Final Minutes: November 4, 2002
Psychopharmacological Drugs Advisory Committee

Issue: Clozaril® (clozapine, Novartis Pharmaceuticals Corporation) proposed for the treatment of suicidality in patients with Schizophrenia and Schizoaffective disorder

The meeting was held at the Holiday Inn in Gaithersburg, Maryland. Prior to the meeting, the members and consultants had reviewed background material from the FDA and from Novartis. There were approximately 130 persons in attendance.

Attendance:
PDAC Members Present: Dan Oren, M.D., Acting Chair, Richard P. Malone, M.D. (**Non -voting)**, Irene Ortiz, M.D., Matthew Rudorfer, M.D.,

PDAC Members Absent
Tana Grady-Weliky, M.D.

PDAC Consultants Present:
Edwin Cook, M.D., Robert Hamer, Ph.D., Neal Ryan M.D., Andrew Winokur, M.D., Ph.D., Jean Bronstein, Consumer Representative, Philip S. Wang, M.D., Dr.P.H.

Industry Representative (Non-voting)
Dilip J. Mehta, M.D., Ph.D.

FDA Participants: Russell Katz, M.D, Thomas Laughren, M.D.,

FDA Overview:
Russell Katz, M.D., welcomed the committee and consultants and outlined the goals for the day. Thomas Laughren, M.D., highlighted the issues that the Agency was asking the committee to address.

Overview of Novartis Presentations:

Introduction
Roy W. Dodsworth, Executive Director, Drug Regulatory Affairs, Novartis

Overview of Suicidal Behavior
Herbert Y. Meltzer, M.D., Bixler Professor, Psychiatry and Pharmacology, Vanderbilt University

InterSePT Study
Rocco Zaninelli, M.D., Executive Director, Clinical Research, Novartis

Suicide Monitoring Board
K Ranga Rama Krishnan, M.B, Ch.B., Professor, Psychiatry and Behavioral Sciences, Duke

Benefit/Risk
John M. Kane, M.D., Chairman, Department of Psychiatry, Long Island Jewish Medical Center

FDA Presentation

Clinical inspection Summary

Ni Khin, M.D., Division of Scientific Investigations

Open Public Hearing Participants

James McNulty, NAMI

David Goldman, M.D., private citizen's comments

Discussion Issues:

There was an ongoing dialogue between the committee members and the sponsor on the following questions. The transcript is far more accurate than any comments provided below:

1. Potential bias in referral of events to the safety monitoring board

The selection of cases could have been biased. For the Clozaril subjects 268 were not referred in contrast to 233 for Zyprexa. And for those referred there were 115 Clozaril subjects in contrast to 164 for Zyprexa.

Other forms of bias/problems were discussed.

There were 68 psychiatrists in the study and thus there was a higher potential to lose the blind.

Rating scale refers to the week before the visit.

No training to psychiatrists on how to evaluate entry criteria

The monitor was unblinded and could refer independently

No structured interview and so no standardization on diagnosis.

Psychiatrist could decide on appropriate dose.

Psychiatrist decided concomitant drugs

Concomitant drugs could make it worse and not have anything to do with clozaril (since more concomitant drugs were given to olanzapine subjects)

Hard to know how to interpret – maybe olanzapine makes suicide worse, instead of clozaril making it less likely to occur

Type 2 is mostly composed of type 1 events

Since some patients had blood draws and others did not, it is possible that subjects talked to their doctor about this and caused the blind to be broken.

No evaluation of appropriateness of diagnosis that were made

No data on how or if the sponsor checked source documents to validate data accuracy

2. Claim focusing on suicidality in schizophrenia or schizoaffective disorder

There was a lengthy discussion on these two categories. Those who believed that there was no data to support a schizoaffective claim believed that the DSM IV had not been used and so the claim could not be supported. Others felt that the two categories represented the fact that the patients were psychotic and not just a suicidal patient from the general population.

There was also a discussion on whether it was appropriate to approve a drug for a symptom rather than for a specific claim.

And there was a discussion on the problem with the use of the word “emergent”. Some people viewed this to mean an acute event. Others felt that the population was already high risk for suicide and thus one can’t call them emergent when they already were in the class.

There was concern that Clozaril will be used in primary care for any suicidal patient and not be restricted to the population that was studied.

The committee individually voted on whether they believe the data supported both claims or only schizophrenia. (This is subject to interpretation of lengthy comments that some members made.)

4=Both claims **4= Only schizophrenia claim** **1 abstention**

(NOTE: 2 non-voters - Malone and Mehta)

3. Expansion of Clozaril claim beyond treatment resistant schizophrenia

This was not discussed

4. Interpretation of the InterSePT study with regard to olanzapine

It appears that Clozaril is better, not that olanzapine makes it worse.

Claim could say that Clozaril is superior to standard drug instead of stating the comparative drug.

Most consensus reached on stating that clozaril was effective not better than others (because we do not know if the comparison was fair).

5. Adequacy of a single randomized controlled trial to support suicidality claim

Members felt that it would be hard to repeat because the next study would need to disclose to subjects that there had been a positive study with Clozaril.

One statistician pointed out that two studies could have initially been carried out so we would have had data from two studies while equipoise was still present.

Question for which FDA would like a committee vote:

Do the data from the InterSePT Study, along with other data provided in this NDA supplement, provide a sufficient basis for a new claim involving suicidality in schizophrenia and schizoaffective disorder [Note: Part of the challenge to the committee is to articulate what the new claim should be.]?

The committee voted on the adequacy of the study without specifying the actual indication. They left the indication to the FDA to work out. They had worked on the claim in question 2 and were about equally split on the indication.

Yes = 8 No =1

This vote is an interpretation of a lengthy discussion. There was no formal vote. And it is possible that a few of the yes votes were actually less definitive and not quite a yes.

For instance,
One member stated that assuming that non-blinding does not bother the FDA, then InterSePT and other studies are persuasive.

Another member stated that it is not a robust study in the normal sense of the word, but if it is real and not explained by bias then it is robust enough for approval.

A verbatim transcript of this meeting will be available on the FDA's Dockets Management Branch Website approximately 30 days after the meeting. The address is HTTP://www.fda.gov/ohrms/dockets/ac/acmenu.htm.

I certify that I attended the November 5, 2002 meeting of the Psychopharmacologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/S/ _____ **/S/** _____

Sandra Titus, Ph.D. Date
Executive Secretary, PDAC

Dan Oren, M.D. Date
Acting Chair, PDAC

Prepared on November 4, 20021
Sandra Titus, Ph.D.