 1% of the 700 patients not having an event and about 5% of the 280 patients having an event. All 21 patients selected for audit are listed in **Appendix VI-19**.

The primary goal of this audit was to verify that patients were appropriately classified with respect to suicidality based on clinical documentation in the CRF's. For patients with multiple Type 1 Events, this review focused on the first such event. Clinical data from the CRF forms listed in **Appendix VI-20** were examined.

This audit revealed only one finding that was present for 3 of the patients classified as having a Type 1 Event (Zyprexa patient 102-0012, Clozaril patient 127-0007, and Zyprexa patient 201-0004). In each of these 3 cases, the blinded psychiatrist indicated the absence of a Type 1 Event on a particular date whereas the Suicide Monitoring Board (SMB) found that a Type 1 Event had occurred on that date. Curiously, in each case, one of the SMB members initially voted that no event had occurred but subsequently changed to indicate the presence of a Type 1 Event.

To evaluate these discrepancies, I examined clinical documentation provided by the Principal Investigators regarding these events (mainly the "Imminent Risk of Suicide Requiring Hospitalization" and "Suicide Attempt" forms). In each case, I found that the evidence in support of a Type 1 Event was weak. For example, the Principal Investigator indicated a low risk of self-injury for 2 patients who were hospitalized "for imminent risk of suicide." In the third patient, the Principal Investigator clearly indicated that an attention-getting suicide gesture of low risk had occurred although the SMB later determined that this was a suicide attempt. While the accuracy of the SMB determinations is arguable, it is notable that all 3 cases involved a possible error in designating a non-suicidal event as a suicidal-event; I detected no cases where the SMB had made a possible error in the reverse direction.

To better assess this potential source of bias, it is recommended that all SMB documentation (e.g., conference minutes) related to these 3 patients be requested to better assess the determinations made. If that assessment is not reassuring, it is further recommended that relevant CRF forms for all remaining patients for whom there was a discrepancy between the SMB and the blinded psychiatrist be requested from the sponsor and examined. Finally, if that examination reveals a large number of cases with questionable SMB determinations, a reanalysis of the primary efficacy variables excluding these cases is recommended.

An additional audit searched for documentation indicating that the blinded psychiatrist had become unblinded during study ABA 451. Each blinded psychiatrist had the opportunity at each CGI-SS assessment of indicating in the CRF whether they had become unblinded to the patient's treatment. The relevant CRT (CGI002.xpt) was searched for any investigators who indicated unblinding at any visit. This search revealed 6 blinded psychiatrists at 6 different sites who indicated that they had become unblinded to the treatment of the following patients: 110-0001, 117-0001, 119-0002, 122-0006, 131-0005, and 701-0001. The ways in which unblinding occurred were not indicated. The sponsor should be requested to determine, to the extent possible, how these breaches occurred so that the adequacy of blinding in this trial can be more fully evaluated.

In summary, an audit of the suicidality data revealed two potential findings (possible biased SMB determinations and unblinding) that could impact on the reliability of these data. These findings should be further investigated, as recommended above.

F. Conclusions Regarding Efficacy

The findings of study ABA 451 cannot support the approval of Clozaril for the treatment of suicidality in patients with schizophrenia and schizoaffective disorder, as proposed by the sponsor (see the discussion in section VI.C.1 above).

Nonetheless, this study is capable, by design, of demonstrating a reduced risk of suicidality associated with long-term Clozaril treatment compared to long-term Zyprexa treatment. In this regard, the study results are considered inconclusive at this time given a number of irregularities in the conduct and analysis of this trial, which are discussed in section VI.B.12 above.

The published studies reviewed above suggest, on the whole, that Clozaril may be associated with a reduced risk of suicide compared to other treatments. However, each study suffers flaws which preclude any convincing demonstration of such an effect.

VII. Integrated Review of Safety

A. Methodology of the Safety Review

Clozaril has been marketed in the U.S. and abroad for several years and the safety profile of Clozaril has been extensively evaluated. Thus, the examination of safety in this review was limited to an assessment of the more serious adverse events observed in study ABA 451, namely: 1) deaths, 2) non-fatal serious adverse events, and 3) adverse events that led to premature termination from the study.

The safety population for study ABA 451 was defined as all randomized patients who took at least one dose of study medication (479 Clozaril-treated patients and 477 Zyprexa-treated patients). The last patient completed this trial on 2-14-01.

For patients who dropped out, the investigator was to maintain regular contact with the patient or family member every 12 weeks up to the time that would have been study week 104 for that patient (i.e., for the remainder of the 2 year observation period).

B. Safety Findings

1. Deaths

A total of 22 patients died during the 2 year observation period or within 30 days of discontinuing study medication: 13 Clozaril patients and 9 Zyprexa patients. Thus, the crude all-cause mortality rate was 2.7% (13/479) for Clozaril and 1.9% (9/477) for Zyprexa. These rates are not significantly different (p=0.39; Mantel-Haenszel Chi-Square).

I reviewed the Narrative Summary for each patient who died. **Appendix VII-1** is a line listing of all 22 deaths with the cause of death as determined by my review.

Among the 13 Clozaril patient deaths, 2 occurred more than 30 days after discontinuing treatment and were unlikely to be related to Clozaril treatment (patients 122-0010 and 802-0012). Among the remaining 11 Clozaril deaths, 4 were the result of suicide or complications of a suicide attempt and there was one death each due to pulmonary embolism, overdose, cancer, and cardiac arrest. In 3 cases, the cause of death could not be determined with reasonable certainty.

2. All Serious Adverse Events

The protocol for study ABA 451 defined serious adverse events (SAE's) as those which meet any of the following criteria:

- fatal or life-threatening.
- requires or prolongs hospitalization.
- significantly or permanently disabling or incapacitating.
- cancer, congenital anomaly, or birth defect.
- resulting from an overdose.

All SAE's occurring after signing informed consent until 28 days after stopping study drug were reported.

In the Clozaril group, 48.2% (231/479) of the patients experienced an adverse event classified as serious compared to 49.3% (235/477) of the Zyprexa patients. Appendix 7.2, Listing 10.2-1, of the report for study ABA 451 contains a line listing by patient of all patients who experienced an SAE. An enumeration by treatment group of all SAE's (by MedDRA preferred term) experienced by at least one Clozaril-treated patient is provided in **Appendix VII-2** of this review.

I reviewed the Narrative Summaries for a number of patients with SAE's to obtain further clinical information about the nature and circumstances of the events. The Narrative Summaries reviewed are listed in **Appendix VII-3**. Also, this information was supplemented in many cases by data from the Case Report Tabulations.

Based on a consideration of the above clinical data, I considered the following events reasonably attributable to Clozaril treatment: bowel obstruction, WBC's decreased, hyperglycemia, dizziness, and somnolence. These events will be discussed in **section VII.E** below.

3. Dropouts due to Adverse Events

In the Clozaril treatment group, 8.6% (41/479) of the patients prematurely discontinued treatment due to an adverse event compared to 6.9% (33/477) of the Zyprexa patients. The adverse experiences most commonly leading to dropout in the Clozaril group were WBC's decreased (1.7% of Clozaril and 0.0% of Zyprexa patients) and somnolence (1.0% of Clozaril and 0.2% of Zyprexa patients).

A line listing of all patients who dropped out due to an adverse event may be found in Appendix 7.1, Listing 10.1-2, of the study report for ABA 451. An enumeration of the Clozaril patients who discontinued treatment due to specific adverse events is provided in **Appendix VII-4** of this review.

My examination of the events leading to dropout among the Clozaril-treated patients revealed no clinically important events which I considered attributable to Clozaril beyond those events identified in the above review of SAE's.

C. Adequacy of Patient Exposure and Safety Assessments

Clozaril has been marketed for over a decade for use in patients with schizophrenia. This supplement seeks to add patients with schizoaffective disorder to the target population. There were only 190 patients with schizoaffective disorder randomized to Clozaril in study ABA 451. Although this exposure is small, there is no known reason not to extrapolate the primary safety experience in schizophrenic patients to the schizoaffective disorder population. Thus, this limited exposure should not preclude the approval of this supplement.

The safety assessments in study ABA 451 are considered adequate to detect frequently occurring major toxicities associated with extended Clozaril use in the study population. However, one deficiency was the lack of some routine safety assessments which may have yielded useful long-term data, such as fasting blood glucose levels, cholesterol and triglyceride levels, and ECG's.

D. Safety Data Quality and Completeness

Approximately 5% of the 68 Case Report Forms (CRF's) submitted for patients in study ABA 451 who died or experienced other designated serious adverse events were audited by the undersigned. This audit consisted of an examination of the consistency of adverse event information across the CRF, Narrative Summary, and Case Report Tabulation (CRT) adverse event line listing (AEV001.xpt) for four randomly selected patients (patients 117-0004, 120-0014, 301-0003, and 502-0008). This audit revealed no important discrepancies.

The appropriateness of the coding of reported adverse event terms to MedDRA preferred terminology for patients in study ABA 451 was evaluated by the undersigned. This consisted of an examination of the CRT adverse event line listing, sorted by preferred term and also by reported (verbatim) term. This examination revealed no errors in adverse event coding.

In terms of data completeness, two deficiencies were noted:

- safety findings discovered by non-trial healthcare providers and facilities were often missing.

• follow-up information on abnormalities observed during the trial was often not available, making evaluation of the outcome of these events impossible.

Given the wealth of postmarketing safety data available for Clozaril, these deficiencies should not preclude approval of this supplement.

E. Summary of Important Drug-Related Safety Findings

1. WBC Count Decreased

Eight Clozaril (1.7%) and no Zyprexa patients experienced decreases in white blood cell (WBC) counts that were classified as serious (p=0.005, MH Chi-Square). Six of these patients dropped out for this reason. None of these patients experienced sepsis, a total WBC count under 1,000/cmm, or an absolute neutrophil count under 500/cmm. The lowest counts were observed in patient 701-0025, who experienced a decrease in total WBC's from 5,900 to 1,700/cmm and in neutrophils from 3,500 to 650/cmm. No follow-up counts were available for this patient.

In terms of the proportions of patients who had a total WBC count ≤2,800/cmm at any point during the trial, 1.3% (6/474) of the Clozaril and 0.6% (3/474) of the Zyprexa patients met this criterion (p=0.32, MH Chi-Square).

No cases of agranulocytosis or aplastic anemia were reported.

Leukopenia is a well-known effect of Clozaril and is the reason Clozaril is available only through a controlled distribution system. Clozaril is considered to be adequately labeled for this adverse event.

2. Bowel Obstruction

In study ABA 451, three Clozaril patients experienced bowel obstructions consistent with paralytic ileus. One of these patients (129-0010) experienced two episodes of obstruction during Clozaril treatment, the last leading to treatment discontinuation. Another patient (301-0019) underwent surgery for a perforated appendix about 2 weeks prior to symptoms of obstruction. Clozaril was stopped, with recovery of bowel function 8 days later. The third patient (302-0010) had a grossly distended transverse colon and

evidence of renal impairment due to dehydration. Clozaril was stopped but he experienced a cardiac arrest of uncertain etiology 2 days later and died. Obstruction in all of these patients resulted in hospitalization and intervention.

Only one Zyprexa-treated patient experienced a bowel obstruction.

Constipation was reported by 25.1% (120/479) of Clozaril patients; 48 of these events were rated as moderate or severe. In the Zyprexa group, 9.6% (46/477) of the patients reported constipation. The difference between the groups was highly statistically significant ($p<0.001$, Mantel-Haenszel Chi-Square).

These events are probably related to the potent anticholinergic effects of Clozaril, which are described in current labeling under PRECAUTIONS/Anticholinergic Toxicity.

3. Hyperglycemia

At least one treatment-emergent adverse event suggesting a problem with glucose regulation was reported in 4.8% (23/479) of the Clozaril and 5.5% (26/477) of the Zyprexa patients in study ABA 451. These events had been coded to one of the following MedDRA preferred terms: hyperglycemia NOS, diabetes mellitus NOS, ketoacidosis, blood glucose increased, glucose tolerance decreased, and glycosuria.

Plasma glucose levels were not routinely assessed during this study. Thus, a more systematic evaluation of glucose dysregulation is not possible.

There have been a number of spontaneous adverse event reports as well as literature reports documenting problems with glucose regulation during treatment with either Clozaril and Zyprexa.[21] The above data are consistent with the possibility that hyperglycemia and diabetes may be causally linked to these agents although such a relationship has not been convincingly demonstrated. Current Clozaril labeling contains a statement under

[21] For example, see Newcomer JW, et al. Abnormalities in Glucose Regulation During Antipsychotic Treatment of Schizophrenia. Arch Gen Psychiatry. 2002;59:337-345.

PRECAUTIONS/Hyperglycemia that adequately advises prescribers of this possible relationship.

4. Dizziness

Non-vertiginous dizziness was reported as an adverse event in 26.9% (129/479) of the Clozaril group and 12.4% (59/477) of the Zyprexa group in study ABA 451; this difference is highly significant ($p<0.001$, MH Chi-Square). Events coded to this MedDRA term included dizziness, lightheadedness, and feeling faint. Four Clozaril patients and no Zyprexa patients dropped out due to this adverse experience.

An etiologic explanation for this event is not clear. According to the ADVERSE REACTIONS section of Clozaril labeling, dizziness, to include vertigo, was reported in 19% of Clozaril patients in premarketing clinical trials (N=842). Given that these trials were probably much shorter than study ABA 451, the above finding is considered to be consistent with the figure cited in labeling.

5. Somnolence

Somnolence was reported as a treatment-emergent adverse experience in 45.9% (220/479) of Clozaril and 24.7% (118/477) of Zyprexa patients in ABA 451. This difference is highly statistically significant ($p<0.001$, MH Chi-Square). This MedDRA preferred term subsumed reported events including drowsiness, sedation, and sleepiness. Five Clozaril patients and one Zyprexa patient dropped out due to this adverse event.

This finding is felt to be consistent with information in the ADVERSE REACTIONS section of Clozaril labeling, which describes drowsiness or sedation in 39% of Clozaril-treated patients in premarketing clinical trials.

F. Safety Conclusions

This limited review of safety data from study ABA 451 revealed no previously unrecognized toxicities associated with Clozaril which would preclude the approval of this supplement or require amendment of Clozaril labeling.

VIII. Dosing, Regimen, and Administration Issues

The dosing scheme utilized in study ABA 451 is consistent with that currently labeled for the treatment of patients with refractory schizophrenia. If the sponsor elects to pursue approval of a claim for the reduction of suicide risk with long-term therapy, this dosing regimen would be appropriate. However, before approval for this use, it will be critical to decide whether to grant approval as a new indication (as opposed to simply describing the study in labeling under Clinical Trials) and, if so, to delineate in labeling an appropriate target population.

IX. Use in Special Populations

Neither gender nor age group were significant predictors of time to a Type 1 or time to a Type 2 event in covariate analyses using a full Cox proportional hazards regression model. Race was not examined as an explanatory variable in these analyses.

X. Review of Proposed Labeling

Since it is recommended that this supplement not be approved, the sponsor's proposed labeling will not be discussed in this review.

XI. Conclusions and Recommendations

It is recommended that the claim for the use of Clozaril to treat suicidality not be approved. Study ABA 451 was not designed to assess the efficacy of Clozaril in the treatment of suicidality.

If Novartis elects to pursue approval of Clozaril as a long-term measure to reduce the risk of suicidality, it is recommended that the sponsor address the following concerns regarding study ABA 451:

1) Apparently a total of 72 study patients were lost to follow-up. Further efforts should be made to ascertain whether the 33 Clozaril and 39 Zyprexa patients who were lost to follow-up committed suicide, attempted suicide, or were hospitalized or placed under increased surveillance due to imminent suicide risk around the time of study discontinuation.

2) The primary efficacy analysis, using the method of Wei, Lin, and Weissfeld, is described as including Type 1 and Type 2 events regardless of whether the patient was taking study medication at the time of the event. This makes attribution of event occurrence or non-occurrence to drug very tenuous in this long-term trial. Additionally, Amendment #9 to the study protocol allowed patients who had dropped out of the study to later return to full study participation. This is may have introduced a confounding influence of suicide risk in this trial. Therefore, the primary efficacy analysis should be repeated after right-censoring patients who discontinued study drug, even if those patients later re-entered the study as full participants. Also, this analysis should incorporate any and all new information on the 72 patients who were reported as lost to follow-up (see item 1 above).

3) An audit of suicidality information, including Case Report Forms, on a small sample of study patients revealed three cases in which the SMB determinations are questionable. To permit a more complete understanding of how these determinations were made, all SMB documentation, to include SMB conference minutes, related to the following three patients should be submitted for Agency examination: 102-0012, 127-0007, and 201-0004.

4) It is noted that six Blinded Psychiatrists acknowledged becoming unblinded during the study. These individuals performed CGI-SS-BP ratings on the following study patients: 110-0001, 117-0001, 119-0002, 122-0006, 131-0005, and 701-0001. These instances of unblinding should be investigated to determine how these breaches occurred. The explanations should be provided for our review so that the adequacy of blinding in the trial can be more fully evaluated.

Furthermore, if the sponsor amends this application to pursue the suicidality prevention claim, it may be helpful for the Division to obtain the advice of the Psychopharmacological Drugs Advisory Committee with respect to the following questions:

1) Does study ABA 451 provide adequate evidence to support a claim of reduction in the risk of suicidality? The response should include a consideration of the following:

a) The difference between Clozaril and Zyprexa was not very large. For example, at the end of two years, the cumulative probability of a Type 1 event was 0.24 for Clozaril and 0.32 for Zyprexa, with a 95% confidence interval for the intergroup difference being 0.02 to 0.14.
b) Unlike most claims for psychiatric conditions, this would be based on a single study against a single comparator agent. While published studies do provide evidence suggesting a reduction in suicide risk, none are of such quality that they are capable of providing data that would truly replicate the findings of ABA 451.
c) A large proportion of patients in this trial took concomitant medication that could confound assessment of suicide risk, such as antipsychotics and antidepressants. It would admittedly be virtually impossible to entirely rule out a differential confounding influence that might bias the study results and, to some extent, the sponsor's analysis of such use might be considered reassuring. Nonetheless, there is a need to reasonably judge whether this treatment was so extensive that it significantly degraded the scientific credibility of this trial.
d) For over 40% of the patients in each treatment group, there was a change in the Blinded Psychiatrist who rated the change in the patient's suicidality at each visit relative to the patient's baseline condition. This was a key outcome measure. The reliability of a new rater in assessing change from the baseline condition is questionable.

2) If the answer to the above question is affirmative, what guidance should be provided in labeling to assist prescribers in selecting patients for Clozaril therapy under this claim?

Gregory M. Dubitsky, M.D.
August 1, 2002

cc: NDA 19-758
HFD-120/Division File
HFD-120/GDubitsky
/TLaughren
/SHardeman

SECTION XII:

APPENDICES

APPENDIX IV-1
STUDY ABA 451
BASELINE DEMOGRAPHIC CHARACTERISTICS
(ALL RANDOMIZED PATIENTS)

	No. (%) of patients unless otherwise noted	
	Clozaril (n=490)	Zyprexa (n=490)
Age (year)		
Mean (SD)	37.1 (10.3)	37.0 (10.3)
Median	37	36
Range	18-69	18-65
18-32	168 (34.3%)	178 (36.3%)
33-44	216 (44.1%)	204 (41.6%)
≥45	106 (21.6%)	108 (22.0%)
Sex		
Male	301 (61.4%)	301 (61.4%)
Female	189 (38.6%)	189 (38.6%)
Race		
Caucasian	356 (72.7%)	337 (68.8%)
Black	65 (13.3%)	86 (17.6%)
Oriental	6 (1.2%)	7 (1.4%)
Other	63 (12.9%)	60 (12.2%)
Weight (kg)– Females	n=181	n=180
Mean (SD)	74.0 (20.1)	73.2 (18.4)
Median	70	70
Range	40-152	36-133
Weight (kg)– Males	n=283	n=289
Mean (SD)	82.8 (18.3)	84.3 (20.9)
Median	80.9	80
Range	45-156	44-166

APPENDIX IV-2
STUDY ABA 451
OVERALL EXPOSURE BY TREATMENT DURATION
(SAFETY POPULATION)

Duration of treatment (days)*	No. (%) of patients	
	Clozaril (n=479)	Zyprexa (n=477)
1 – 30	54 (11.3)	26 (5.5)
31 – 90	36 (7.5)	31 (6.5)
91 – 180	25 (5.2)	25 (5.2)
181 – 270	12 (2.5)	22 (4.6)
271 – 360	10 (2.1)	6 (1.3)
361 – 450	17 (3.5)	16 (3.4)
451 – 540	10 (2.1)	22 (4.6)
541 – 630	6 (1.3)	11 (2.3)
≥ 631	304 (63.5)	312 (65.4)
Missing	5 (1.0)	6 (1.3)

* Number of days from date of first dose of study medication to date of last known dose of study medication; if either date was missing, the patient was counted in the "missing" category.

APPENDIX V-1 ITEMS REVIEWED	
Submission Date	**Item Description**
2-28-02	Volume 1 Proposed labeling Debarment certification Financial disclosure information Volume 4 Published literature reports Electronic Format Study report: ABA 451 Case Report Tabulations: ABA 451 Case Report Forms: ABA 451
3-29-02	Median dose by visit data Diagnostic subgroup efficacy analysis
5-17-02	Correction to ABA 451 Study Report
6-24-02	Analysis of concomitant medication

APPENDIX V-2: SELECTED SERIOUS ADVERSE EVENTS
Myocardial infarction
Pericarditis NOS
Appendicitis perforated
Hematemesis
Intestinal obstruction NOS
Pancreatitis NOS
Neuroleptic malignant syndrome
Hepatic disorder NOS
Colitis pseudomembranous
Accidental overdose (therapeutic agent)
Ketoacidosis
Tetany
Rhabdomyolysis
Paraplegia
Intra-uterine death
Renal failure NOS
Pleural effusion
Respiratory distress
Respiratory failure (exc neonatal)
Acute circulatory failure
Transient ischemic attack

APPENDIX VI-1
STUDY ABA 451
STUDY SITES, NUMBER OF PATIENTS ENROLLED, AND PRINCIPAL INVESTIGATORS

Center Number	Location (country)	Number Enrolled (Clozapine/Zyprexa)	Principal Investigator
101	USA	8/9	H. Edward Logue, M.D.
102	USA	6/7	Pedro Delgado, M.D. Francisco Moreno, M.D.
103	USA	6/5	Dennis Pavlinac, M.D.
104	USA	10/11	Mark H. Rapaport, M.D.
105	USA	14/14	Steven Potkin, M.D.
106	USA	7/8	David A. Sack, M.D.
107	USA	14/14	George M. Simpson, M.D.
108	USA	2/2	Dan L. Zimbroff, M.D.
109	USA	3/2	Ira D. Glick, M.D. Ben H. Flores, M.D.
110	USA	2/1	Doris Gunderson, M.D.
111	USA	4/4	Phillip Seibel, M.D. Adam Lowy, M.D.
112	USA	9/10	Carl Eisdorfer, M.D., Ph.D. Richard Douyon, M.D.
113	USA	3/ 4	Michael G. Plopper, M.D.
114	USA	16/16	James Chou, M.D. Jean-Pierre Lindenmayer, M.D.
115	USA	2/2	Vinod Kumar, M.D. Jack Krasuski, M.D.
116	USA	6/6	Alan I. Green, M.D.
117	USA	8/6	George Hsu, M.D.

APPENDIX VI-1
STUDY ABA 451
STUDY SITES, NUMBER OF PATIENTS ENROLLED, AND PRINCIPAL INVESTIGATORS

Center Number	Location (country)	Number Enrolled (Clozapine/Zyprexa)	Principal Investigator
118	USA	3/2	Oladapo Tomori, M.D.
119	USA	1/1	Richard Balon, M.D.
120	USA	7/7	George T. Grossberg, M.D. Winston W. Shen, M.D. Ricky S. Mofsen, D.O.
122	USA	5/6	Ronald Centric, D.O. Mark W. Viner, M.D. Saide Altinsan, M.D.
123	USA	4/4	Delbert Robinson, M.D.
124	USA	6/7	Jean-Pierre Lindenmayer, M.D.
125	USA	10/11	Naveed Iqbal, M.D.
126	USA	9/8	Jorg J. Pahl, M.D.
127	USA	8/6	Jeffrey-Lee Peters, M.D. Daniel P. VanKammen, M.D., Ph.D.
128	USA	4/6	Richard C. Josiassen, Ph.D.
129	USA	7/6	Herbert Y. Meltzer, M.D.
130	USA	8/8	Mary Ann Knesevich, M.D.
131	USA	4/5	Michael Lesem, M.D. Vaidyanath Iyer, M.D.
132	USA	2/0	Richard Greenberg, M.D.
201	Canada	6/5	Guy Chouinard, M.D., Sc. FRCP, FAPA
203	Canada	4/4	Siemion Altman, M.D., FRCPC
301	UK	9/9	Thomas A. Fahy, M.D.
302	UK	25/24	Prof. Stephen Martin, M.D.

APPENDIX VI-1
STUDY ABA 451
STUDY SITES, NUMBER OF PATIENTS ENROLLED, AND PRINCIPAL INVESTIGATORS

Center Number	Location (country)	Number Enrolled (Clozapine/Zyprexa)	Principal Investigator
303	UK	13/12	Sophie Frangou, M.D.
304	UK	7/6	Prof. Ann Mortimer
305	UK	2/4	Anthony Maden, M.D.
401	France	17/16	Prof. Marc Bourgeois
402	France	5/6	Marie-Agathe Zimmermann, M.D.
403	France	11/11	Frederic Khidichian, M.D.
404	France	6/6	Muriel Maurel, M.D.
405	France	4/5	Pierre-Michel Llorca, M.D.
406	France	7/6	Prof. Jean Dalery
501	Italy	2/2	Prof. Alberto Giannelli, M.D.
502	Italy	4/4	Prof. Liliana Dell'Osso
505	Italy	4/4	Bernardo Carpiniello, M.D.
506	Italy	3/2	Rosaria Pioli, M.D.
601	Hungary	11/11	Akos Kassai-Farkas, M.D.
602	Hungary	16/16	Eva Morik, M.D.
604	Hungary	16/17	Gyorgy Ostorharics-Horvath, M.D.
605	Hungary	6/6	Laszlo Mod, M.D.
701	Croatia	13/12	Prof. Miro Jakovljevic
702	Croatia	16/18	Prof. Vera Folnegovic-Smale
801	S. Africa	4/4	Prof. Robin A. Emsley
802	S. Africa	7/7	Prof. Carllo Gagiano
803	S. Africa	7/8	Elisabeth Borkowska, M.D. Mohamed Coovadia, M.D.

APPENDIX VI-1
STUDY ABA 451
STUDY SITES, NUMBER OF PATIENTS ENROLLED, AND PRINCIPAL INVESTIGATORS

Center Number	Location (country)	Number Enrolled (Clozapine/Zyprexa)	Principal Investigator
901	Czech Republic	5/6	Jaroslav Hronek, M.D. Vanda Benesova, M.D.
902	Czech Republic	7/7	Zdenka Vyhnankova, M.D.
903	Czech Republic	2/4	Ivo Paclt, M.D.
904	Czech Republic	5/5	Libor Chvila, M.D.
951	Argentina	5/4	Pedro Rafael Gargoloff, M.D.
952	Argentina	7/6	Liliana Avigo, M.D.
953	Argentina	5/6	Luis Antonio Bengochea, M.D.
954	Argentina	5/5	Carlos Alberto Morra, M.D.
955	Argentina	9/8	Alberto Bertoldi, M.D.
956	Chile	17/16	Veronica Larach, M.D.

APPENDIX VI-2: STUDY ABA 451 DISTRIBUTION OF CGI-SS-BP SCORES AT BASELINE		
Baseline CGI-SS-BP Score	**Clozaril (N=490) n (n/N%)**	**Zyprexa (N=490) n (n/N%)**
1 (not at all suicidal)	152 (31%)	153 (31%)
2 (mildly suicidal)	131 (27%)	132 (27%)
3 (moderately suicidal)	140 (29%)	141 (29%)
4 (severely suicidal)	58 (12%)	51 (10%)
5 (attempted suicide)	3 (<1%)	4 (<1%)
Missing	6 (1%)	9 (2%)

APPENDIX VI-3 STUDY ABA 451 ENUMERATION OF DROPOUTS BY REASON		
Reason for Discontinuation	**Clozaril N=490**	**Zyprexa N=490**
Adverse Events (incl. death)	49	38
Abnormal Laboratory Value/Test Result	3	0
Unsatisfactory Effect on Psychosis	5	9
Unsatisfactory Effect on Suicide Risk	0	6
Protocol Violation	29	20
Withdrawn Consent	50	49
Lost to Follow-Up	33	39
Administrative Reason	23	26
TOTAL DISCONTINUATIONS	**192**	**187**

APPENDIX VI-4 STUDY ABA 451 PATIENTS IN-STUDY BY VISIT		
Visit (week)	**Clozaril n (% of ITT)**	**Zyprexa n (% of ITT)**
8	411 (84%)	432 (88%)
16	382 (78%)	414 (85%)
24	361 (74%)	399 (81%)
32	356 (73%)	382 (78%)
40	344 (70%)	370 (76%)
48	338 (69%)	364 (74%)
52	337 (69%)	362 (74%)
60	327 (67%)	352 (72%)
68	318 (65%)	344 (70%)
80	308 (63%)	324 (66%)
92	304 (62%)	314 (64%)
104	298 (61%)	303 (62%)

APPENDIX VI-5 STUDY ABA 451 MEDIAN PRESCRIBED DOSES (mg/day) BY VISIT[22]		
Visit (week)	**Clozaril**	**Zyprexa**
8	250.0	15.0
16	300.0	20.0
24	300.0	20.0
32	300.0	20.0
40	300.0	20.0
48	300.0	20.0
52	300.0	20.0
60	300.0	20.0
68	300.0	20.0
80	300.0	20.0
92	300.0	20.0
104	300.0	20.0

[22] This information was provided by the sponsor in a 3-29-02 submission.

APPENDIX VI-6
STUDY ABA 451
ENUMERATION OF PATIENTS WITH CONCOMITANT PSYCHOTROPIC MEDICATION USAGE[23]

Medication Class	Clozaril		Zyprexa	
	All Usage	Analysis Usage	All Usage	Analysis Usage
Antipsychotics	429	410	413	390
Antidepressants	269	241	301	270
Sed/Anxiolytics	341	295	363	325
Mood Stabilizers	147	120	154	144

APPENDIX VI-7
STUDY ABA 451
OVERALL LEAST SQUARES MEAN DOSAGE
BY CONCOMITANT MEDICATION CLASS AND TREATMENT GROUP

Medication Class	Clozaril	Zyprexa	p-value
Antipsychotics	2.1	3.8	0.0002
Antidepressants	16.7	20.7	0.0014
Sed/Anxiolytics	6.3	10.1	<0.0001
Mood Stabilizers	487	621	0.0107

APPENDIX VI-8
STUDY ABA 451
LEAST SQUARES MEAN **DOSAGE FOR CONCOMITANT ANTIPSYCHOTIC** USAGE BY **TREATMENT INTERVAL**

Interval	Clozaril	Zyprexa	p-value
1-6 months	2.7	3.9	0.0060
7-12 months	1.1	3.3	<0.0001
13-18 months	1.1	3.5	<0.0001
19-24 months	1.2	3.4	<0.0001

[23] All Usage enumerates all patients who took at least one dose of concomitant medication in that class. Analysis Usage enumerates patients who took concomitant medication after analysis exclusion criteria were applied.

APPENDIX VI-9 STUDY ABA 451 LEAST SQUARES MEAN DOSAGE FOR CONCOMITANT ANTIDEPRESSANT USAGE BY TREATMENT INTERVAL			
Interval	**Clozaril**	**Zyprexa**	**p-value**
1-6 months	15.9	19.4	0.0005
7-12 months	15.4	20.4	0.0032
13-18 months	16.9	19.7	0.1106
19-24 months	18.1	21.2	0.0914

APPENDIX VI-10 STUDY ABA 451 LEAST SQUARES MEAN DOSAGE FOR CONCOMITANT SEDATIVE/ANXIOLYTIC USAGE BY TREATMENT INTERVAL			
Interval	**Clozaril**	**Zyprexa**	**p-value**
1-6 months	6.8	10.1	0.0001
7-12 months	5.5	9.1	0.0002
13-18 months	5.7	10.4	0.0002
19-24 months	6.3	10.7	0.0027

APPENDIX VI-11 STUDY ABA 451 LEAST SQUARES MEAN DOSAGE FOR CONCOMITANT MOOD STABILIZER USAGE BY TREATMENT INTERVAL			
Interval	**Clozaril**	**Zyprexa**	**p-value**
1-6 months	473.2	573.4	0.0166
7-12 months	441.6	638.7	0.0022
13-18 months	455.2	618.3	0.0253
19-24 months	493.1	592.7	0.2157

APPENDIX VI-12
STUDY ABA 451
PRIMARY SUICIDALITY EFFICACY ANALYSIS: MULTIPLE EVENTS ANALYSIS OF TIME TO FIRST TYPE 1 OR TYPE 2 EVENT (ITT POPULATION)

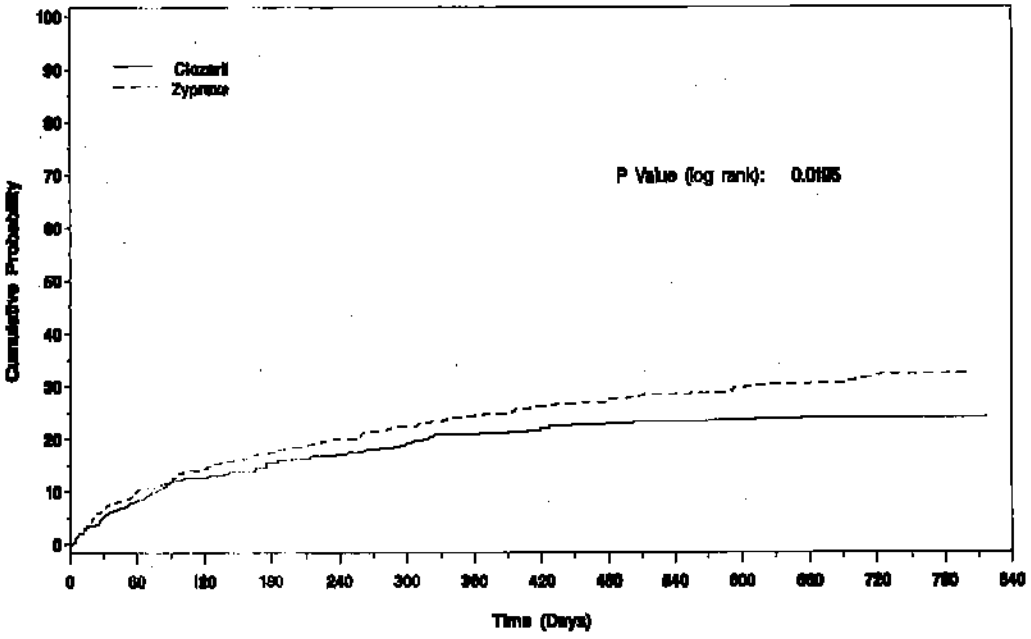
Event Type [1]	Coefficient for Treatment Effect (Beta) [2]	Robust Standard Error of Beta	Weight	P-value [3]	95% C.I. of Beta	Hazard Ratio (exp(Beta)) [2]	95% C.I. of Hazard Ratio
Type 1	-0.280	0.130	0.50	0.0316	(-.54, -.02)	0.76	(0.58, 0.98)
Type 2	-0.250	0.121	0.50	0.0388	(-.49, -.01)	0.78	(0.61, 0.99)
Combined	-0.265	0.123	-	0.0309	(-.51, -.02)	-	-

[1] Event type 1: Occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance). Only time to the first occurrence (SMB-confirmed) was used in the survival analysis. Event type 2: Occurrence of a significant suicide attempt, hospitalization due to imminent suicide risk (including increased level of surveillance), or worsening of severity of suicidality measured by C01-SS-BP (change score) of level 7 or 7. Only time to the first occurrence was used in the survival analysis.

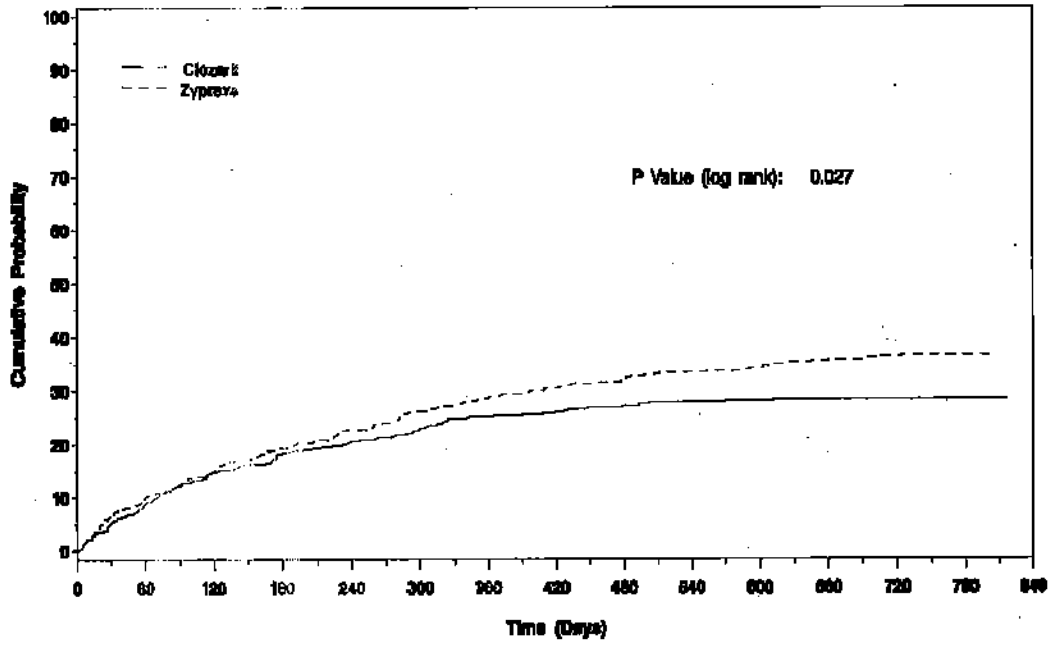
[2] A negative value of beta and a hazard ratio less than 1 indicate that Treatment Group 1 (Clozaril) is better than Treatment Group 2 (Fluoxetine).

[3] P-values were generated using the Normal Approximation Z-test with robust standard error estimates obtained from the WLW survival analysis model, stratified on pooled country and with treatment as the only covariate. Equal weights were applied for each event type.

APPENDIX VI-13
STUDY ABA 451
KAPLAN-MEIER SURVIVAL CURVES FOR TYPE 1 EVENTS



APPENDIX VI-14
STUDY ABA 451
KAPLAN-MEIER SURVIVAL CURVES FOR TYPE 2 EVENTS



APPENDIX VI-15
STUDY ABA 451
KAPLAN-MEIER ESTIMATES OF THE CUMULATIVE PROBABILITY OF A TYPE 1 OR TYPE 2 EVENT BY VISIT

	CLOZARIL (n=490)				ZYPREXA (n=490)				
	n1[2]	N2[3]	Cum Prob	95% C.I.	n1[2]	n2[3]	Cum Prob	95% C.I.	95% C.I. of the difference
Type 1 Event									
Week 0 (Day 0)	490	0	0.00	(0.00, 0.00)	490	0	0.00	(0.00, 0.00)	(0.00, 0.00)
Week 8 (Day 70)	393	43	0.09	(0.09, 0.10)	411	50	0.11	(0.10, 0.11)	(-0.03, 0.05)
Week 24 (Day 182)	346	69	0.16	(0.15, 0.17)	365	81	0.17	(0.16, 0.18)	(-0.03, 0.07)
Week 52 (Day 378	308	91	0.21	(0.20, 0.22)	312	112	0.25	(0.23, 0.26)	(-0.02, 0.09)
Week 80 (Day 574)	277	100	0.23	(0.22, 0.25)	269	128	0.29	(0.27, 0.30)	(-0.01, 0.11)
Week 104 (Day 742)	36	102	0.24	(0.23, 0.25)	40	141	0.32	(0.31, 0.34)	(0.02, 0.14)
Type 2 Event									
Week 0 (Day 0)	490	0	0.00	(0.00, 0.00)	490	0	0.00	(0.00, 0.00)	(0.00, 0.00)
Week 8 (Day 70)	389	47	0.10	(0.10, 0.11)	410	51	0.11	(0.10, 0.11)	(-0.03, 0.04)
Week 24 (Day 182)	334	81	0.18	(0.17, 0.20)	356	90	0.19	(0.18, 0.21)	(-0.04, 0.06)
Week 52 (Day 378	290	109	0.25	(0.24, 0.27)	294	132	0.29	(0.28, 0.31)	(-0.02, 0.10)
Week 80 (Day 574)	261	119	0.28	(0.27, 0.30)	251	150	0.34	(0.32, 0.35)	(0.00, 0.12)
Week 104 (Day 742)	34	120	0.28	(0.27, 0.30)	36	161	0.37	(0.35, 0.38)	(0.02, 0.15)

[1] Kaplan-Meier estimates compute the probability of an event (cumulative). Two weeks were added to the visit week when calculating the actual day, e.g., Visit Week 8 = Day (8+2)x7 = Day 70.
[2] n1 represents number of patients at risk.
[3] n2 represents the number of cumulative events.

APPENDIX VI-16
STUDY ABA 451
COVARIATE ANALYSIS OF TIME TO TYPE 1 EVENT USING A FULL COX PROPORTIONAL HAZARDS MODEL

Explanatory Variable[1]	Regression Coefficient (SE)[2]	Hazard Ratio[2]	P- value[3]
Treatment	-0.318 (0.133)	0.73	0.0172
Sex	-0.022 (0.147)	0.98	0.8822
Age Group (33-44)	-0.236 (0.148)	0.79	0.1117
Age Group (≥ 45)	-0.205 (0.184)	0.81	0.2643
No. of Lifetime Suicide Attempts	0.024 (0.006)	1.03	0.0001
CGI-SS-BP Severity Score (Q1-Q3)	0.175 (0.239)	1.19	0.4658
CGI-SS-BP Severity Score (≥Q3)	0.475 (0.317)	1.61	0.1344
ISST-BP Total Score[2] (Q1-Q3)[4]	0.100 (0.264)	1.11	0.7042
ISST-BP Total Score (≥Q3)[4]	0.253 (0.323)	1.29	0.4334
CDS (Q1-Q3)	-0.144 (0.223)	0.87	0.5183
CDS (≥Q3)	0.018 (0.296)	1.02	0.9520
Diagnosis	0.101 (0.141)	1.11	0.4749
Substance or Alcohol Abuse	0.395 (0.149)	1.48	0.0081
ESRS Total Score	-0.000 (0.004)	1.00	0.9344
Lindenmayer's PANSS Positive[5]	-0.015 (0.014)	0.99	0.3012
CDS Hopelessness Item	0.059 (0.098)	1.06	0.5393
Covi Anxiety Scale Total Score	0.041 (0.027)	1.04	0.1317

[1] All values of explanatory variables are determined from baseline values. Variable Codes: Treatment (0=Zyprexa, 1=Clozaril); Sex (1=Male, 2=Female); Diagnosis (1=Schizophrenia, 2=Schizoaffective); Substance or Alcohol Abuse (0=No, 1=Yes); CDS hopelessness (0=Absent, 1=Mild, 2=Moderate, 3=Severe).

[2] Refer to detailed statistical analysis plan in Appendix 6.1, §1.1.5.3, for information on calculation of these parameters. Hazard ratios for age group are relative to age group (18-32). Hazard ratios for (Q1-Q3) and (≥Q3) of the CGI-SS-BP, ISST-BP, and CDS scores are relative to (<Q1).

[3] P-values were generated using a full Cox's proportional hazards regression model, stratified on pooled country and with explanatory variables noted above.

[4] ISST is the total score of the 11 ratings (except for item 9) (Lindenmayer, in press).

[5] Lindenmayer et al, 1995

APPENDIX VI-17
STUDY ABA 451
MULTIPLE EVENT ANALYSIS OF TIME TO TYPE 1 AND TYPE 2 EVENTS BY DIAGNOSTIC SUBGROUP

Subgroup	Event Type [1]	Estimate of Treatment Effect (Beta) [2]	Standard Error of Beta	Weight	P-value [3]	95% C.I. of Beta	Hazard Ratio (exp(Beta)) [2]	95% C.I. of Hazard Ratio
Diagnosis of Schizophrenia	Type 1	-0.402	0.179	0.50	0.0251	(-.75, -.05)	0.67	(0.47, 0.95)
	Type 2	-0.309	0.159	0.50	0.0516	(-.62, 0.00)	0.73	(0.54, 1.00)
	Combined	-0.355	0.164	-	0.0298	(-.68, -.03)	-	-
Diagnosis of Schizoaffective	Type 1	-0.138	0.191	0.50	0.4700	(-.51, 0.24)	0.87	(0.60, 1.27)
	Type 2	-0.160	0.186	0.50	0.3905	(-.53, 0.21)	0.85	(0.59, 1.23)
	Combined	-0.149	0.187	-	0.4256	(-.52, 0.22)	-	-

[1] Event type 1: Occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance). Only time to the first occurrence (SMB-confirmed) was used in the survival analysis. Event type 2: Occurrence of a significant suicide attempt, hospitalization due to imminent suicide risk (including increased level of surveillance), or worsening of severity of suicidality measured by CGI-SS-BP (change score) of level 6 or 7. Only time to the first occurrence was used in the survival analysis.

[2] A negative value of beta and a hazard ratio less than 1 indicate that Treatment Group 1 (Clozaril) is better than Treatment Group 2 (Zyprexa).

[3] P-values were generated using the Normal Approximation Z-test using robust standard error estimates obtained following the WLW method (c=0.5), stratified on pooled country and with treatment as the only covariate.

APPENDIX VI-18
STUDY ABA 451
MULTIPLE EVENT ANALYSIS OF TIME TO TYPE 1 AND TYPE 2 EVENTS BY GEOGRAPHIC SUBGROUP

Subgroup	Event Type [1]	Estimate of Treatment Effect (Beta) [2]	Standard Error of Beta	Weight	P-value [3]	95% C.I. of Beta	Hazard Ratio (exp(Beta)) [2]	95% C.I. of Hazard Ratio
North America	Type 1	-0.249	0.168	0.50	0.1387	(-.58, 0.08)	0.78	(0.56, 1.08)
	Type 2	-0.282	0.162	0.50	0.0922	(-.60, 0.04)	0.75	(0.55, 1.04)
	Combined	-0.266	0.153	-	0.1031	(-.59, 0.05)	-	-
East of the World	Type 1	-0.327	0.207	0.50	0.1135	(-.73, 0.08)	0.72	(0.48, 1.08)
	Type 2	-0.209	0.181	0.50	0.2487	(-.56, 0.15)	0.81	(0.57, 1.16)
	Combined	-0.268	0.187	-	0.1525	(-.64, 0.10)	-	-

[1] Event type 1: Occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance). Only time to the first occurrence (SMB-confirmed) was used in the survival analysis. Event type 2: Occurrence of a significant suicide attempt, hospitalization due to imminent suicide risk (including increased level of surveillance), or worsening of severity of suicidality measured by CGI-SS-BP (change score) of level 6 or 7. Only time to the first occurrence was used in the survival analysis.

[2] A negative value of beta and a hazard ratio less than 1 indicate that Treatment Group 1 (Clozaril) is better than Treatment Group 2 (Zyprexa).

[3] P-values were generated using the Normal Approximation Z-test using robust standard error estimates obtained following the WLW method (c=0.5), stratified on pooled country and with treatment as the only covariate.

APPENDIX VI-19 CASE REPORT FORMS AUDITED FOR EFFICACY DATA (by center-patient)
Patients without a Type 1 or Type 2 Event
112-0020
114-0033
201-0011
601-0020
604-0021
902-0004
956-0032
Patients with a Type 1 or Type 2 Event
102-0012
105-0030
112-0005
116-0002
120-0006
122-0010
127-0007
201-0004
304-0005
401-0029
406-0004
604-0032
702-0004
954-0003

APPENDIX VI-20 Audit of Efficacy Data CRF Forms Examined
Adverse Events
Clinical Global Impression for Severity of Suicidality by Blinded Psychiatrist
Imminent Risk of Suicide Requiring Hospitalization
Suicide Attempt Form
Suicide Event Form-Blinded Psychiatrist
Suicide Event Form-Suicide Monitoring Board

APPENDIX VII-1: LINE LISTING OF ALL DEATHS (STUDY ABA 451)					
Center/ Subject#	Age	Sex	Last Dose (mg/day)	Days of TX [post-TX]	Cause of Death
CLOZARIL PATIENTS					
101/0016	56	F	300	106	Unknown
114/0003	31	M	400	278	Pulmonary Embolism
117/0004	37	M	50	261	Unknown
122/0010	20	M	400	30 [+45]	Suicide
125/0027	37	F	500	393	Unknown
132/0001	33	F	25	64	Overdose (oxycodone)
302/0010	35	M	450	526	Cardiac Arrest
303/0010	35	F	100	703 [+?]	Complications 2° Suicide Attempt
401/0001	36	M	200	26	Suicide
401/0022	46	F	325	15 [+19]	Cancer
702/0010	38	M	250	79 [+1]	Suicide
802/0012	37	M	200	225 [+139]	Motor Vehicle Accident
902/0002	42	M	150	417	Suicide
ZYPREXA PATIENTS					
105/0007	40	F	20	770	Overdose (narcotics)
112/0019	47	M	15	15	Overdose (heroin)
117/0005	32	M	20	82	Unknown
301/0002	40	M	15	82 [+15]	Suicide
302/0007	48	F	0	0	Myocardial Infarction (prior to TX)
302/0012	58	M	20	482 [+6]	Cancer
303/0022	21	M	10	19 [+132]	Suicide
953/0007	60	F	10	695	Unknown
953/0011	54	F	20	66	Stroke

APPENDIX VII-2
ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS[24]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
CARDIAC DISORDERS	9 (1.9%)	7 (1.5%)
Angina Pectoris	2 (0.4%)	2 (0.4%)
Arrhythmia NOS	3 (0.6%)	2 (0.4%)
Cardiomegaly NOS	3 (0.6%)	0 (0.0%)
Coronary Artery Disease NOS	1 (0.2%)	1 (0.2%)
Myocardial Infarction	1 (0.2%)	1 (0.2%)
Pericarditis NOS	1 (0.2%)	0 (0.0%)
EAR AND LABYRINTH DISORDERS	1 (0.2%)	0 (0.0%)
Vertigo NEC	1 (0.2%)	0 (0.0%)
ENDOCRINE DISORDERS	2 (0.4%)	0 (0.0%)
Hypothyroidism	1 (0.2%)	0 (0.0%)
Thyroid Disorder NOS	1 (0.2%)	0 (0.0%)
EYE DISORDERS	1 (0.2%)	0 (0.0%)
Conjunctivitis NEC	1 (0.2%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	19 (4.0%)	12 (2.5%)
Abdominal Distention	1 (0.2%)	0 (0.0%)
Abdominal Pain NOS	5 (1.0%)	4 (0.8%)
Abdominal Pain Upper	1 (0.2%)	0 (0.0%)
Appendicitis Perforated	1 (0.2%)	0 (0.0%)
Colitis Ulcerative	1 (0.2%)	0 (0.0%)

[24] Excludes SAE's reported only in Zyprexa patients. Denominators adjusted for gender, as appropriate.

APPENDIX VII-2
ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS[24]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Constipation	2 (0.4%)	0 (0.0%)
Gastric Ulcer Hemorrhage	1 (0.2%)	0 (0.0%)
Gastritis NOS	1 (0.2%)	0 (0.0%)
Gastrointestinal Hemorrhage NOS	2 (0.4%)	1 (0.2%)
Hematemesis	2 (0.4%)	1 (0.2%)
Hiatus Hernia	1 (0.2%)	0 (0.0%)
Incisional Hernia NOS	1 (0.2%)	0 (0.0%)
Inguinal Hernia NOS	1 (0.2%)	0 (0.0%)
Intestinal Obstruction NOS	3 (0.6%)	1 (0.2%)
Irritable Bowel Syndrome	1 (0.2%)	0 (0.0%)
Malabsorption	1 (0.2%)	0 (0.0%)
Nausea	2 (0.4%)	1 (0.2%)
Esophageal Stenosis	1 (0.2%)	0 (0.0%)
Esophagitis NOS	2 (0.4%)	0 (0.0%)
Pancreatitis NOS	1 (0.2%)	2 (0.4%)
Proctitis NOS	1 (0.2%)	0 (0.0%)
Reflux Esophagitis	1 (0.2%)	0 (0.0%)
Vomiting NOS	5 (1.0%)	2 (0.4%)
GENERAL DISORDERS/ADMINISTRATION SITE CONDITIONS	10 (2.1%)	7 (1.5%)
Chest Pain NEC	5 (1.0%)	5 (1.0%)
Fall	1 (0.2%)	0 (0.0%)
Fatigue	2 (0.4%)	1 (0.2%)
Neuroleptic Malignant Syndrome	1 (0.2%)	0 (0.0%)

APPENDIX VII-2
ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS[24]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Pyrexia	2 (0.4%)	0 (0.0%)
HEPATOBILIARY DISORDERS	4 (0.8%)	2 (0.4%)
Cholelithiasis	3 (0.6%)	1 (0.2%)
Hepatic Disorder NOS	1 (0.2%)	0 (0.0%)
INFECTIONS AND INFESTATIONS	18 (3.8%)	11 (2.3%)
Abscess NOS	1 (0.2%)	0 (0.0%)
Bronchopneumonia NOS	1 (0.2%)	0 (0.0%)
Cellulitis Gangrenous	1 (0.2%)	0 (0.0%)
Colitis Pseudomembranous	1 (0.2%)	0 (0.0%)
Hepatitis Viral NOS	1 (0.2%)	0 (0.0%)
Lung Infection NOS	1 (0.2%)	0 (0.0%)
Meningitis Pneumococcal	1 (0.2%)	0 (0.0%)
Peritoneal Abscess	1 (0.2%)	0 (0.0%)
Pneumonia NOS	7 (1.5%)	4 (0.8%)
Pyelonephritis NOS	1 (0.2%)	1 (0.2%)
Salpingitis NOS	1 (0.5%)	0 (0.0%)
Sepsis NOS	1 (0.2%)	0 (0.0%)
Skin Infection NOS	1 (0.2%)	1 (0.2%)
Upper Respiratory Tract Infection NOS	1 (0.2%)	0 (0.0%)
Viral Infection NOS	1 (0.2%)	0 (0.0%)
Vulvovaginitis Trichomonal	1 (0.5%)	0 (0.0%)
INJURY AND POISONING	18 (3.8%)	17 (3.6%)
Accident NOS	2 (0.4%)	1 (0.2%)

APPENDIX VII-2
ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS[24]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Accidental Overdose (therapeutic agent)	4 (0.8%)	2 (0.4%)
Alcohol Intoxication Acute	1 (0.2%)	4 (0.8%)
Ankle Fracture	1 (0.2%)	0 (0.0%)
Burns NOS	1 (0.2%)	0 (0.0%)
Drug Toxicity NOS	1 (0.2%)	1 (0.2%)
Forearm Fracture	1 (0.2%)	0 (0.0%)
Non-accidental Overdose	5 (1.0%)	4 (0.8%)
Overdose NOS	2 (0.4%)	2 (0.4%)
Self Mutilation	1 (0.2%)	1 (0.2%)
Wrist Fracture	1 (0.2%)	0 (0.0%)
INVESTIGATIONS	11 (2.3%)	3 (0.6%)
Blood Test NOS	1 (0.2%)	0 (0.0%)
Hemoglobin Decreased	1 (0.2%)	0 (0.0%)
Platelet Count Decreased	1 (0.2%)	0 (0.0%)
White Blood Cell Decreased	8 (1.7%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	13 (2.7%)	7 (1.5%)
Dehydration	4 (0.8%)	1 (0.2%)
Diabetes Mellitus NOS	4 (0.8%)	6 (1.3%)
Hyperglycemia	3 (0.6%)	0 (0.0%)
Hypokalemia	2 (0.4%)	0 (0.0%)
Ketoacidosis	1 (0.2%)	0 (0.0%)
Polydipsia	1 (0.2%)	0 (0.0%)
Tetany	1 (0.2%)	0 (0.0%)

APPENDIX VII-2 ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS[24] STUDY ABA 451		
Body System/MedDRA Preferred Term	**Number (%) of Pts. Reporting SAE**	
	Clozaril (N=479)	**Zyprexa (N=477)**
MUSCULOSKELETAL/CONNECTIVE TISSUE/BONE DISORDERS	5 (1.0%)	3 (0.6%)
Back Pain	2 (0.4%)	2 (0.4%)
Muscle Twitching	1 (0.2%)	0 (0.0%)
Pain in Limb	1 (0.2%)	0 (0.0%)
Pseudoarthrosis	1 (0.2%)	0 (0.0%)
Rhabdomyolysis	1 (0.2%)	0 (0.0%)
Sensation of Heaviness	1 (0.2%)	0 (0.0%)
NEOPLASMS BENIGN AND MALIGNANT	4 (0.8%)	4 (0.8%)
Basal Cell Carcinoma	1 (0.2%)	0 (0.0%)
Breast Lump NOS	1 (0.2%)	0 (0.0%)
Lymphoma NOS	1 (0.2%)	0 (0.0%)
Uterine Cancer NOS	1 (0.5%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	26 (5.4%)	15 (3.1%)
Cerebrovascular Accident NOS	1 (0.2%)	1 (0.2%)
Complex Partial Seizures	1 (0.2%)	0 (0.0%)
Convulsions NOS	4 (0.8%)	2 (0.4%)
Disturbance in Attention NEC	1 (0.2%)	0 (0.0%)
Dizziness (excl. vertigo)	3 (0.6%)	0 (0.0%)
Dyskinesia NEC	1 (0.2%)	0 (0.0%)
Dysphonia	1 (0.2%)	0 (0.0%)
Epilepsy NOS	1 (0.2%)	1 (0.2%)
Grand Mal Convulsion	1 (0.2%)	2 (0.4%)
Hypotonia	1 (0.2%)	0 (0.0%)

APPENDIX VII-2
ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS[24]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Insomnia NEC	3 (0.6%)	4 (0.8%)
Myoclonic Seizure	1 (0.2%)	0 (0.0%)
Paresthesia NEC	1 (0.2%)	0 (0.0%)
Paraplegia	1 (0.2%)	0 (0.0%)
Sedation	1 (0.2%)	0 (0.0%)
Sleep Apnea Syndrome	1 (0.2%)	0 (0.0%)
Somnolence	3 (0.6%)	0 (0.0%)
Syncope	1 (0.2%)	0 (0.0%)
Tremor NEC	1 (0.2%)	0 (0.0%)
PREGNANCY, PUERPERIUM, AND PERINATAL CONDITIONS	2 (0.4%)	0 (0.0%)
Intrauterine Death	1 (0.5%)	0 (0.0%)
Placenta Previa	1 (0.5%)	0 (0.0%)
Pregnancy NOS	1 (0.5%)	0 (0.0%)
PSYCHIATRIC DISORDERS	185 (38.6%)	206 (43.2%)
Abnormal Behavior NOS	2 (0.4%)	0 (0.0%)
Acute Psychosis	3 (0.6%)	6 (1.3%)
Aggression	5 (1.0%)	7 (1.5%)
Agitation	9 (1.9%)	13 (2.7%)
Agitation Aggravated	3 (0.6%)	2 (0.4%)
Alcoholic Withdrawal Symptoms	1 (0.2%)	1 (0.2%)
Alcoholism	5 (1.0%)	6 (1.3%)
Anhedonia	2 (0.4%)	1 (0.2%)
Anxiety NEC	30 (6.3%)	38 (8.0%)

APPENDIX VII-2
ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS[24]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Catatonia	1 (0.2%)	1 (0.2%)
Completed Suicide	5 (1.0%)	3 (0.6%)
Confusion	1 (0.2%)	0 (0.0%)
Confusional State	1 (0.2%)	0 (0.0%)
Delirium	1 (0.2%)	1 (0.2%)
Delusion NOS	14 (2.9%)	16 (3.4%)
Delusion of Grandeur	1 (0.2%)	0 (0.0%)
Depressed Mood	5 (1.0%)	8 (1.7%)
Depression NEC	42 (8.8%)	44 (9.2%)
Drug Addiction	1 (0.2%)	0 (0.0%)
Exacerbation of Anxiety	1 (0.2%)	1 (0.2%)
Hallucination NOS	8 (1.7%)	11 (2.3%)
Hallucination, Auditory	13 (2.7%)	25 (5.2%)
Homicidal Ideation	9 (1.9%)	7 (1.5%)
Intentional Self-Injury	2 (0.4%)	4 (0.8%)
Irritability	1 (0.2%)	4 (0.8%)
Major Depressive Disorder NOS	1 (0.2%)	0 (0.0%)
Mental Disorder NEC	3 (0.6%)	0 (0.0%)
Obsessive Thoughts	1 (0.2%)	1 (0.2%)
Obsessive-Compulsive Disorder	1 (0.2%)	0 (0.0%)
Panic Attack	3 (0.6%)	1 (0.2%)
Paranoia	7 (1.5%)	6 (1.3%)
Psychomotor Retardation	1 (0.2%)	0 (0.0%)

APPENDIX VII-2
ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS[24]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Psychotic Disorder NOS	72 (15.0%)	75 (15.7%)
Schizoaffective Disorder	6 (1.3%)	7 (1.5%)
Schizophrenia NOS	11 (2.3%)	15 (3.1%)
Schizophrenia, Disorganized Type	1 (0.2%)	0 (0.0%)
Schizophrenia, Paranoid Type	2 (0.4%)	2 (0.4%)
Self-Induced Vomiting	1 (0.2%)	0 (0.0%)
Self-Injurious Ideation	2 (0.4%)	2 (0.4%)
Sleep Disorder NOS	1 (0.2%)	1 (0.2%)
Stress Symptoms	1 (0.2%)	3 (0.6%)
Suicidal Ideation	77 (16.1%)	109 (22.9%)
Suicide Attempt	32 (6.7%)	56 (11.7%)
Tension	1 (0.2%)	1 (0.2%)
Thinking Abnormal NEC	3 (0.6%)	1 (0.2%)
RENAL AND URINARY DISORDERS	5 (1.0%)	3 (0.6%)
Calculus Bladder	1 (0.2%)	0 (0.0%)
Polyuria	1 (0.2%)	0 (0.0%)
Renal Failure NOS	1 (0.2%)	1 (0.2%)
Urinary Incontinence	2 (0.4%)	0 (0.0%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	5 (1.0%)	2 (0.4%)
Amenorrhea NOS	1 (0.5%)	0 (0.0%)
Orchitis NOS	1 (0.3%)	0 (0.0%)
Ovarian Cyst	1 (0.5%)	1 (0.5%)
Pelvic Pain NOS	1 (0.2%)	0 (0.0%)

APPENDIX VII-2
ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS[24]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
Vulval Ulceration	1 (0.5%)	0 (0.0%)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	12 (2.5%)	7 (1.5%)
Asthma NOS	1 (0.2%)	3 (0.6%)
Chronic Obstructive Airways Disease	1 (0.2%)	2 (0.4%)
Dyspnea	3 (0.6%)	1 (0.2%)
Hyperventilation	1 (0.2%)	0 (0.0%)
Hypoventilation	1 (0.2%)	0 (0.0%)
Pharyngeal Disorder NOS	1 (0.2%)	0 (0.0%)
Pleural Effusion	1 (0.2%)	0 (0.0%)
Pneumonia Aspiration	1 (0.2%)	0 (0.0%)
Respiratory Distress	1 (0.2%)	0 (0.0%)
Respiratory Failure (excl. neonatal)	2 (0.4%)	1 (0.2%)
SKIN AND CUTANEOUS TISSUE DISORDERS	5 (1.0%)	1 (0.2%)
Dermatitis Medicamentosa	1 (0.2%)	0 (0.0%)
Epidermal Cyst	1 (0.2%)	0 (0.0%)
Hemangioma NOS	1 (0.2%)	0 (0.0%)
Hidradenitis	1 (0.2%)	0 (0.0%)
Rash Papular	1 (0.2%)	0 (0.0%)
SOCIAL CIRCUMSTANCES	12 (2.5%)	18 (3.8%)
Bereavement NOS	1 (0.2%)	0 (0.0%)
Drug Abuse	1 (0.2%)	5 (1.0%)
Social Problem NOS	11 (2.3%)	13 (2.7%)
Treatment Noncompliance	1 (0.2%)	2 (0.4%)

APPENDIX VII-2
ENUMERATION OF SERIOUS ADVERSE EVENTS AMONG CLOZARIL-TREATED PATIENTS[24]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. Reporting SAE	
	Clozaril (N=479)	Zyprexa (N=477)
SURGICAL AND MEDICAL PROCEDURES	2 (0.4%)	2 (0.4%)
Hospitalization NOS	1 (0.2%)	1 (0.2%)
Orthopedic Procedure	1 (0.2%)	0 (0.0%)
VASCULAR DISORDERS	5 (1.0%)	5 (1.0%)
Acute Circulatory Failure	1 (0.2%)	0 (0.0%)
Deep Venous Thrombosis NOS	1 (0.2%)	0 (0.0%)
Postural Hypotension	1 (0.2%)	0 (0.0%)
Pulmonary Embolism	2 (0.4%)	1 (0.2%)
Transient Ischemic Attack	1 (0.2%)	1 (0.2%)

APPENDIX VII-3:
NARRATIVE SUMMARIES REVEIEWED FOR PATIENTS WITH SERIOUS ADVERSE EVENTS (BY CENTER#-PATIENT#)

109-0016	126-0022	302-0041
117-0004	129-0010	403-0008
120-0003	301-0019	502-0008
120-0014	302-0010	701-0022
126-0017	302-0011	702-0021

APPENDIX VII-4
ENUMERATION OF ADVERSE EVENTS LEADING TO DROPOUT AMONG CLOZARIL-TREATED PATIENTS[25]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. with AE Leading to Dropout	
	Clozaril (N=479)	Zyprexa (N=477)
CARDIAC DISORDERS	3 (0.6%)	0 (0.0%)
Cardiomegaly NOS	1 (0.2%)	0 (0.0%)
Palpitations	1 (0.2%)	0 (0.0%)
Tachycardia NOS	1 (0.2%)	0 (0.0%)
EYE DISORDERS	1 (0.2%)	0 (0.0%)
Bloodshot Eye	1 (0.2%)	0 (0.0%)
GASTROINTESTINAL DISORDERS	6 (1.3%)	2 (0.4%)
Abdominal Pain NOS	1 (0.2%)	0 (0.0%)
Aptyalism	1 (0.2%)	0 (0.0%)
Diarrhea NOS	1 (0.2%)	0 (0.0%)
Intestinal Obstruction NOS	3 (0.6%)	0 (0.0%)
Nausea	1 (0.2%)	1 (0.2%)
Salivary Hypersecretion	1 (0.2%)	0 (0.0%)
Vomiting NOS	1 (0.2%)	0 (0.0%)
GENERAL DISORDERS/ADMINISTRATION SITE CONDITIONS	1 (0.2%)	0 (0.0%)
Pyrexia	1 (0.2%)	0 (0.0%)
INVESTIGATIONS	11 (2.3%)	8 (1.7%)
Blood Test NOS	1 (0.2%)	0 (0.0%)
Weight Increased	2 (0.4%)	7 (1.5%)

[25] Excludes AE's leading to dropout only in Zyprexa patients. Denominators adjusted for gender.

APPENDIX VII-4
ENUMERATION OF ADVERSE EVENTS LEADING TO DROPOUT AMONG CLOZARIL-TREATED PATIENTS[25]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. with AE Leading to Dropout	
	Clozaril (N=479)	Zyprexa (N=477)
White Blood Cell Decreased	8 (1.7%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS	2 (0.4%)	2 (0.4%)
Diabetes Mellitus NOS	1 (0.2%)	2 (0.4%)
Hyperglycemia NOS	1 (0.2%)	0 (0.0%)
MUSCULOSKELETAL/CONNECTIVE TISSUE/BONE DISORDERS	2 (0.4%)	1 (0.2%)
Muscle Twitching	1 (0.2%)	0 (0.0%)
Myalgia	1 (0.2%)	0 (0.0%)
Sensation of Heaviness	1 (0.2%)	0 (0.0%)
NEOPLASMS BENIGN AND MALIGNANT	1 (0.2%)	1 (0.2%)
Lymphoma NOS	1 (0.2%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS	11 (2.3%)	2 (0.4%)
Cerebrovascular Accident NOS	1 (0.2%)	0 (0.0%)
Disturbance in Attention NEC	1 (0.2%)	0 (0.0%)
Dizziness (excl. vertigo)	4 (0.8%)	0 (0.0%)
Dysarthria	1 (0.2%)	0 (0.0%)
Memory Impairment	1 (0.2%)	0 (0.0%)
Sedation	1 (0.2%)	0 (0.0%)
Somnolence	5 (1.0%)	1 (0.2%)
Vegetative State Chronic	1 (0.2%)	0 (0.0%)
PREGNANCY, PUERPERIUM, AND PERINATAL CONDITIONS	1 (0.5%)	0 (0.0%)
Pregnancy NOS	1 (0.5%)	0 (0.0%)
PSYCHIATRIC DISORDERS	12 (2.5%)	17 (3.6%)

APPENDIX VII-4
ENUMERATION OF ADVERSE EVENTS LEADING TO DROPOUT AMONG CLOZARIL-TREATED PATIENTS[25]
STUDY ABA 451

Body System/MedDRA Preferred Term	Number (%) of Pts. with AE Leading to Dropout	
	Clozaril (N=479)	Zyprexa (N=477)
Acute Psychosis	2 (0.4%)	0 (0.0%)
Agitation	1 (0.2%)	0 (0.0%)
Anxiety NEC	2 (0.4%)	0 (0.0%)
Depression NEC	1 (0.2%)	1 (0.2%)
Irritability	1 (0.2%)	0 (0.0%)
Obsessive-Compulsive Disorder	1 (0.2%)	0 (0.0%)
Paranoia	2 (0.4%)	0 (0.0%)
Psychotic Disorder NOS	2 (0.4%)	9 (1.9%)
Suicidal Ideation	1 (0.2%)	4 (0.8%)
Suicide Attempt	1 (0.2%)	3 (0.6%)
RENAL AND URINARY DISORDERS	1 (0.2%)	1 (0.2%)
Urinary Incontinence	1 (0.2%)	0 (0.0%)

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/s/

Greg Dubitsky
8/1/02 06:06:20 PM
MEDICAL OFFICER

Thomas Laughren
8/22/02 09:03:43 AM
MEDICAL OFFICER

I believe the findings from study ABA 451 are sufficiently positive to justify an approvable action, however, several key questions will need to be satisfactorily addressed before a final action; see memo to file for more detailed comments.--TPL

AMENDMENT TO:

Review and Evaluation of Clinical Data
NDA #19-758/S-047

Sponsor:	Novartis
Drug:	Clozaril
Proposed Indication:	Suicidality
Material Submitted:	Twenty-five Potential Endpoint Packages (PEP's)
Correspondence Date:	August 26, 2002
Date Received:	August 27, 2002

I. Background

Supplement S-047 seeks approval for the use of Clozaril to reduce the risk of suicidality in patients with schizophrenia or schizoaffective disorder. Evidence of this effect rests primarily on the results of study ABA 451. In this trial, patients were randomized to treatment with either Clozaril or Zyprexa over a period of 2 years and monitored for the emergence of suicide-related events (completed suicides, significant suicide attempts, and hospitalizations or increased surveillance due to imminent suicide risk, all called Type 1 events), or changes in a global rating of suicidality (CGI-SS) by a blinded psychiatrist at the site (Type 2 events). The protocol specified that all clinical data regarding events considered potential Type 1 events by the unblinded principal investigator at each site were to be referred to a CRO (Ingenix), which was to censor any information that might reveal the patient's treatment group. After censoring, these data constituted Potential Endpoint Packages (PEP's) which were forwarded to an independent panel of 3 clinicians with expertise in suicidality (the Suicide Monitoring Board or SMB) for determination of whether the patient had experienced a Type 1 event. Additionally, these censored data were forwarded to the blinded psychiatrist (BP) for assessment. However, the primary efficacy analysis utilized only the determination of the SMB.

In all, PEP's for 254 potential Type 1 events among Clozaril patients and 309 among Zyprexa patients were

referred to the SMB. These events are cross-tabulated by the determination of the SMB and by the BP in the table below.

ENUMERATION OF PEP'S REFERRED TO THE SMB BY SMB & BP DETERMINATIONS				
	Clozaril (N=254)		Zyprexa (N=309)	
	BP Event	BP No Event	BP Event	BP No Event
SMB Event	208	9	227	37
SMB No Event	28	9	29	16

Most of the events were classified the same way by both the SMB and the BP's (85% and 79% in the Clozaril and Zyprexa groups, respectively). But, it was noted that the percentage of referred events which were confirmed by the SMB but not deemed to be events by the BP differed significantly between the two groups (9/254 or 4% of the Clozaril events and 37/309 or 12% of the Zyprexa events; p=0.0003, Mantel-Haenszel Chi-Square).[1] This raised the possibility that the SMB differentially over-read the events in the Zyprexa group, leading to an inflated number of Type 1 events in the Zyprexa group and, thus, biasing the study results in favor in Clozaril. Also, this observation suggests the possibility that perhaps the SMB had become unblinded to the treatment assignment of some patients.

To investigate this possibility, it was decided to audit a 25% sample of the 103 events for which the SMB and BP determinations were discrepant. A random sample of 25 of these 103 events was selected (in proportion to the number of events in the corresponding four cells in the above table). The PEP's for these 25 events were then requested from Novartis.

Upon submission, each PEP was examined by the undersigned to determine whether the SMB determination appeared reasonable and to detect any information in the PEP that could have unblinded the SMB members. The results of this audit are presented below.

[1] The percentages of events confirmed by the BP's but not confirmed by the SMB were about equal between the two groups: 11% and 9% for Clozaril and Zyprexa, respectively.

II. Review of PEP's

A listing of the 25 audited PEP events is provided in the appendix to this review. For each event, this listing indicates whether a Type 1 event was deemed to have occurred by 1) the SMB, 2), the BP, and 3) by me.

Despite discrepant judgements between the SMB and BP for all of these events, I identified only 3 events in which I felt that the SMB may have erred. These events are summarized below.

#1 Clozaril patient 131-0001, 8-6-98 event: The PI indicated on the IRSRH form that the event had low risk of injury and there was only occasional suicidal ideation. The SAF indicates that this was an attention-seeking gesture. Clinical progress notes indicate that the patient did not want to live but does not mention any plan to attempt suicide. The patient was admitted to a crisis unit to remove her from a stressful situation. The SMB classified this event as a hospitalization due to imminent suicide risk. I feel that the evidence does not support an imminent suicide risk.

#2 Clozaril patient 120-0003, 9-2-98 event: A consultation report indicates that the patient wished to kill himself and was contemplating taking an overdose. This led to hospital admission. The SMB did not feel that this was due to imminent suicide risk. I feel that there is sufficient evidence to indicate the presence of an imminent suicide risk.

#3 Zyprexa patient 106-0010, 1-3-99 event: The PI stated on the IRSRH form that the patient "wasn't suicidal." However, a hospital assessment note indicates that the patient had command hallucinations to kill himself and planned to buy drugs and take an overdose. The patient was admitted with q15 minute checks. The SMB did not feel that this was a Type 1 event. I believe that this admission was due to an imminent risk of suicide.

Thus, it appears that the SMB overreported one event and underreported one event in the Clozaril group and underreported one event in the Zyprexa group. If these findings are projected to the entire study sample and adjustments made, there would be no change in the number of Clozaril Type 1 events and an increase in the number of

Zyprexa Type 1 events, which would favor the Clozaril group to an even greater extent than the face determinations.

In the course of reviewing these records, I noted 23 instances among events in 6 Clozaril and 9 Zyprexa patients where the assigned treatment group was clearly indicated in the PEP. This could have unblinded SMB members to treatment assignment and possibly led to bias in their determinations. However, in only one of these 15 patients did I feel that the SMB had possibly erred in their determination (event #2 above). In that case, the SMB did not confirm a Type 1 event in a Clozaril patient which I felt had occurred. Such a finding has the potential to produce a bias in favor of Clozaril. However, the SMB determinations appeared to be appropriate for the other 14 events where unblinding and bias could have occurred; this includes four events where knowledge of treatment assignment could have been used to make determinations that favored Clozaril but were not. Thus, it is difficult to conclude that unblinding and consequent biased determinations had occurred at the SMB level in this study.

III. Conclusions

This audit revealed no evidence of systematic, inappropriate SMB determinations of suicidality that, on the whole, would have biased the study results in favor of Clozaril. Although there was evidence of possible unblinding at the SMB level, it cannot be concluded that this produced biased determinations by the SMB.

Gregory M. Dubitsky, M.D.
August 30, 2002

cc: NDA #19-758
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/SHardeman

APPENDIX
LIST OF AUDITED POTENTIAL ENDPOINT PACKAGES AND DETERMINATIONS OF TYPE 1 EVENTS[2]

Patient Number	Event Date	TX	+/- Type 1 Event		
			SMB	BP	FDA Reviewer
131-0001	06AUG1998	CLOZ	**+**	-	**-**
402-0008	16MAR2000	CLOZ	+	-	+
105-0014	26APR1999	ZYP	+	-	+
105-0020	17NOV1998	ZYP	+	-	+
105-0030	04FEB2000	ZYP	+	-	+
106-0005	11OCT1998	ZYP	+	-	+
115-0001	03FEB1999	ZYP	+	-	+
115-0001	18AUG1999	ZYP	+	-	+
302-0030	31MAR1999	ZYP	+	-	+
304-0001	23JUL1998	ZYP	+	-	+
956-0003	26DEC1998	ZYP	+	-	+
110-0003	06JAN1999	CLOZ	-	+	-
116-0009	14AUG1999	CLOZ	-	+	-
117-0016	11MAY1999	CLOZ	-	+	-
120-0003	15AUG1998	CLOZ	-	+	-
120-0003	02SEP1998	CLOZ	**-**	+	**+**
122-0006	26SEP1998	CLOZ	-	+	-
125-0004	09NOV1998	CLOZ	-	+	-
103-0001	13OCT1998	ZYP	-	+	-
106-0010	03JAN1999	ZYP	**-**	+	**+**
120-0006	09MAY1999	ZYP	-	+	-
401-0023	24MAR2000	ZYP	-	+	-
401-0023	27OCT2000	ZYP	-	+	-
604-0011	25FEB2000	ZYP	-	+	-
701-0019	09NOV1999	ZYP	-	+	-

[2] +/- means Type 1 event deemed to have occurred/not occurred. TX= treatment group, SMB= Suicide Monitoring Board assessment, BP= Blinded Psychiatrist assessment, FDA Reviewer= my assessment. Instances of disagreement between the SMB and my assessment are bolded.

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/s/

Greg Dubitsky
8/30/02 04:04:16 PM
MEDICAL OFFICER

Thomas Laughren
9/6/02 10:18:30 AM
MEDICAL OFFICER
I agree that this audit provides reassurance about the correctness of SMB classifications of potential Type 1 events.--TPL

AMENDMENT TO:

Review and Evaluation of Clinical Data
NDA #19-758/S-047

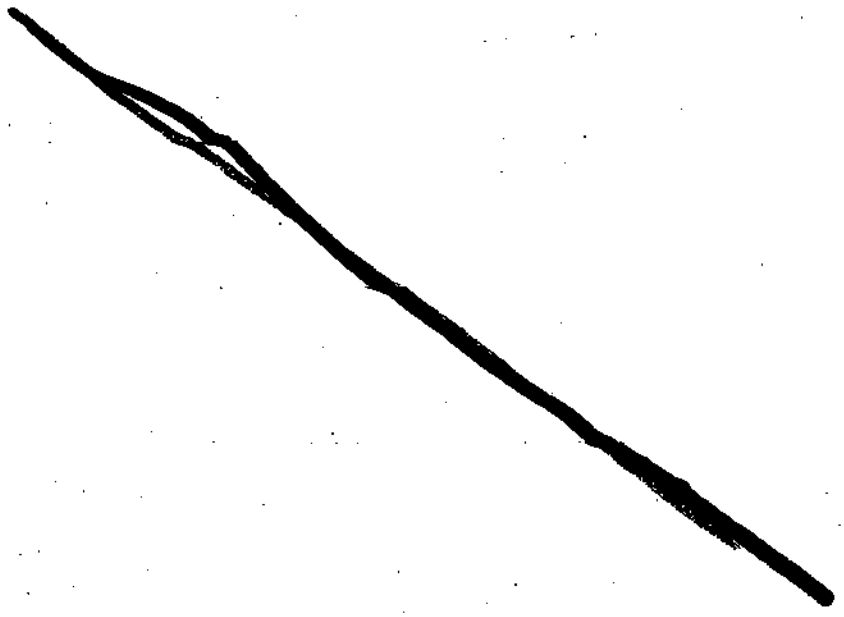
Sponsor:	Novartis
Drug:	Clozaril
Proposed Indication:	Suicidality
Material Submitted:	Draft Labeling Counterproposal
Correspondence Date:	October 25, 2002
Date Received:	November 4, 2002

I. Background

This supplement is intended to support the approval of Clozaril to reduce the risk of suicidality in patients with schizophrenia or schizoaffective disorder. An approvable letter, which included draft labeling, was issued on 8-30-02. This submission conveys the sponsor's counterproposal to that draft labeling.

II. Review of Draft Labeling Counterproposal

Summarized below are the important changes to the approvable draft labeling which are proposed by the sponsor, followed by my comments.



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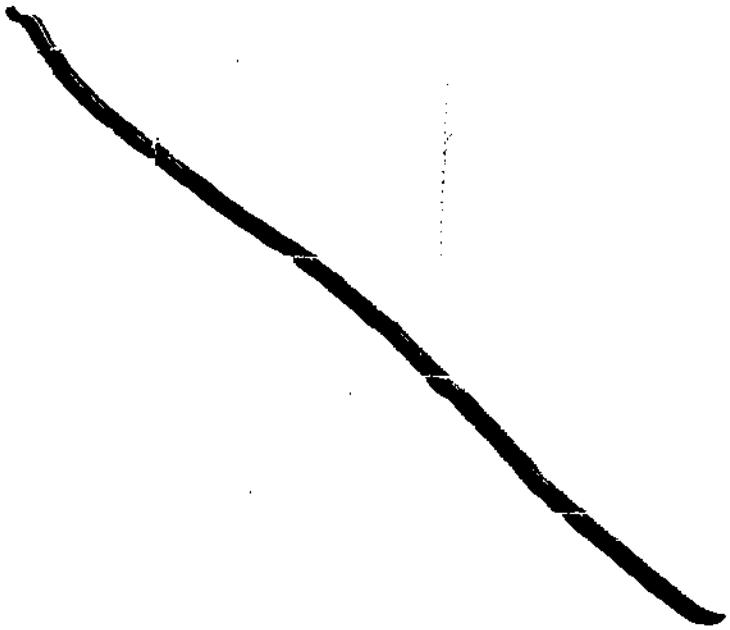
✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)



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III. Conclusions and Recommendations

At this point, the concerns I raised in my Review and Evaluation of Clinical Data dated 8-1-02, in which I recommended a non-approvable action, have been addressed. The Division is currently waiting for a final report of study ABA 451 site inspections from the Division of Scientific Investigations. Assuming that report is favorable, I support approval of this supplement with the labeling changes I have recommended in this review.

Gregory M. Dubitsky, M.D.
November 21, 2002

cc: NDA #19-758
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/SHardeman

172 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Greg Dubitsky
11/21/02 05:51:07 PM
MEDICAL OFFICER

Thomas Laughren
12/6/02 02:59:07 PM
MEDICAL OFFICER
I agree that this supplement can now be approved, once we reach agreement on final labeling with the sponsor; see memo to file for more detailed comments.--TPL

AMENDMENT TO:

Review and Evaluation of Clinical Data
NDA #19-758/S-047

Sponsor:	Novartis
Drug:	Clozaril
Proposed Indication:	Suicidality
Material Submitted:	Response to Items #1-3 of the 8-30-02 Approvable Letter
Correspondence Date:	October 25, 2002
Date Received:	October 30, 2002

I. Background

Supplement S-047 seeks approval for the use of Clozaril to reduce the risk of suicidality in patients diagnosed with schizophrenia or schizoaffective disorder. Evidence of this effect depends primarily on the results of study ABA 451, which is briefly described below.

In study ABA 451, patients were randomized to treatment with either Clozaril or Zyprexa for 2 year period and monitored for 1) the emergence of a suicide-related event (completed suicide, significant suicide attempt, or hospitalization or increased surveillance due to imminent suicide risk, all called Type 1 events) and 2) a rating of 6 or 7 (worse or very much worse compared to baseline) on a global rating of suicidality by a blinded psychiatrist (CGI-SS-BP) (called Type 2 events). All clinical data regarding events considered potential Type 1 events by the unblinded principal investigator (PI) were referred to a blinded Suicide Monitoring Board (SMB) for final determination of whether a Type 1 event had, in fact, occurred.

On face, study ABA 451 demonstrated that Clozaril was statistically superior to Zyprexa in reducing the risk of a Type 1 or Type 2 event.

An approvable letter for this supplement was issued on 8-30-02. This letter delineated four items relevant to study ABA 451 that would need to be addressed before an approval action could be taken. One of these items, Item

#4 (Potential Bias in the Referral of Information to the SMB), was addressed by the sponsor in a previous submission (dated 10-11-02) and was reviewed by the undersigned on 10-24-02. This item will not be further discussed in this review. Items #1-3 are presented below followed by Novartis' response to each and my comments.

Finally, the approvable letter indicated our plans to bring this application to the Psychiatric Drugs Advisory Committee (PDAC) on 11-4-02 for discussion of a number of significant issues, to include the results of study ABA 451.

II. Response to Items #1-3 of the Approvable Letter

A. Item #1: Change in Blinded Raters

Large proportions of patients (42% of Clozaril and 44% of Zyprexa patients) had a change in blinded psychiatrist (BP) raters during their participation in this trial. Since CGI-SS-BP ratings were assessed relative to baseline and a new rater probably did not see the patient at baseline, the fact that raters changed for almost half of the patients raised a concern about the reliability of CGI-SS-BP ratings. The sponsor was requested to comment on the potential impact of this finding on the study results.

Novartis responded that the CGI and its variants (e.g., the CGI-SS-BP) allow for minimal individual rater interpretation and, thus, it is unlikely that post-baseline rater changes would affect the CGI-SS-BP ratings to a significant extent. They further state that CGI-SS-BP assessments contributed minimally to Type 2 events, which were driven mainly by suicidal behavior. Also, since the fractions of patients who had a change in blinded psychiatrist raters is about equal between the two treatment groups, it is reasonable to assume that any impact of a rater change on the analysis would have been balanced between the Clozaril and Zyprexa groups.

Additionally, they point out that, of the 205 Clozaril and 214 Zyprexa patients who had a change in BP rater, 7 Clozaril and 5 Zyprexa patients experienced a Type 2 event based on worsening on the CGI-SS-BP score prior to the change in rater. For these patients, there was no impact on the primary efficacy analysis.

Reviewer's Comments

Given the long duration of this trial (2 years), it is doubtful that many of the original CGI-SS-BP raters accurately recalled the baseline condition of patients much beyond the first few months of the study. Ratings were more likely based on reference to the documented baseline severity of suicidal ideation by both original and new raters. Thus, a change of rater is unlikely to have significantly impacted on the results of this trial.

B. Item #2: SMB Performance

The clinical review of study ABA 451 included an audit of potential Type 1 event assessments by the SMB and the BP's. This audit revealed 3 instances in which the SMB determinations were questionable, the SMB and BP disagreed, and SMB decision initially was not unanimous. To help reassure ourselves that potential Type 1 events were correctly classified, we requested that the sponsor submit any additional documentation for these 3 patients as well as 25 Potential Endpoint Packages (PEP's) in which there were discrepancies between the SMB and BP determinations.[1]

In this submission, Novartis explained that the SMB members initially rated each case independently and, in cases where there was less than unanimity among the 3 members, discussions were held via teleconference to achieve a unanimous decision, if possible. Of all potential Type 1 events reviewed by the SMB, a unanimous decision regarding the presence or absence of a Type 1 event was reached in 72% of the cases.[2]

Additional SMB documentation regarding the 3 cases identified in the clinical review audit was provided by the sponsor under separate cover and examined by the undersigned. This documentation was not helpful in elucidating the decisions of the SMB in these cases.

On 8-26-02, the sponsor submitted PEP's for 25 potential Type 1 events for which the SMB and BP determinations were

[1] PEP's consisted of all blinded information provided to the SMB and BP's for their assessment of potential Type 1 events.

[2] In cases where unanimity could not be achieved, the final SMB determination was dictated by the majority opinion.

discrepant.[3] These were examined by the undersigned and the results summarized in a review dated 8-30-02. There was no evidence of systematic, inappropriate SMB determinations that, on the whole, would have biased the study results. Several instances of possible SMB unblinding were noted but it could not be concluded that these produced biased determinations by the SMB.

Reviewer's Comments
Based on the above audits, it appears that SMB classifications of potential Type 1 events were appropriate.

C. Item #3: Unblinding of Blinded Psychiatrists

Six BP raters indicated that they had become unblinded to treatment during the course of study ABA 451. We asked the sponsor to provide information on how unblinding occurred in these cases.

In three cases, the BP was unblinded by the patient and, in one case, the BP received a document which resulted in unblinding. In the remaining 2 cases, the mechanism of unblinding was not known.

They also responded that the raters who had become unblinded were replaced by a blinded rater. Thus, they consider it unlikely that these instances of unblinding had a significant impact on the study results.

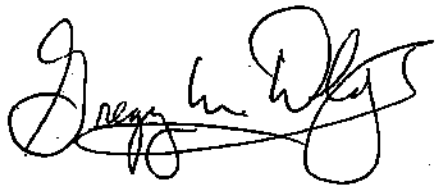
Reviewer's Comments
The small number of cases of acknowledged unblinding in this large, 2-year study is not unusual and is unlikely to have substantially impacted on the results of study ABA 451.

III. Conclusions and Recommendations

To date, the sponsor has adequately addressed the concerns raised in the approvable letter. Their responses contain no information that would preclude the approval of this supplement.

[3] This represented a 25% sample of 103 events for which the SMB and BP determinations differed. This sample was randomly selected by the undersigned reviewer.

Final action on this supplement now awaits completion of additional site inspections by the FDA Division of Scientific Investigations to audit the referral of potential Type 1 events to the SMB and consideration of the deliberations of the PDAC in their 11-4-02 meeting.



Gregory M. Dubitsky, M.D.
November 7, 2002

cc: NDA #19-758
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PDavid
/SHardeman

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/s/

Greg Dubitsky
11/7/02 04:52:05 PM
MEDICAL OFFICER

Thomas Laughren
12/6/02 03:10:10 PM
MEDICAL OFFICER
I agree that this supplement can be approved, once we reach agreement on final labeling with the sponsor; see memo to file for more detailed comments.--TPL

AMENDMENT TO:

Review and Evaluation of Clinical Data
NDA #19-758/S-047

Sponsor:	Novartis
Drug:	Clozaril
Proposed Indication:	Suicidality
Material Submitted:	Response to Item #4 of the 8-30-02 Approvable Letter
Correspondence Date:	October 11, 2002
Date Received:	October 17, 2002

I. Background

Supplement S-047 seeks approval for the use of Clozaril to reduce the risk of suicidality in patients with schizophrenia or schizoaffective disorder. Evidence of this effect depends primarily on the results of study ABA 451.

In this trial, patients were randomized to treatment with either Clozaril or Zyprexa over a period of 2 years and monitored for the emergence of suicide-related events (completed suicides, significant suicide attempts, and hospitalizations or increased surveillance due to imminent suicide risk, all called Type 1 events), or changes in a global rating of suicidality (CGI-SS) by a blinded psychiatrist at the site (Type 2 events). The protocol specified that all clinical data regarding events considered potential Type 1 events by the unblinded principal investigator (PI) were to be referred to a blinded Suicide Monitoring Board (SMB) for final determination of whether a Type 1 event had, in fact, occurred. Also, reviews of source documents by Clinical Research Associates and of Serious Adverse Event Forms by the Medical Monitor were conducted to detect evidence of any unreported Type 1 event. Such events prompted a query to the PI and, if the opinion of the PI was that an event was not related to suicidal behavior, referral to the SMB was not completed.

Since the decision to refer potential Type 1 events ultimately rested with the unblinded PI and the

preponderance of suicidality-related events in this study were Type 1 events, it was considered possible that bias could have influenced the referral of events to the SMB and, thus, the overall study results. To investigate whether such referral bias existed, Novartis performed a retrospective review as described below.

II. Novartis Review

A. Methodology

Novartis utilized the following 3 sources of data to identify events potentially related to suicidal behavior:

1) verbatim adverse event (AE) terms from the CRF AE page.
2) documented queries generated during the study.
3) site staff comments from the CRF Comments page.

A search term dictionary was developed which was intended to include all terms related to suicidal behavior. This dictionary is provided as Appendix 1 to this submission.

Then a search was conducted to locate matches between a dictionary term and the same term in each of the above data sources. This was done for each patient not referred to the SMB (i.e., without a potential Type 1 event during the study).

The CRF's of patients with matches were examined to identify unreported potential Type 1 events.

B. Findings

There was a total of 701 patients not referred to the SMB. For 279 (40%) of these patients, matches to at least one search term were found.

Clinical data for these 279 patients were reviewed by Novartis to detect any events that should have been referred to the SMB. It was found that 5 of these patients (3 in the Clozaril and 2 in the Zyprexa group) experienced an event that may have warranted referral. For only two of these 5 patients did Novartis conclude that a referral to the SMB should have been executed.[1]

---

[1] Clozaril patient 404-0008 and Zyprexa patient 955-0014. Please see Appendix 5, which summarizes the clinical data for these 5 patients.

On the basis of this finding, Novartis asserts that it seems unlikely that referral bias toward either treatment group existed during the study.

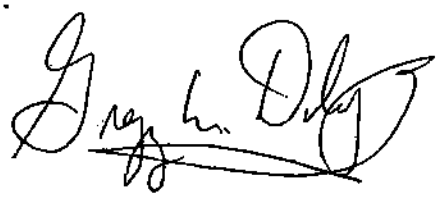
III. Conclusions

The results of the sponsor's analysis revealed no appreciable evidence of bias in referring patients with possible Type 1 events to the SMB. However, this analysis suffers from significant flaws that limit its usefulness:

1) Novartis evaluations of clinical data from the 279 patients with search matches were not done under blinded conditions, raising the possibility that the analysis itself could have been biased.

2) The search was performed only on data that was entered in the CRF's or which was the subject of a documented query. A biased investigator could have omitted information pertinent to an actual Type 1 event from the CRF and, thereby, such an event would have escaped detection by this review.

In sum, this analysis does not convincingly rule out the possibility of referral bias in study ABA 451. The report of recent, focused inspections by the Division of Scientific Investigations (DSI), although based on a small subset of the study population, may be more reliable. This report is pending at this time.



Gregory M. Dubitsky, M.D.
October 24, 2002

cc: NDA #19-758
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/SHardeman

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/s/

Greg Dubitsky
10/24/02 02:16:17 PM
MEDICAL OFFICER

Thomas Laughren
10/25/02 01:49:22 PM
MEDICAL OFFICER
I agree that the sponsor's approach to exploring for potential bias in the referral of patient events to the SMB has significant flaws, and that the DSI audit should provide a definitive answer to this question.--TPL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

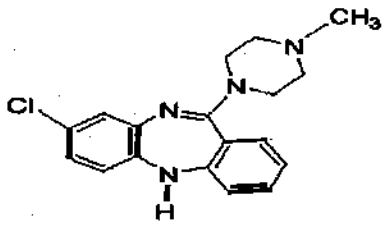
CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF SUPPLEMENT

1. ORGANIZATION: HFD-120
2. NDA: 19-758
3. SUPPLEMENT NUMBERS/ DATES: SE1-047
Efficacy Supplement
letter date: February 28, 2002
stamp date: March 1, 2002
4. AMENDMENTS/REPORTS/DATES:
5. RECEIVED BY CHEMIST: March 5, 2001

6. APPLICANT NAME & ADDRESS: Novartis Pharmaceuticals Corporation
One Health Plaza, East Hanover, New Jersey 07936-1080

7. NAME OF DRUG: Clozaril® Tablets
8. NONPROPRIETARY NAME: Clozapine
9. CHEMICAL NAME/STRUCTURE: 8-chloro-11-(4-methyl-1-piperazinyl-5*H*-dibenzo[*b*,*e*][1,4]diazepine
MW: 326.83 $C_{18}H_{19}N_4Cl$



10. DOSAGE FORM(S): Tablets
11. POTENCY: 25 and 100 mg
12. PHARMACOLOGICAL CATEGORY: Schizophrenia
13. HOW DISPENSED: X (Rx) ____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes ____ No
15. RELATED IND/NDA/DMF: NA

SUPPLEMENT PROVIDES FOR: Use of Clozaril® for the treatment of suicidality in patients with schizophrenia or schizoaffective disorder.

COMMENTS: Clozaril® is currently approved for management of severely ill patients with schizophrenia in N19-758. This efficacy supplement is for the additional indication of treatment of suicidality for these patients. The drug substance and drug products are referenced to approved NDA 19-758. In addition, no changes are reported for the package insert sections of DESCRIPTION and HOW SUPPLIED. Novartis has provided adequate information for exclusion to the environmental assessment. Please see review notes for detail.

CONCLUSIONS & RECOMMENDATIONS: N19-758/SE1-047 is recommended for **APPROVAL** from the CMC standpoint.

Cc:
NDA 19-758/SE1-047
DISTRICT OFFICE
HFD-120/Division File
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✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Gurpreet Gill-Sangha
8/1/02 01:51:13 PM
CHEMIST

CMC review for efficay supplement

Thomas Oliver
8/1/02 01:55:39 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

NDA:	19,758 (SE1-047)
DRUG NAME:	Clozaril ® (clozapine) Tablets
INDICATION:	Reduction of Suicidality in Patients with Schizophrenia or Schizoaffective disorder who are at risk for suicide
SPONSOR:	Novartis Pharmaceuticals Corporation
STATISTICAL REVIEWER:	Kun He (HFD-710)
DATE OF DOCUMENT:	February 28, 2002
HFD-710	Kun Jin, Ph.D., Team Leader
	George Chi, Ph.D., Director
HFD-120	Steven Hardeman, R. Ph., Project Manager
	Gregory Dubitsky, M.D., Clinical Reviewer
	Thomas Laughren, M.D., Team Leader
	Russell Katz, M.D., Director
HFD-700	Charles Anello, Sc. D., Deputy Director

TABLE OF CONTENTS

Statistical Review and Evaluation

0. Executive Summary

0.1. Brief Overview of Clinical Studies

The current submission NDA 19-758 for Clozaril ® (clozapine HCL) Tablets includes one study to demonstrate decreased risk for suicide among schizophrenic patients treated with Clozaril as compared to those treated with Zyprexa. This was a multicenter, randomized, open-label, 24-month study, using Zyprexa 5 to 20 mg/day as active control treatment or using Clozaril 200 to 900 mg/day as the treatment, conducted in US, Canada, U.K., France, Italy, Hungary, Croatia, South Africa, Czech Republic, Argentina, and Chile. A total of 980 males or females aged 18-65 and diagnosed with schizophrenia or schizoaffective disorder using DSM-IV criteria and who were deemed at high risk for suicide were included and randomized equally to two treatment groups.

The primary endpoint is the time (in days, after randomization) to either of a Type 1 Event which is defined as occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance) as confirmed by a Suicide Monitoring Board (SMB); or a Type 2 Event which is defined as occurrence of a worsening of severity of suicidality as demonstrated by a score of 6 or 7 (much worse or very much worse) on the change score of the Clinical Global Impression for Severity of Suicidality (CGI-SS-BP), rated by the Blinded Psychiatrist (BP), or an implicit worsening of severity of suicidality as indicated by the occurrence of a Type 1 event.

The Principal Investigator (PI) is unblinded to the randomized treatment. If a complete suicide, suicide attempt, or hospitalization for imminent risk of suicide is reported during the study, the Principal Investigator (PI) will prepare a brief narrative, and complete a Suicide Attempt Form (SAF) or a Imminent Risk Requiring Hospitalization Form (IRH), and send the information to Worldwide Clinical Trials (WCT) medical monitor within 24 hours. The WCT medical monitor will send the information to the Suicide Monitoring Board (SMB) and Blinded Psychiatrist (BP). The SMB and BP will independently evaluate and complete a Suicide Event Form, respectively, regarding whether it met a primary efficacy outcome criterion. The primary efficacy endpoint of Type 1 event is determined by the SMB.

CGI-SS will be formally evaluated at baseline, Week 2, Week 4 and every 4 weeks up to Week 52, and then at Weeks 60, 68, 80, 92, and 104 by the PI; and at baseline and at Weeks 8, 16, 24, 32, 40, 48, 52, 60, 68, 80, 92, and 104 by the BP. Part of CGI-SS by the BP is used in defining a Type 2 event.

0.2 Issues and Conclusion

The key issue is whether there is any bias caused by open-label as the Principal Investigator (PI) is unblinded. P-values on CGI-SS for the PI are always smaller than that for the BP, .0946 for the PI and .2803 for the BP in 7-point CGI-SS, and .2767 for the PI and .8708 for the BP in 5-point CGI-SS. The difference between p-values indicates that the PI might have bias favoring Clozaril.

The Type 1 event is determined by the SMB but it is the PI who determines who should be referred to the SMB. There are 122 patients in Clozaril and 157 patients in Zyprexa, respectively, who were referred to the SMB. The difference between the number of referred patients is 35. However, there are 102 patients in Clozaril and 141 patients in Zyprexa, respectively, who were judged by the SMB as the Type 1 event. The difference of the number of Type 1 event is 39. It is also noted that the correlation between the number of referred and the number of event is high. Based on the above, it is seen that the less referred will have the less Type 1 event, or the number of event is determined by the number of referred. Consequently this affects the number of censored patients.

In this study, for Type 1 event, there are 102 failed, 352 censored, and 36 completed in Clozaril, and 141 failed, 309 censored, and 40 completed in Zyprexa, respectively. The significance of analysis based on Type 1 event is due to 39, the difference of the number of event. The significance of analysis based on Type 2 event is mainly due to the contribution of Type 1 event because analysis on CGI-SS is not statistically nominally significant.

The conclusion is that although the primary analysis is statistically nominally significant with p-value .0309, one should interpret the result with caution due to the issues discussed above.

1. Introduction

The current submission NDA 19-758 for Clozaril ® (clozapine HCL) Tablets includes one study to demonstrate decreased risk for suicide among schizophrenic patients treated with Clozaril as compared to that for patients treated with Zyprexa.

This was a multicenter, randomized, open-label, 24-month study, using Zyprexa 5 to 20 mg/day as active control treatment or using Clozaril 200 to 900 mg/day as the treatment under study, conducted in US, Canada, U.K., France, Italy, Hungary, Croatia, South Africa, Czech Republic, Argentina, and Chile. A total of 980 males or females aged 18-65 and diagnosed with schizophrenia or schizoaffective disorder using DSM-IV criteria and who were deemed at high risk for suicide were included and randomized equally to two treatment groups.

2. Study ABA 451

2.1. Objective

The primary efficacy objective was to demonstrate decreased risk for suicide among schizophrenic patients treated with Clozaril as compared to that treated with Zyprexa using multiple events analysis techniques applied to time (in days, after randomization) to either of a Type 1 Event which is defined as occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance) as confirmed by a Suicide Monitoring Board (SMB); or a Type 2 Event which is defined as occurrence of a worsening of severity of suicidality as demonstrated by a score of 6 or 7 (much worse or very much worse) on the change score of the Clinical Global Impression for Severity of Suicidality (CGI-SS-BP), rated by the Blinded Psychiatrist (BP), or an implicit worsening of severity of suicidality as indicated by the occurrence of a Type 1 event.

2.2. Study Design

This was a prospective, randomized, open-label, 24-month study with an active control treatment, designed to evaluate the effects of Clozaril and Zyprexa on suicidality in patients with schizophrenia and schizoaffective disorder, who are known to be at high risk for suicide.

A total of 980 males or females patients aged 18-65 years (inclusive) and diagnosed with schizophrenia or schizoaffective disorder using DSM-IV criteria and who were deemed at high risk for suicide were included in the trial. Patients were randomized to treatment with either Clozaril or Zyprexa in an approximate 1:1 ratio within each center. The suggested dosage for patients assigned to Clozaril was 200 to 900 mg/day and for patients assigned to Zyprexa was 5 to 20 mg/day. Throughout the study, prescribed doses were based on a clinical assessment of tolerability and efficacy.

At each medication dispensing visit to the clinic (weekly for the first 26 weeks and thereafter, every 2 weeks for the remainder of the study), the patient's overall psychiatric condition was assessed by a health care professional. On the basis of this assessment, the need for a referral to the Principal Investigator (PI)/sub-investigator for psychiatric evaluation and treatment was considered. At designated visits, the patients' suicidality were evaluated by the PI and the Blinded Psychiatrist (BP) on the CGI-SS (CGI-SS-PI, and CGI-SS-BP) and on the InterSePT Scale for Suicidal Thinking (ISST-PI, and ISST-BP).

2.3. Efficacy Measures

The primary efficacy variable was time (in days, after randomization) to first occurrence of any of the following events: a Type 1 event, which included a significant suicide attempt or hospitalization due to imminent suicide risk including an increased level of surveillance as confirmed by the Suicide Monitoring Board (SMB); or a Type 2 event, defined as worsening of severity of suicidality as demonstrated by a 7-point CGI-SS-BP change scale score of 6 or 7 or an implicit worsening of severity of suicidality as indicated by the occurrence of a Type 1 event.

Completed Suicides: all deaths that occur during the study will require full documentation. Hospital summaries, autopsy reports, and coroner's reports will be collected and utilized by the PI to prepare a narrative which includes all relevant details but deletes information relating to the patient's treatment prior to sending it to the Worldwide Clinical Trials (WCT) medical monitor. If any required material is unavailable the PI must notify the WCT medical monitor in writing. A Suicide Attempt Form (SAF) must also be completed and sent to the WCT medical monitor. All information must be reviewed by the WCT medical monitor before it is sent to both the BP at the site and the SMB that is constituted of three experts in the study. Both will make independent determinations as to whether the death was a suicide and will complete a Suicide Event Form-Blinded Psychiatrist (SEF-BP)/SEF-SMB. Any requests for further information by the SMB or BP must be made through the WCT medical monitor.

Suicide Attempts: during the study, if a suicide attempt is reported, the PI will contact the relevant hospital/physician and obtain all necessary documents to objectively categorize the attempt as life-threatening or non-life-threatening, recording such information as type of event (e.g., violent/non-violent), treatment received (e.g., gastric lavage, surgery, stitches), name of hospital/physician providing care. Using this information, the PI will complete an SAF with a brief narrative and forward the information to the WCT medical monitor within 24 hours of learning of the event. The WCT medical monitor will ensure that the information will not compromise the blinding of the BP at the site or the SMB. The BP and the SMB will make independent decisions as to whether the attempt was serious, will categorize its lethality and will record this information on the SEF-BP and SEF-SMB, respectively.

Hospitalization for Imminent Risk of Suicide: the PI will notify the WCT medical monitor within 24

hours of learning that a patient has been hospitalized for imminent risk of suicide. However, hospitalizations driven more by logistical concerns (e.g., patient's residence being very distant from the site, mild increases of depression, or lack of caregiver) will not be considered as imminent risk and as such the WCT medical monitor will not need to be notified. Whenever a patient has been admitted to a hospital for imminent risk of suicide reason the PI will contact the WCT medical monitor within 24 hours of learning of the hospitalization and will complete the Imminent Risk Requiring Hospitalization Form (IRH) which will include a brief narrative. Information about patients who are hospitalized for imminent risk of suicide will be sent by the WCT medical monitor to the BP and to the SMB. They will independently evaluate the hospitalization and complete an SEF-BP and SEF-SMB regarding whether it met a primary efficacy outcome criterion.

CGI-SS is a 2-part assessment that evaluated patient suicidality. In the first part, which is referred to throughout the report as the 5-point CGI-SS severity score, the rater chose the most severe level of suicidality experienced by the patient over the previous 7 days on a 5-point scale ranging from 1 (not at all suicidal) to 5 (attempted suicide). In the second part, which is referred to as the 7-point CGI-SS change score, the rater assessed how much the patient's suicidality had changed since baseline on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). The patient's suicidality will be formally evaluated at baseline, Week 2, Week 4 and every 4 weeks up to Week 52, and then at Weeks 60, 68, 80, 92, and 104 by the PI; and at baseline and at Weeks 8, 16, 24, 32, 40, 48, 52, 60, 68, 80, 92, and 104 by the BP.

The endpoints defined in the original protocol (dated 1/16/98) for Study ABA 451 were either time from baseline until first significant suicide attempt or hospitalization due to imminent risk of suicide confirmed by the blinded SMB; or change from baseline in the CGI-SS-BP severity score (5-point scale).

2.4. Statistical Analysis Plan

The primary analysis is WLW (Wei, Lin, and Weissfeld (1989)) method, submitted in Amendment 6 dated 12/19/2000. The WLW method is a semiparametric method used to analyze multivariate failure time data, and models the marginal distribution with a Cox's proportional hazards model without imposing any particular structure of dependence on each event time. Following the approach of WLW for the primary analysis, time to the first occurrence of a Type 1 event and time to the first occurrence of a Type 2 event were modeled using a proportional hazards model, with pooled country as strata and treatment group as the only covariate. The WLW method provided estimates of treatment effects for the 2 types of events, the combined estimator of treatment effect is defined as:

$$\hat{\beta}_c = c\hat{\beta}_1 + c\hat{\beta}_2$$

where $\hat{\beta}_1$ and $\hat{\beta}_2$ represent the maximum partial likelihood estimators of β_1 and β_2, respectively Based on negotiations with the FDA, c=0.5 will be used in the analysis. Using this estimate of the combined treatment effect and the corresponding robust standard error, a single two-sided test was performed at a 5% level of significance using the null hypothesis of no treatment effect on either

event type. The test statistic (T = estimate/SE) has an asymptotic standard normal distribution. Only the ITT population was used for the analysis of the primary efficacy variables. In this report, the analyses of revised primary efficacy variables suggested by the FDA are presented as the main analyses for primary efficacy.

Due to the revision of the primary efficacy variables in this study based on an agreement with the FDA prior to database lock, the analyses defined in the original protocol (dated 1/16/98) were considered as supportive analyses for primary efficacy. The main analysis defined in the original protocol (dated 1/16/98) of the time to suicide attempt or hospitalization to prevent suicide (later called Type 1 event) was to be performed based on Cox's proportional hazards regression model. Explanatory variables in this model included treatment and the following baseline measurements: number of lifetime suicide attempts, active substance/alcohol abuse, pooled country, sex, and age group (at 3 levels: 18-32 years, 33-44 years, and ≥45 years). The main analysis of the change from baseline in the CGI-SS-BP severity score (5-point scale) was to be performed using an analysis of covariance (ANCOVA) model with the following explanatory variables: treatment, number of suicide attempts, active substance/alcohol abuse, country, sex, age group (at 3 levels: 18-32 years, 33-44 years, and ≥45 years), and baseline CGI-SS-BP severity score.

2.5. Study Population

2.5.1. Patient disposition

A total of 980 patients were randomized in Study ABA 451. Of these, 956 (97.6%) actually received study medication, 379 (38.7%) discontinued early, and 671 (68.5%) completed the study. A summary of patient entry to the study and completion by treatment group, including reasons for withdrawals and status of retrieved dropout patients, is given in Table 2.5.1. (adapted from Study report, Table 7-1).

Table 2.5.1. Patient disposition for each treatment group

	Clozaril	Zyprexa
Patient disposition	No. (%) of patients	
Screened: 1065 total		
Randomized	490 (100%)	490 (100%)
Did not receive study drug	10 (2.0%)	11 (2.2%)
Dispensed study drug	480 (98.0%)	479 (97.8%)
Took study drug	479 (97.8%)	477 (97.3%)
Completed[1]	332 (67.8%)	339 (69.2%)
Total discontinuations from the study	192 (39.2%)	167 (36.2%)
Reason for discontinuation:		
Adverse event	41 (8.4%)	33 (6.7%)
Abnormal laboratory value	2 (0.4%)	0 (0.0%)
Abnormal test procedure result	1 (0.2%)	0 (0.0%)
Unsatisfactory therapeutic effect on psychosis	5 (1.0%)	9 (1.8%)
Unsatisfactory therapeutic effect on suicide risk	0 (0.0%)	6 (1.2%)
Protocol violation	29 (5.9%)	20 (4.1%)
Patient withdrew consent	50 (10.2%)	49 (10.0%)
Lost to follow-up	33 (6.7%)	39 (8.0%)
Administrative problems	23 (4.7%)	26 (5.3%)
Death[2]	8 (1.6%)	5 (1.0%)
Retrieved Dropouts	61 (12.4%)	60 (12.2%)
Completed[3]	34 (55.7%)	37 (61.7%)
Discontinued	27 (44.3%)	23 (38.3%)

[1]Includes subjects whose Study Completion form indicated that the subject had completed and Retrieved Dropout (RDO) subjects whose last assessment occurred after Week 102 in relation to randomization date.

[2]Includes only discontinuations for death, a more complete summary of deaths can be found in Section 10.2.1.1.

[3]Includes RDO subjects whose last assessment occurred after Week 102 in relation to randomization date. Completed and discontinued percentages use total number of RDO subjects in denominator.

Source: Post-Text Table 7.1-1

Withdrawal of consent was the most common reason for discontinuation in both groups, occurring in 10.2% and 10.0% of Clozaril and Zyprexa patients, respectively. Reasons for discontinuation did not differ significantly between the two treatment groups.

2.5.2. Baseline demographic and background characteristics

Demographic and key baseline characteristics are summarized for the ITT population in Tables 2.5.2.1 and 2.5.2.2 (adapted from Study report, Tables 7-3 and 7-4).

Table 2.5.2.1. Summary of demographic characteristics at baseline by treatment group

	No. (%) of patients unless otherwise noted	
	Clozaril (n=490)	Zyprexa (n=490)
Age (year)		
Mean (SD)	37.1 (10.3)	37.0 (10.3)
Median	37	36
Range	18-69	18-65
18-32	168 (34.3%)	178 (36.3%)
33-44	216 (44.1%)	204 (41.6%)
≥45	106 (21.6%)	108 (22.0%)
Sex		
Male	301 (61.4%)	301 (61.4%)
Female	189 (38.6%)	189 (38.6%)
Race		
Caucasian	356 (72.7%)	337 (68.8%)
Black	65 (13.3%)	86 (17.6%)
Oriental	6 (1.2%)	7 (1.4%)
Other	63 (12.9%)	60 (12.2%)
Weight (kg)– Females	n=181	n=180
Mean (SD)	74.0 (20.1)	73.2 (16.4)
Median	70	70
Range	40-152	36-133
Weight (kg)– Males	n=283	n=289
Mean (SD)	82.8 (18.3)	84.3 (20.9)
Median	80.9	80
Range	45-156	44-166

Source: Post-Text Table 7.4-1

The treatment groups were comparable for sex, age, weight, and race. There were more males than females in the study (61.4% of all patients were male).

Table 2.5.2.2. Disease characteristics and lifetime suicide history at baseline by treatment group

	Clozaril (n=490)	Zyprexa (n=490)
Diagnosis	No. (%) of patients	
Schizophrenia	300 (61.2%)	309 (63.1%)
Schizoaffective	190 (38.8%)	181 (36.9%)
Treatment resistant[1]	135 (27.6%)	128 (26.1%)
Suicide History		
No. of lifetime suicide attempts	(n=480)	(n=489)
0	77 (15.7%)	86 (17.6%)
1	124 (25.3%)	99 (20.2%)
2-3	154 (31.4%)	157 (32.0%)
4-5	60 (12.2%)	75 (15.3%)
>5	75 (15.3%)	72 (14.7%)
Missing	0 (0.0%)	1 (0.2%)
Mean (SD)	3.6 (7.5)	3.2 (4.5)
Median	2	2
Range	0-120	0-50
No. of lifetime hospitalizations to prevent a suicide attempt	(n=487)	(n=483)
0	79 (16.1%)	75 (15.3%)
1	126 (25.7%)	145 (29.6%)
2-3	145 (29.6%)	135 (27.6%)
4-5	63 (12.9%)	52 (10.6%)
>5	74 (15.1%)	76 (15.5%)
Missing	3 (0.6%)	7 (1.4%)
Mean (SD)	3.7 (7.7)	3.2 (4.6)
Median	2	2
Range	0-100	0-50

[1] Treatment resistance determined by clinical assessment

Source: Post-Text Tables 7.1-1 (diagnosis) and 7.4-2 (other characteristics)

2.6. Sponsor's Efficacy Results

2.6.1. Primary efficacy results

The main analyses for all efficacy variables were performed on the ITT population. The primary analysis was WLW analysis of time to the first occurrence of a Type 1 event or a Type 2 (adapted from Study report Table 9-1).

Table 2.6.1. Primary analysis: Multiple event analysis of time to first occurrence of Type 1 and Type 2 events

Event Type[1]	Coefficient of Treatment Effect (Beta[2,3]) (SE)	p-value [2]	Hazard Ratio[2,3]	95% C.I. for Hazard Ratio[2]
Type 1	-0.280 (0.130)	0.0316	0.76	0.58, 0.98
Type 2	-0.250 (0.121)	0.0388	0.78	0.61, 0.99
Combined	-0.265 (0.123)	0.0309	--	--

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

Type 2 event = worsening of suicidality severity as demonstrated by 7-point CGI-SS-BP change scale score of 6 or 7, or by implicit worsening of suicidality severity as demonstrated by occurrence of a Type 1 event.

[2]Refer to detailed statistical analysis plan in Appendix 5.1, §1.1.5.3, for information on calculation of these parameters.

[3]Hazard ratio < 1 and beta < 0 indicate that Clozaril is better than Zyprexa.

Source: Post-Text Table 9.1-1

As shown above, an overall treatment effect favoring Clozaril was statistically significant with p-value 0.0309.

2.6.2. Original Protocol Analyses

The analyses defined in the original protocol are presented in Table 2.6.2. (adapted from Study report Table 9-2).

Table 2.6.2. Per protocol primary analysis: Analysis of time to first occurrence of Type 1 event and analysis of change from baseline in 5-point CGI-SS-BP severity score

Event Type	Regression Coefficient for Treatment (SE)[2]	p-value[3]	95% C.I. of Regression Coefficient[2]	HR[2]	95% C.I. for HR[2]
Type 1 event[1]	-0.304 (0.132)	0.0211	--	0.74	0.57, 0.96
5-point CGI-SS-BP severity score	0.007 (0.048)	0.8884	-0.09, 0.10	--	--

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

[2]Refer to detailed statistical analysis plan in Appendix 5.1, §1.1.5.3, for information on calculation of these parameters.

[3]P-value for Type 1 event was generated using a full Cox's proportional hazards regression model; p-value for 5-point CGI-SS-BP severity score was generated using an ANCOVA model

Source: Post-Text Tables 9.1-3 and 9.1-4

P-values are .0211 for Type 1, and .8884 for 5-point CGI-SS-BP, respectively.

2.6.3. Survival analyses

Kaplan-Meier estimates of cumulative probabilities for Type 1 and Type 2 events were estimated for the two treatment groups and are summarized for the ITT population in Table 2.6.3. (adapted from Study report Table 9-4).

Table 2.6.3.1. Kaplan-Meier estimates for the cumulative probability of a Type 1 or Type 2 event by visit (ITT population)

	CLOZARIL (n=490)				ZYPREXA (n=490)				
	n1[2]	N2[3]	Cum Prob	95% C.I.	n1[2]	n2[3]	Cum Prob	95% C.I.	95% C.I. of the difference
Type 1 Event									
Week 0 (Day 0)	490	0	0.00	(0.00, 0.00)	490	0	0.00	(0.00, 0.00)	(0.00, 0.00)
Week 8 (Day 70)	393	43	0.09	(0.09, 0.10)	411	50	0.11	(0.10, 0.11)	(-0.03, 0.05)
Week 24 (Day 182)	346	69	0.16	(0.15, 0.17)	365	81	0.17	(0.16, 0.18)	(-0.03, 0.07)
Week 52 (Day 378	308	91	0.21	(0.20, 0.22)	312	112	0.25	(0.23, 0.26)	(-0.02, 0.09)
Week 80 (Day 574)	277	100	0.23	(0.22, 0.25)	269	126	0.29	(0.27, 0.30)	(-0.01, 0.11)
Week 104 (Day 742)	36	102	0.24	(0.23, 0.25)	40	141	0.32	(0.31, 0.34)	(0.02, 0.14)
Type 2 Event									
Week 0 (Day 0)	490	0	0.00	(0.00, 0.00)	490	0	0.00	(0.00, 0.00)	(0.00, 0.00)
Week 8 (Day 70)	389	47	0.10	(0.10, 0.11)	410	51	0.11	(0.10, 0.11)	(-0.03, 0.04)
Week 24 (Day 182)	334	81	0.18	(0.17, 0.20)	356	90	0.19	(0.18, 0.21)	(-0.04, 0.06)
Week 52 (Day 378	290	109	0.25	(0.24, 0.27)	294	132	0.29	(0.28, 0.31)	(-0.02, 0.10)
Week 80 (Day 574)	261	119	0.28	(0.27, 0.30)	251	150	0.34	(0.32, 0.35)	(0.00, 0.12)
Week 104 (Day 742)	34	120	0.28	(0.27, 0.30)	36	161	0.37	(0.35, 0.38)	(0.02, 0.15)

[1] Kaplan-Meier estimates compute the probability of an event (cumulative). Two weeks were added to the visit week when calculating the actual day, e.g., Visit Week 8 = Day (8+2)x7 = Day 70.
[2] n1 represents number of patients at risk.
[3] n2 represents the number of cumulative events.
Source: Post-Text Table 9.1-2

The log-rank tests give p-values .0195 for Type 1, and .027 for Type 2, respectively.

3. Reviewer's Analysis

The reviewer verified the sponsor's efficacy analyses according to the protocol. In this section, the issues of open-label and censoring, retrieved dropouts, and subgroup will be performed on the ITT population.

3.1. The Issue of Open-Label

Both 7-point CGI-SS and 5-point CGI-SS for the PI and BP will be discussed. The relation between

the number of referred and the number of Type 1 event will also be discussed.

3.1.1. CGI-SS

Table 3.1.1 gives summary information for 5-point CGI-SS (Study report, Appendix 5.3.1 Table 9.3-21). The p-value is calculated from ANOVA with terms for treatment, pooled country, and CGI-SS at baseline. The percentage is calculated using actual number of patients.

Table 3.1.1. Summary for 5-point CGI-SS (LOCF)

	Blinded Psychiatrist (BP)		Principal Investigator (PI)	
At end of study	Clozaril (n=490)	Zyprexa (n=490)	Clozaril (n=490)	Zyprexa (n=490)
n mean change from baseline ± sd	484 -0.812 ± 1.1	481 -0.807 ± 1.1	482 -1.102 ± 1.1	480 -0.983 ± 1.1
p-value	.8708		.2767	
Distribution				
-4	3 (0.62%)	2 (0.42%)	2 (0.41%)	3 (0.63%)
-3	33 (6.24%)	30 (6.82%)	41 (8.51%)	29 (6.04%)
-2	87 (17.98%)	102 (21.21%)	143 (29.67%)	129 (26.88%)
-1	131 (27.07%)	121 (25.16%)	130 (26.97%)	140 (29.17%)
0	214 (44.21%)	201 (41.79%)	154 (31.95%)	158 (32.92%)
1	13 (2.69%)	17 (3.53%)	10 (2.07%)	17 (3.54%)
2	1 (0.21%)	6 (1.25%)	1 (0.21%)	4 (0.83%)
3	0	2 (0.42%)	0	0
4	2 (0.41%)	0	1 (0.21%)	0

Table 3.1.2 gives summary information for 7-point CGI-SS (Study report, Appendix 5.3.1 Table 9.3-15). The p-value is calculated from ANOVA with terms for treatment and pooled country.

Table 3.1.2. Summary for 7-point CGI-SS (LOCF)

	Blinded Psychiatrist (BP)		Principal Investigator (PI)	
At end of study	Clozaril (n=490)	Zyprexa (n=490)	Clozaril (n=490)	Zyprexa (n=490)
n mean ± sd	422 2.64 ± 1.4	440 2.73 ± 1.4	464 2.40 ± 1.3	468 2.54 ± 1.4
p-value	.2803		.0946	
Distribution				
1 = very much improved	125 (29.62%)	123 (27.95%)	170 (36.64%)	155 (33.12%)
2 = much improved	86 (20.38%)	90 (20.45%)	100 (21.55%)	105 (22.44%)
3 = minimally improved	49 (11.61%)	49 (11.14%)	52 (11.21%)	49 (10.47%)
4 = no change	145 (34.36%)	150 (34.09%)	123 (26.51%)	131 (27.99%)
5 = minimally worse	13 (3.08%)	16 (3.64%)	18 (3.88%)	18 (3.85%)
6 = much worse	3 (0.71%)	11 (2.5%)	1 (0.22%)	7 (1.5%)
7 = very much worse	1 (0.24%)	1 (0.23%)	0	3 (0.64%)

Since p-values for the PI are always smaller than that for the BP, this indicates that the PI might have bias favoring Clozaril.

3.1.2. Number of Referred (PI) and Event (SMB)

If there is a completed suicide, suicide attempt, or hospitalization for imminent risk of suicide, it is the PI who will prepare a brief narrative, complete SAF or IRH, and report to the SMB through WCT.

The Type 1 event is determined by the SMB but it is the PI who determines who should be referred to the SMB. There are 122 patients in Clozaril and 157 patients in Zyprexa, respectively, who were referred to the SMB. The difference between the number of referred patients is 35. However, there are 102 patients in Clozaril and 141 patients in Zyprexa, respectively, who were judged by the SMB as the Type 1 event. The difference of the number of Type 1 event is 39. It is also noted that the correlation between the number of referred and the number of event is high. Based on the above, it is seen that the less referred will have the less Type 1 event, or the number of event is determined by the number of referred.

A patient might be referred multiple times. 122 patients in Clozaril were referred 261 times, in which 217 times were judged by the SMB as Type 1 event, and 44 times were not. 157 patients in Zyprexa were referred 316 times, in which 266 times were judged by the SMB as Type 1 event, and 50 times were not.

The above analyses indicate that if the PI might have bias favoring Clozaril and the PI's referral determines the number of event, then the open-label does introduce the bias.

3.2. The Issue of Censoring

The time to treatment failure (TTF) and time to lost to follow-up will be discussed.

3.2.1. Time to Treatment Failure

The time to treatment failure (TTF) is defined from date of randomization until the date that a patient withdrew (failed or censored) from the study. A patient who completed the study will be censored at the end of study.

For Type 1, there are 454 failed and 36 completed in Clozaril, and 450 failed and 40 completed in Zyprexa, respectively. The log-rank test for TTF gives p-value .6845. The survival probabilities from the KM estimates at 104 weeks are .0735 for Clozaril and .0816 for Zyprexa, respectively.

For Type 2, there are 456 failed and 34 completed in Clozaril, and 454 failed and 36 completed in

Zyprexa, respectively. The log-rank test for TTF gives p-value .7877. The survival probabilities from the KM estimates at 104 weeks are .0694 for Clozaril and .0735 for Zyprexa, respectively.

3.2.2. Lost to follow-up

For Type 1, lost to follow-up are 33 (8 failed and 25 censored) in Clozaril, and 39 (13 failed and 26 censored) in Zyprexa, respectively. Table 3.2.2.1 gives number of failed, censored, and mean and standard deviation of the primary efficacy variable TIMETO (time to event).

Table 3.2.2.1 Lost to Follow-up

Type=1	Clozaril (n=33)	TIMETO Mean (sd)	Zyprexa (n=39)	TIMETO Mean (sd)
failed	8	97 (101)	13	163 (198)
censored	25	169 (233)	26	241 (226)

After counting the censored in the lost to follow-up as failed, there are 127 failed, 327 censored, and 36 completed in Clozaril, and 167 failed, 283 censored, and 40 completed in Zyprexa, respectively. The log-rank test gives p-value .031. The survival probabilities from the KM estimates at 104 weeks are .6985 for Clozaril and .6296 for Zyprexa, respectively.

For Type 2, after counting the censored in the lost to follow-up as failed, there are 145 failed, 311 censored, and 34 completed in Clozaril, and 187 failed, 267 censored, and 36 completed in Zyprexa, respectively. The log-rank test gives p-value .0387. The survival probabilities from the KM estimates at 104 weeks are .6571 for Clozaril and .5859 for Zyprexa, respectively.

3.3. Retrieved Dropout

The sponsor used the retrieved dropout (RDO) assessment in defining ITT. The retrieved dropout assessments were made on patients who withdrawn prematurely from the study, and were collected and recorded in the Retrieved Drop Out CRF Booklet. It is possible that a patient might not be still on the treatment between the withdrawn date and the retrieved date.

For Type 1, there are 61 in Clozaril and 60 in Zyprexa, respectively, who are identified as RDO. Table 3.3.1 gives mean and standard deviation of TIMETO and DUREOS (end of study duration days).

Table 3.3.1. Retrieved Dropout

Type=1	Clozaril (n=61)	TIMETO Mean (sd)	DUREOS Mean (sd)	Zyprexa (n=60)	TIMETO Mean (sd)	DUREOS Mean (sd)
failed	20	176 (175)	145 (153)	25	143 (162)	266 (250)
censored	33	553 (204)	134 (143)	24	558 (224)	142 (165)
completed	8	765 (22)	372 (286)	11	764 (18)	214 (199)

If the end of study date is used instead of the retrieved date, then the smaller of TIMETO and DUREOS will be used as the time to event. Furthermore, if a failed patient's TIMETO were greater than DUREOS, then the patient would be classified as censored.

There are 12 failed in Clozaril and 3 failed in Zyprexa, respectively, whose TIMETO are greater than DUREOS. After counting those 12 failed and 8 completed in Clozaril and 3 failed and 11 completed in Zyprexa as censored, respectively, and using the smaller of TIMETO and DUREOS as the time to event, Table 3.3.2 gives summary information.

Table 3.3.2. DUREOS

Type=1	Clozaril (n=61)	TIMETO Mean (sd)	DUREOS Mean (sd)	Zyprexa (n=60)	TIMETO Mean (sd)	DUREOS Mean (sd)
failed	8	62 (50)	225 (186)	22	120 (139)	294 (254)
censored	53	161 (185)	161 (185)	38	156 (172)	156 (172)
completed	0			0		

Using Table 3.3.2, there are 90 failed, 372 censored, and 28 completed in Clozaril, and 138 failed, 323 censored, and 29 completed in Zyprexa, respectively. The log-rank test gives p-value .0035. The survival probabilities from the KM estimates at 104 weeks are .7749 for Clozaril and .6689 for Zyprexa, respectively.

For Type 2, Table 3.3.3 gives the similar information as Table 3.3.1.

Table 3.3.3. Retrieved Dropout

Type=2	Clozaril (n=61)	TIMETO Mean (sd)	DUREOS Mean (sd)	Zyprexa (n=60)	TIMETO Mean (sd)	DUREOS Mean (sd)
failed	20	176 (175)	145 (153)	27	137 (153)	263 (241)
censored	33	553 (204)	134 (143)	22	561 (225)	135 (171)
completed	8	765 (22)	372 (286)	11	764 (18)	214 (199)

Table 3.3.4 gives the similar information as Table 3.3.2.

Table 3.3.4. DUREOS

Type=2	Clozaril (n=61)	TIMETO Mean (sd)	DUREOS Mean (sd)	Zyprexa (n=60)	TIMETO Mean (sd)	DUREOS Mean (sd)
failed	8	62 (50)	225 (186)	24	115 (128)	288 (244)
censored	53	161 (185)	161 (185)	36	153 (176)	153 (176)
completed	0			0		

Using Table 3.3.4, there are 108 failed, 356 censored, and 26 completed in Clozaril, and 158 failed, 306 censored, and 25 completed in Zyprexa, respectively. The log-rank test gives p-value .0069. The survival probabilities from the KM estimates at 104 weeks are .7276 for Clozaril and .6212 for Zyprexa, respectively.

Based on the above analyses, RDO analysis doesn't show bias favoring Clozaril but one needs to consider the labeling if patients might not be still on the treatment between EOS and RDO.

3.4. Subgroup Analyses

Analyses on gender, age, region, and diagnosis group will be performed.

3.4.1. Gender

For Type 1, there are 301 males (66 failed, 217 censored, and 18 completed) in Clozaril, and 301 males (92 failed, 187 censored, and 22 completed) in Zyprexa, respectively. The log-rank test gives p-value .0576. The survival probabilities from the KM estimates at 104 weeks are .7434 for Clozaril and .6521 for Zyprexa, respectively.

For Type 1, there are 189 females (36 failed, 135 censored, and 18 completed) in Clozaril, and 189 females (49 failed, 122 censored, and 18 completed) in Zyprexa, respectively. The log-rank test gives p-value .1736. The survival probabilities from the KM estimates at 104 weeks are .7857 for Clozaril and .7176 for Zyprexa, respectively.

For Type 2, there are 301 males (78 failed, 207 censored, and 16 completed) in Clozaril, and 301 males (105 failed, 175 censored, and 21 completed) in Zyprexa, respectively. The log-rank test gives p-value .0742. The survival probabilities from the KM estimates at 104 weeks are .6951 for Clozaril and .604 for Zyprexa, respectively.

For Type 2, there are 189 females (42 failed, 129 censored, and 18 completed) in Clozaril, and 189 females (56 failed, 118 censored, and 15 completed) in Zyprexa, respectively. The log-rank test gives p-value .1903. The survival probabilities from the KM estimates at 104 weeks are .75 for Clozaril and .6775 for Zyprexa, respectively.

3.4.2. Age

For Type 1 in age group 18-32, there are 168 (35 failed, 120 censored, and 13 completed) in Clozaril, and 178 (54 failed, 109 censored, and 15 completed) in Zyprexa, respectively. The log-rank test gives p-value .111. The survival probabilities from the KM estimates at 104 weeks are .7589 for Clozaril and .6633 for Zyprexa, respectively.

For Type 1 in age group 33-44, there are 216 (46 failed, 153 censored, and 17 completed) in Clozaril, and 204 (59 failed, 128 censored, and 17 completed) in Zyprexa, respectively. The log-rank test gives p-value .2061. The survival probabilities from the KM estimates at 104 weeks are .7493 for Clozaril and .6804 for Zyprexa, respectively.

For Type 1 in age group ≥ 45, there are 106 (21 failed, 79 censored, and 6 completed) in Clozaril, and 108 (28 failed, 72 censored, and 8 completed) in Zyprexa, respectively. The log-rank test gives p-value .2391. The survival probabilities from the KM estimates at 104 weeks are .7826 for Clozaril and .6975 for Zyprexa, respectively.

For Type 2 in age group 18-32, there are 168 (40 failed, 116 censored, and 12 completed) in Clozaril, and 178 (63 failed, 102 censored, and 13 completed) in Zyprexa, respectively. The log-rank test gives p-value .0631. The survival probabilities from the KM estimates at 104 weeks are .7218 for Clozaril and .6066 for Zyprexa, respectively.

For Type 2 in age group 33-44, there are 216 (54 failed, 145 censored, and 17 completed) in Clozaril, and 204 (66 failed, 122 censored, and 16 completed) in Zyprexa, respectively. The log-rank test gives p-value .3096. The survival probabilities from the KM estimates at 104 weeks are .706 for Clozaril and .6419 for Zyprexa, respectively.

For Type 2 in age group ≥ 45, there are 106 (26 failed, 75 censored, and 5 completed) in Clozaril, and 108 (32 failed, 69 censored, and 7 completed) in Zyprexa, respectively. The log-rank test gives p-value .369. The survival probabilities from the KM estimates at 104 weeks are .7303 for Clozaril and .6588 for Zyprexa, respectively.

3.4.3. Region

Six pooled regions will be discussed: U.S. & Canada, U.K. & South Africa, France & Italy, Hungary, Croatia & Czech Republic, and Argentina & Chile. Except France & Italy, the survival probabilities from the KM estimates at 104 weeks for both Type 1 and Type 2 for Clozaril are greater than that for Zyprexa.

For Type 1 in U.S. & Canada, there are 208 (62 failed, 135 censored, and 11 completed) in Clozaril, and 207 (83 failed, 111 censored, and 13 completed) in Zyprexa, respectively. The log-rank test gives p-value .1367. The survival probabilities from the KM estimates at 104 weeks are .6273 for

Clozaril and .5247 for Zyprexa, respectively.

For Type 1 in U.K. & South Africa, there are 74 (8 failed, 60 censored, and 6 completed) in Clozaril, and 74 (15 failed, 55 censored, and 4 completed) in Zyprexa, respectively. The log-rank test gives p-value .0892. The survival probabilities from the KM estimates at 104 weeks are .8782 for Clozaril and .7681 for Zyprexa, respectively.

For Type 1 in France & Italy, there are 63 (16 failed, 43 censored, and 4 completed) in Clozaril, and 62 (13 failed, 39 censored, and 10 completed) in Zyprexa, respectively. The log-rank test gives p-value .2867. The survival probabilities from the KM estimates at 104 weeks are .7081 for Clozaril and .7783 for Zyprexa, respectively.

For Type 1 in Hungary, there are 49 (4 failed, 42 censored, and 3 completed) in Clozaril, and 50 (9 failed, 39 censored, and 2 completed) in Zyprexa, respectively. The log-rank test gives p-value .1897. The survival probabilities from the KM estimates at 104 weeks are .9112 for Clozaril and .8064 for Zyprexa, respectively.

For Type 1 in Croatia & Czech Republic, there are 48 (10 failed, 33 censored, and 5 completed) in Clozaril, and 52 (12 failed, 34 censored, and 6 completed) in Zyprexa, respectively. The log-rank test gives p-value .8545. The survival probabilities from the KM estimates at 104 weeks are .77 for Clozaril and .7587 for Zyprexa, respectively.

For Type 1 in Argentina & Chile, there are 48 (2 failed, 39 censored, and 7 completed) in Clozaril, and 45 (9 failed, 31 censored, and 5 completed) in Zyprexa, respectively. The log-rank test gives p-value .0192. The survival probabilities from the KM estimates at 104 weeks are .9583 for Clozaril and .7875 for Zyprexa, respectively.

For Type 2 in U.S. & Canada, there are 208 (66 failed, 131 censored, and 11 completed) in Clozaril, and 207 (91 failed, 104 censored, and 12 completed) in Zyprexa, respectively. The log-rank test gives p-value .0799. The survival probabilities from the KM estimates at 104 weeks are .6029 for Clozaril and .4788 for Zyprexa, respectively.

For Type 2 in U.K. & South Africa, there are 74 (12 failed, 56 censored, and 6 completed) in Clozaril, and 74 (18 failed, 52 censored, and 4 completed) in Zyprexa, respectively. The log-rank test gives p-value .1815. The survival probabilities from the KM estimates at 104 weeks are .8221 for Clozaril and .7272 for Zyprexa, respectively.

For Type 2 in France & Italy, there are 63 (19 failed, 40 censored, and 4 completed) in Clozaril, and 62 (19 failed, 35 censored, and 8 completed) in Zyprexa, respectively. The log-rank test gives p-value .5742. The survival probabilities from the KM estimates at 104 weeks are .6504 for Clozaril and .6779 for Zyprexa, respectively.

For Type 2 in Hungary, there are 49 (7 failed, 40 censored, and 2 completed) in Clozaril, and 50 (10 failed, 38 censored, and 2 completed) in Zyprexa, respectively. The log-rank test gives p-value .5689. The survival probabilities from the KM estimates at 104 weeks are .8422 for Clozaril and .7851 for Zyprexa, respectively.

For Type 2 in Croatia & Czech Republic, there are 48 (11 failed, 33 censored, and 4 completed) in Clozaril, and 52 (13 failed, 34 censored, and 5 completed) in Zyprexa, respectively. The log-rank test gives p-value .9035. The survival probabilities from the KM estimates at 104 weeks are .7472 for Clozaril and .7381 for Zyprexa, respectively.

For Type 2 in Argentina & Chile, there are 48 (5 failed, 36 censored, and 7 completed) in Clozaril, and 45 (10 failed, 30 censored, and 5 completed) in Zyprexa, respectively. The log-rank test gives p-value .1199. The survival probabilities from the KM estimates at 104 weeks are .8923 for Clozaril and .7629 for Zyprexa, respectively.

3.4.4. Schizophrenia and Schizoaffective Group

For Type 1 in Schizophrenia group, there are 300 (51 failed, 227 censored, and 22 completed) in Clozaril, and 309 (82 failed, 204 censored, and 23 completed) in Zyprexa, respectively. The log-rank test gives p-value .0153. The survival probabilities from the KM estimates at 104 weeks are .7888 for Clozaril and .6847 for Zyprexa, respectively.

For Type 1 in Schizoaffective group, there are 190 (51 failed, 125 censored, and 14 completed) in Clozaril, and 181 (59 failed, 105 censored, and 17 completed) in Zyprexa, respectively. The log-rank test gives p-value .4121. The survival probabilities from the KM estimates at 104 weeks are .69 for Clozaril and .6282 for Zyprexa, respectively.

For Type 2 in Schizophrenia group, there are 300 (67 failed, 212 censored, and 21 completed) in Clozaril, and 309 (98 failed, 192 censored, and 19 completed) in Zyprexa, respectively. The log-rank test gives p-value .0365. The survival probabilities from the KM estimates at 104 weeks are .7411 for Clozaril and .6487 for Zyprexa, respectively.

For Type 2 in Schizoaffective group, there are 190 (53 failed, 124 censored, and 13 completed) in Clozaril, and 181 (63 failed, 101 censored, and 17 completed) in Zyprexa, respectively. The log-rank test gives p-value .3311. The survival probabilities from the KM estimates at 104 weeks are .6787 for Clozaril and .6053 for Zyprexa, respectively.

4. Conclusion

The key issue is whether there is any bias caused by open-label as the Principal Investigator (PI) is unblinded. P-values on CGI-SS for the PI are always smaller than that for the BP, .0946 for the PI and .2803 for the BP in 7-point CGI-SS, and .2767 for the PI and .8708 for the BP in 5-point CGI-

SS. The difference between p-values indicates that the PI might have bias favoring Clozaril.

The Type 1 event is determined by the SMB but it is the PI who determines who should be referred to the SMB. There are 122 patients in Clozaril and 157 patients in Zyprexa, respectively, who were referred to the SMB. The difference between the number of referred patients is 35. However, there are 102 patients in Clozaril and 141 patients in Zyprexa, respectively, who were judged by the SMB as the Type 1 event. The difference of the number of Type 1 event is 39. It is also noted that the correlation between the number of referred and the number of event is high. Based on the above, it is seen that the less referred will have the less Type 1 event, or the number of event is determined by the number of referred. Consequently this affects the number of censored patients.

In this study, for Type 1 event, there are 102 failed, 352 censored, and 36 completed in Clozaril, and 141 failed, 309 censored, and 40 completed in Zyprexa, respectively. The significance of analysis based on Type 1 event is due to 39, the difference of the number of event. The significance of analysis based on Type 2 event is mainly due to the contribution of Type 1 event because analysis on CGI-SS is not statistically nominally significant.

The conclusion is that although the primary analysis is statistically nominally significant with p-value .0309, one should interpret the result with caution due to the issues discussed in this reivew.

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/s/

Kun He
8/9/02 12:11:18 PM
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Kun Jin
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George Chi
8/21/02 11:58:29 AM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: November 27, 2002

TO: Steven D. Hardeman, Senior Regulatory Project Manager
Gregory M. Dubitsky, M.D., Medical Officer
Thomas P. Laughren, M.D., Team Leader
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Associate Director AEH 1/30/02

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 19-758/SE1-047

APPLICANT: Novartis

DRUG: Clozaril (clozapine) Tablets

THERAPEUTIC CLASSIFICATION: Type P, Priority Review

INDICATION: Reduction of Suicidal Behavior in Schizophrenia or Schizoaffective Disorder

CONSULTATION REQUEST DATE: September 6, 2002

ACTION GOAL DATE: December 20, 2002

I. BACKGROUND:

CLOZARIL® (clozapine) is 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. It is reserved for use in the treatment of severely ill patients with schizophrenia because of a significant risk of agranulocytosis.

In this NDA application, the sponsor has requested the use of clozaril in treatment of suicidality in patients with schizophrenia or schizoaffective disorder. The application was based on results

from a single pivotal study: protocol ABA 451 entitled "A Prospective, Randomized, International, Parallel-Group Comparison of Clozaril/Leponex vs. Zyprexa in the Reduction of Suicidality in Patients with Schizophrenia and Schizoaffective Disorder Who are at Risk for Suicide."

Protocol ABA 451, also known as the InterSePT study, was a prospective, randomized, open-label, blinded-rater, 24-month study, which compared the effects of Clozaril and Zyprexa on suicidality in patients with schizophrenia or schizoaffective disorder. Because less than expected endpoints were occurring, there were several changes in the study including the primary efficacy variable, which was later defined as:

Type 1 Event: Occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance) as confirmed by a Suicide Monitoring Board (SMB).

Type 2 Event: Occurrence of a worsening of severity of suicidality as demonstrated by a score of 6 or 7 (much worse or very much worse) on the change score of the Clinical Global Impression for Severity of Suicidality (CGI-SS-BP), rated by the blinded psychiatrist, or an implicit worsening of severity of suicidality as indicated by the occurrence of a Type 1 event.

The inspection assignments were issued following a consult request from the Review Division (HFD-120) to address the concern that potential bias may exist in the referral of suicide event information to the suicide monitoring board (SMB). The unblinded investigators at each site apparently had the final say regarding whether or not a particular event would be referred to the SMB. These four sites contributed a high rate of non-referral subjects in clozapine group.

II. INSPECTIONAL FINDINGS

The following sites were inspected:

NAME	Center #	Prior Inspection History	Location	Assignment Date	Inspection Dates	Classification
Dr. Simpson	107	NAI (4/02)	Los Angeles, CA	9/6/2002	9/30/02-10/1/02	NAI
Dr. Rapaport	104	None	San Diego, CA	9/6/2002	10/2-10/04/02	EIR pending
Dr. Eisdorfer Dr. Douyon	112	None	Miami, FL	10/15/02	11/6/02-11/7/02	EIR pending
Dr. Seibel Dr. Lowy	111	VAI (01/02) VAI (11/01)	Washington, DC	10/15/02	11/12/02	EIR pending

The Review Division provided a list of non-referral subjects for each site (see attached).

An audit of the source documents for a total of 33 subjects from clozapine group for whom events were not referred at these sites was conducted. The purpose was to identify any missed suicide events and to determine whether or not potential events were differentially ignored for subjects assigned to clozapine. The inspection focused on type I events defined as occurrence of

a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance) as confirmed by the SMB.

Source documents included history and physical examinations, progress notes by the unblinded investigators/study coordinators, CGI-suicide rating scales etc. and the case report forms. In addition to these study visit notes, hospital notes including nursing, group therapy and physician assessments were reviewed when applicable (eg. ER visits, inpatient hospitalization).

I note that one subject (0003) at center 111, was reported as lost to follow up at week 100 visit. The site was able to contact the subject approximately two months later for a follow up visit. The subject reportedly was evaluated at the St. Elizabeth Hospital 2 weeks prior to that visit. However, the PI wrote a memo to the file that the site was unable to obtain the hospital record. It was, therefore, not available for my review to determine if there was any missed event.

Regarding the source documents for subject 0024 at Center 107, the initial assessment and psychiatric progress notes for visits 1 and 2 were missing. However, the subject's other source documents for visits 1 and 2, including psychiatric rating scales and laboratory reports, along with the case report forms, were present. Dr. Simpson agreed that those records were missing and offered an acceptable reason. No Form FDA 483 was issued. The subject was given one week supply of 12.5 mg bid dose of clozapine but he did not return for the clinic visits. The subject was discontinued from the study and reported as lost to follow up on day 14.

Based on my review of these 33 subjects' source documents, I did not observe any underreporting of occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk including increased level of surveillance.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the four study sites that were inspected, I did not observe any unreported occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk including increased level of surveillance, based on my limited review of these 33 subjects' source documents. However, I would mention several limitations, which may be an issue in finding missed suicide events during the inspections: non-reporting of event by subjects; non-recording of event by the unblinded investigator in the source documents and limited sampling. The Review Division should take these caveats into consideration, whether or not these would have any impact on primary efficacy outcome measure. Overall, I recommend that data from these centers that had been inspected appear acceptable for use in support of this NDA.

[Note: The EIRs of Drs. Rapaport, Eisdorfer and Seibel are still pending. Should the EIR and exhibits from the audit, when received, contain additional information that would significantly effect the classification or have an impact on the acceptability of the data, we will inform the review division accordingly.]

List of the subjects' records reviewed:

P.I.	Center Number	# subjects in Clozaril group	# non-referrals (rate %)	Subject Number
Dr. George Simpson Los Angeles, CA	107	14	12 (84%)	ABA-451-107-0005 ABA-451-107-0007 ABA-451-107-0008 ABA-451-107-0011 ABA-451-107-0013 ABA-451-107-0018 ABA-451-107-0020 ABA-451-107-0021 ABA-451-107-0023 ABA-451-107-0024 ABA-451-107-0027 ABA-451-107-0029
Dr. Mark Rapaport San Diego, CA	104	10	10 (100%)	ABA-451-104-0003 ABA-451-104-0005 ABA-451-104-0007 ABA-451-104-0009 ABA-451-104-0010 ABA-451-104-0014 ABA-451-104-0016 ABA-451-104-0017 ABA-451-104-0019 ABA-451-104-0020
Dr. Carl Eisdorfer Dr. Richard Douyon Miami, FL	112	9	7 (77%)	ABA-451-112-0010 ABA-451-112-0016 ABA-451-112-0020 ABA-451-112-0006 ABA-451-112-0007 ABA-451-112-0015 ABA-451-112-0018
Dr. Philip Seibel Dr. Adam Lowy Washington DC	111	4	4 (100%)	ABA-451-111-0001 ABA-451-111-0003 ABA-451-111-0008 ABA-451-111-0009

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: August 5, 2002

TO: Steven D. Hardeman, Senior Regulatory Project Manager
Gregory M. Dubitsky, M.D., Medical Officer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Associate Director

FROM: Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 19-758/SE1-047

APPLICANT: Novartis

DRUG: Clozaril (clozapine) Tablets

THERAPEUTIC CLASSIFICATION: Type P, Priority Review

INDICATION: Treatment of Suicidality in Schizophrenia or Schizoaffective Disorder

CONSULTATION REQUEST DATE: April 3, 2002

ACTION GOAL DATE: September 1, 2002

I. BACKGROUND:

CLOZARIL® (clozapine) is 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. It is reserved for use in the treatment of severely ill patients with schizophrenia because of a significant risk of agranulocytosis.

In this NDA application, the sponsor has requested the use of clozaril in treatment of suicidality in patients with schizophrenia or schizoaffective disorder. The application was based on results from a single pivotal study: protocol ABA 451 entitled "A Prospective, Randomized, International, Parallel-Group Comparison of Clozaril/Leponex vs. Zyprexa in the Reduction of

Suicidality in Patients with Schizophrenia and Schizoaffective Disorder Who are at Risk for Suicide."

Protocol ABA 451, also known as the InterSePT study, was a prospective, randomized, open-label, blinded-rater, 24-month study, which compared the effects of Clozaril and Zyprexa on suicidality in patients with schizophrenia or schizoaffective disorder. Because less than expected endpoints were occurring, there were several changes in the study including the primary efficacy variable, which was later defined as:

Type 1 Event: Occurrence of a significant suicide attempt or hospitalization due to imminent suicide risk (including increased level of surveillance) as confirmed by a Suicide Monitoring Board (SMB).

Type 2 Event: Occurrence of a worsening of severity of suicidality as demonstrated by a score of 6 or 7 (much worse or very much worse) on the change score of the Clinical Global Impression for Severity of Suicidality (CGI-SS-BP), rated by the blinded psychiatrist, or an implicit worsening of severity of suicidality as indicated by the occurrence of a Type 1 event.

Inspection assignment was issued in April, 2002 for 2 domestic sites: Drs. Iqbal and Simpson; and 2 non-U.S. sites: Drs. Martin and Dr. Larach, because these investigators enrolled a large number of subjects in the study.

II. RESULTS (by site):

NAME	Center #	Location	ASSIGNED DATE	EIR RECEIVED DATE	CLASSIFICATION
Dr. Larach	956	Santiago, Chile	04-09-2002	07-12-2002	NAI
Dr. Martin	302	Sunderland, U.K.	04-09-2002	07-12-2002	VAI*
Dr. Iqbal	125	Bronx, NY	04-25-2002	pending	VAI**
Dr. Simpson	107	Los Angeles, CA	04-25-2002	05-30-2002	NAI

*Final classification pending; the draft letters are currently with Office of General Counsel (GC) for review.

**Final classification pending; review based on Form FDA 483.

LARACH, M.D.

At this clinical site, 33 subjects were randomized to receive either Clozaril/Leponex or Zyprexa. During the 24-month study, only 1 subject discontinued. The reason for discontinuation was listed as lost to follow up.

Inspectional findings: 1) recording the date on suicide event form (blinded psychiatrist) several months after the event for 2 subjects (#3 and 7). Dr. Larach responded that the blinded psychiatrist did not date the form at the time of evaluation and she dated the form the day when the issue was brought into her attention; 2) Subject 13 experienced nausea, vomiting and

constipation, which were not reported in the CRF.

We note that 6 subjects (#11, 12, 17, 20, 21 and 30) were chronically institutionalized and 1 subject (#31) was periodically institutionalized throughout the study.

All subjects signed the consent form. Limitation to the inspection: all the source documents were in Spanish. Data appear acceptable.

MARTIN, M.D.

Fifty subjects were randomized to receive either Clozaril/Leponex or Zyprexa. During the 24-month study, 15 subjects discontinued: 7 subjects from Clozaril group and 8 subjects from Zyprexa group. Reasons for discontinuation included death, adverse event, protocol violation (1 subject) and withdrawal of consent.

There were 3 deaths reported at this site: arrhythmia for subject 0010 from Clozaril group, myocardial infarction for subject 0007 and oesophageal carcinoma for subject 0012 from Zyprexa group. One discrepancy was the date of death of subject 0012. It was recorded as the subject died on [redacted] in data listing, but was shown as [redacted] in the source documents and case report form. [redacted] was the date of endoscopy that found a malignant lesion. b(6)

Inspectional findings: 1) the first two subjects were enrolled prior to obtaining written IRB approval; 2) a psychiatrist performed blinded ratings for the first year of the study but after she left in mid-1999, the blinded ratings were done by a psychiatric nurse. The sponsor's concurrence was documented in writing as a telephone contract report signed by the CRO, dated July 22, 1999 that Dr. (b) (6) from the sponsor was informed about the situation on June 15 and Dr. (b) (6) recommended that the senior staff nurse completed the full training program.

All subjects signed the consent form. Overall, data appear acceptable.

IQBAL, M.D.

The inspection revealed that the Clinical Global Impression for Severity of Suicidality by Blinded Psychiatrist (CGI-SS-BP) were not completed for 3 subjects: subject #004 ([redacted]) at week 8 visit; subject #012 ([redacted]) at week 8, 16, 24, 60 and 68 visits; and subject #018 ([redacted]) at week 68 visit. b(6)

According to the protocol, dispensing of Clozaril was contingent upon performance of the required blood tests. The study drug Clozaril®/Leponex® was dispensed prematurely to three study subjects. Specifically, Subjects #007 ([redacted]), #015 ([redacted]), and #018 ([redacted]) were dispensed Clozaril at baseline visits, prior to the determination of the subjects' WBC counts. b(6)

Serious adverse event (SAE) was not reported to the IRB in a timely manner. Specifically, a report to the IRB dated October 5, 2000, included seven SAEs which had "start dates" during 1998 (all reported over one year late). For example, subject #003 (; was hospitalized for suicidal ideations on A report of this SAE was not filed with the sponsor until 4/5/99, and was not reported to the IRB until 10/5/00. The clinical investigator (CI) did not use current versions of informed consent for 5 subjects [# 011 , 013 , 015 , 017 , and 018] in obtaining consent prior to enrollment. b(6)

SIMPSON, M.D.

At this clinical site, 30 subjects were screened, 2 subjects failed to qualify and 28 subjects were randomized to receive either Clozaril/Leponex or Zyprexa. During the 24-month study, 11 subjects discontinued. Reasons for discontinuation included lost to follow-up and withdrawal of consent. There were no deaths or serious adverse events, related to the study drug, reported in this study.

An audit of 14 records was performed. No major objectionable conditions noted. All subjects signed the consent form. Data seem acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

For the four study sites that were inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, that all enrolled subjects received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocols and amendments. Instances of minor deviations from protocol, delay in serious adverse event reporting to the IRB and informed consent issues were found at some of the sites as stated above, which were not of clinical significance to require exclusion of any subject from data analysis.

Thus, I recommend that data from these centers that had been inspected appear acceptable for use in support of this NDA. However, I note that the protocol did not seem to address the cultural perspective on suicide; adverse event profile of study medications, particularly, hypersalivation from Clozaril which may effect the blinding; and the fact that subjects were allowed to be on multiple psychotropic medication. The Review Division should take these caveats into consideration whether or not these would have any impact on primary efficacy outcome measure.

There was limitation to the inspection at Dr. Larach's site as all the source documents were in Spanish.

[Note: The review and evaluation of Dr. Iqbal's audit was based on the FDA Investigator's Form FDA 483 inspectional observation. Should the EIR and exhibits from the audit, when received, contain additional information that would significantly effect the classification or have an impact on the acceptability of the data, we will inform the review division accordingly.]

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

cc:
NDA 19-758/SE1-047
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/c/r/s
HFD-47/Khin
HFD-47/Friend
HFD-45/RF

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/s/

Ni Aye Khin
8/5/02 04:35:44 PM
MEDICAL OFFICER

Khin U
8/5/02 04:44:15 PM
MEDICAL OFFICER
Concur with the Clinical Inspection Summary. Signed on behalf of Tony El-Hage in his absence.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-758/S047

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 19-758 **SUPPL #** 047

Trade Name Clozaril **Generic Name** Clozapine

Applicant Name Novartis **HFD-** 120

Approval Date 12/18/02

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /✓/

   b) Is it an effectiveness supplement? YES /✓/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /✓/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /✓/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /✓/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-758 Clozaril (clozapine)

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

N/A

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # N/A _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # ABA451

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /✓/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # ABA 451

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [redacted] YES /✓/ ! NO /___/ Explain: _____

_____ b(4)

_____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

Signature of Preparer
Title: Regulatory Project Manager

8/23/02
Date

Signature of Office or Division Director

9/4/02
Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

~~NDA/BLA #:~~	~~19-758~~
Supplement Type (e.g. SE5):	**Type 6 "P"**
Supplement Number:	**047**
Stamp Date:	**3/1/02**
Action Date:	**12/30/02 (due date)**
Division:	**HFD-120**
Trade/generic name/dosage form:	**Clozaril (clozapine) Tablets**
Applicant:	**Novartis Pharmaceuticals Corp.**
Therapeutic Class:	**2020200 Antipsychotic**

Indication(s) previously approved: **Treatment Resistant Schizophrenia**

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): **One**

Indication #1: **Treatment of patients with schizophrenia or schizoaffective disorder at risk for emergent suicidal behavior**

Is there a full waiver for this indication (check one)?

- ■ Yes: Please proceed to Section A.
- □ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ Products in this class for this indication have been studied/labeled for pediatric population
- ❑ Disease/condition does not exist in children
- ❑ Too few children with disease to study
- ■ There are safety concerns
- ❑ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-758/S-047

PRIOR APPROVAL SUPPLEMENT

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

Dear Dr. Rawls:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Clozaril (clozapine) tablets

NDA Number: 19-758

Supplement Number: S-047

Review Priority Classification: Priority (P)

Date of Supplement: February 28, 2002

Date of Receipt: March 1, 2002

This supplement provides for the use of Clozaril for the treatment of suicidality in patients with schizophrenia or schizoaffective disorder.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 30, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 1, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

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

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Steve Hardeman
3/27/02 11:16:42 AM
Signed for John Purvis

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 5, 2001
TIME: 0830
LOCATION: Woodmont II, Rm 4028
APPLICATION: IND — / Clozaril (clozapine)
TYPE OF MEETING: Pre-sNDA
MEETING CHAIR: Russell Katz, M.D.
MEETING RECORDER: Steve Hardeman, R.Ph.

b(4)

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Russell Katz, M.D.	Director	DNDP / HFD-120
2. Tom Laughren, M.D.	Team Leader, Psychopharm	Same
3. Greg Dubitsky, M.D.	Medical Reviewer	Same
4. Steve Hardeman, R.Ph.	Regulatory Project Manager	Same
5. Kun Jin, Ph.D.	Team Leader	Biometrics / HFD-710
6. George Chi, Ph.D.	Director	Same

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. ———	Clinical Research	Novartis
2. James Rawls, Pharm.D.	Drug Regulatory Affairs	Same
3. Roy Dodsworth	Drug Regulatory Affairs	Same
4. Zahur Islam, Ph.D.	Statistician, Medical Affairs	Same
5. ———	Statistician, Clinical Research	Same

b(6)

BACKGROUND: The purpose of this meeting was to discuss data from Study ABA 451 (International Suicide Prevention Trial). Based on this trial, a supplemental new drug application for the use of Clozaril (clozapine) in the treatment of suicidality in schizophrenia patients will be submitted.

DISCUSSION:

Dr. Katz began the meeting by stating that, based on the preliminary results contained in the Novartis submission of August 22, 2001, study ABA451 (AKA the International Suicide Prevention Trial or InterSePT) demonstrated that clozapine was efficacious in reducing suicidality relative to olanzapine. We were reassured by the fact that this finding was borne out using both the analysis methodology we had recommended (the WLW method with a fixed c value of 0.5 and using the expanded definition of Type II events) and, for Type I events, using the analysis originally proposed (Cox regression model with a number of covariates). The Novartis statistician added that the original analysis of Type I events

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without covariate adjustment yielded a p value of 0.019.

We suggested that the primary analysis for purposes of the study report should be based on the WLW method with c fixed at 0.5 and the expanded definition for Type II events. Other analyses should be provided as supplementary.

Novartis was informed that the review of this sNDA would likely be given priority status and that it would be taken to the Psychopharmacological Drugs Advisory Committee (PDAC). Given these two factors, time will be of the essence and we requested that they submit available data prior to the formal sNDA submission to permit commencement of the review process as soon as possible.

Questions to the PDAC will focus on: 1) a general discussion of the claim for reducing suicidality and 2) an examination of study ABA451 as well as other supporting data such as the ERI mortality study conducted in the mid-1990's and investigations published in the literature.

The content of the sNDA was discussed with Novartis. We indicated that an ISS and ISE would not be warranted since the sNDA would focus mainly on study ABA451. We reiterated that all sources of relevant efficacy data should be presented; however, safety data from only study ABA451 was required. Novartis agreed and stated that the results of a literature search would be included.

They also said that about 1500 serious adverse events (SAE's) occurred in the course of this trial; many, however, consisted of hospitalization due to suicidality or due to worsening of the underlying psychiatric illness. Since the case report forms (CRF's) for these patients are quite voluminous, we agreed that CRF's and narrative summaries for all patients with SAE's would not be required. Instead, we requested that they send us an advance listing of all SAE's from which we would determine which cases warranted a full complement of clinical data.

Additionally, we asked that they send us, in advance of the sNDA, a listing of patients with Type I or Type II events from which we would randomly select cases for auditing with respect to suicidality assessments. This listing could be provided to us under either blinded or unblinded conditions. It should be accompanied by a detailed description of the methodology for suicidality evaluation of patients in the study, to include who was unblinded and how investigators and raters interfaced with the Suicide Monitoring Board (SMB).

Novartis indicated that a draft study report for ABA451, to include SAS datasets, could be ready for submission in a month. It would likely take another 2-3 months beyond that for formal submission of the sNDA.

Dr. Katz inquired about the possibility that updated information on the frequency of white blood cell (WBC) count monitoring might be ready for presentation to the PDAC at the same time as the suicidality question. Admittedly, these two issues are independent and this is actually a matter of convenience. Novartis indicated that preparing this update would likely require considerable time and effort. A proposal for data analysis and presentation is planned for submission in the next 1-2 months. It seemed doubtful that the two issues could be presented at the same PDAC meeting.

In addition, on a separate issue, Dr. Katz asked about the status of the Novartis response to our request for prominent labeling of the risk of myocarditis with clozapine. The sponsor answered that they would provide a response, to include an "expert report" and a draft "Dear Doctor" letter, by the 60 day deadline (September 24, 2001). We said that this issue would not need to be addressed specifically in the report of study ABA451.

Novartis queried us about the scope of the patient population targeted by the labeling change supported by this sNDA. We answered that since both refractory and non-refractory patients were enrolled in this study, the added indication would probably be broadened to include all schizophrenic patients, not just refractory patients.

The meeting was adjourned.

Clinical Action Items

Novartis will provide us with the following:

1) A draft of the study report for ABA451 2-3 months in advance of their sNDA submission.
2) A listing of all SAE's as soon as possible.
3) A listing of all patients with Type I or Type II events as soon as possible.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
9/6/01 10:52:04 AM

Transcript available at:

http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3908T1.htm