

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.

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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
Retrieved 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 Retrieved 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.

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/s/

Russell Katz
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