

MEMORANDUM

**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.
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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 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 Intersect 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 database 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.

-SMB Referrals and Type 1 Designations:

-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=157 patients)

-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=141 patients)

-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 ≥ 1 Type 1 events:

-Clozapine n=102 (out of n=122 referred as possibly having ≥ 1 Type 1 events)

-Olanzapine n=141 (out of n=157 referred as possibly having ≥ 1 Type 1 events)

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

<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):

<u>Event Type</u>	<u>Clozapine</u>	<u>Olanzapine</u>	<u>Log-Rank P-Value</u>
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 retrieved 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 inadvertently 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:

<u>Clozapine</u>	<u>Olanzapine</u>	<u>Difference</u>
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# 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 referrals 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 Type 1 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 451 raised 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

**This is a representation of an electronic record that was signed electronically and
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/s/

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