

Final Minutes: February 14, 2001

Psychopharmacological Drugs Advisory Committee

Issue: NDA 21-253: Zyprexa®(olanzapine intramuscular, Eli Lilly)

The meeting was held at the Holiday Inn in Gaithersberg, Maryland. Prior to the meeting, the members and consultants had reviewed background material from the FDA and from Lilly. There were approximately 200 persons in attendance.

Attendance:

PDAC Members Present: Carol Tamminga, M.D., Chair, Abby Fyer, M.D., Gaurdia Banister, Ph.D., Robert Hamer, Ph.D., Tana Grady-Weliky, M.D., Irene Ortiz, M.D., Richard P. Malone, M.D., Matthew Rudorfer, M.D., Dan Oren, M.D. (phone connection).

PDAC Consultants: Michael Grundman, M.D.

PDAC Members Absent: Edwin Cook, M.D, Andrew Winokur, M.D.

Cardiology Consultants: Jean Barbey, M.D., Edward Pritchett, M.D.

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

FDA Overview:

Tom Laughren highlighted the issues that the Agency was asking the committee to address. This was followed by a general discussion by the committee.

General Discussion Questions (before the review of either specific claim)

The transcript will provide the reader with a richer perspective. The following questions and issues were discussed and the comments should only be viewed as a very truncated view of what was discussed.

Effectiveness Data of Oral formulations and Relationship to IM

1. Are effectiveness data needed to support the approval of a parenteral formulation of an antipsychotic for IM use, or is it sufficient to rely on the efficacy data available for the orally administered immediate release formulation?

The consensus was that efficacy data was needed rather than relying on oral administration.

Effectiveness Data and Relationship to Clinical Symptoms

2. If effectiveness data are needed, what should be the clinical target that is the focus of the required effectiveness studies?

Some of the comments:

Clinical targets may be etiologically diverse.

The outcome should have practical implication (such as ER data).

If not thorough in specifying outcome, many things could for example look similar but we don't know pathophysiology. Pain and anoxia may look like agitation.

If agitation is not defined in terms of mental symptoms in which they are expressed, then one may reach a broader definition than desirable or wanted.

Behavioral qualities that would be recognizable as agitation are hyper-excitability, possibly threatening behavior or being a danger to selves or others.

Effectiveness Data and Relationship to Schizophrenia

3. If effectiveness data are needed, should the focus be on schizophrenia (the approved indication for the oral formulation) or on some other clinical findings present during an acute episode of illness that are deemed to require the use of IM medication?

Consensus was that the diagnosis of schizophrenia would be relevant for treatment with a drug but may not always be possible in an acute episode of agitation.

Consensus that it would be useful to have studies done in situations where agitation was going to occur such as the ER where a diagnosis would be inevitably variable.

3.a If schizophrenia is considered to be the appropriate clinical target for the development of IM formulations of antipsychotic drug products, what study designs would be optimal to support a claim for these products?

Discussion deferred until the committee discussed the specific NDAs.

Efficacy Data and Relationship to "Agitation"

4. Is "agitation" an acceptable clinical target for the development of IM antipsychotic drug products?

4.a. If so, how should "agitation" be defined?

4.b. What outcome measures are optimal for the assessment of "agitation?"

4.c. What study designs are optimal for the study of "agitation?"

4.d. Is it worthwhile distinguishing between what might be considered "acute agitation" and "chronic agitation?"

4.e. Is "agitation" a phenomenon that is specific to different disease states or can this be considered a nonspecific symptom that occurs in identical form in association with different disease states?

4.f. If "agitation" can be considered a nonspecific symptom, is it necessary to study it in different disease models in order to gain a claim?

4. g. If so, in what disease models should it be studied?

Some felt that diagnosis should occur before the use of rating scales and that rating scales should not be used for the diagnosis.

Agitation in acute situations such as ER and ICU should be defined.

Agitation as an entity is different than psychosis, mania, or dementia.

Threatening agitation should be measured in outcome studies (a definition offered was when one was going to put a person into restraints)

IM use is indicated when threatening and when need to treat rapid onset

Agitation in trials has been a judgment. (you know it when you see it)

Agitation is unlikely to occur in chronic state although it is possible.

Agitation may be an impediment to diagnosis.

Overview of Lilly's Presentations:

John Kane, M.D., Chairman, Department of Psychiatry, Hillside Hospital; Professor of Psychiatry, Neurology and Neuroscience, The Albert Einstein College of Medicine made a presentation on **The Agitated Patient**. Alan Breier, M.D., Leader, Zyprexa Product Team, Lilly; Professor of Psychiatry, Indiana University reviewed the **Clinical Development of IM Olanzapine**.

Open Public Hearing: Dr. Rex Cowdrey from NAMI made a presentation.

Committee Discussion Specific to Safety and Efficacy for Zyprexa

1. Has the sponsor provided evidence from more than one adequate and well-controlled clinical investigation that supports the conclusion that (olanzapine IM) is effective for the treatment of agitation?

The committee clarified the question and answered the following question:
Has the sponsor provided evidence from more than one adequate and well-controlled clinical investigation that supports the conclusion that (olanzapine IM) is effective for the treatment of agitation **in the populations studied (psychosis, bipolar, dementia)**.

Yes =9

No =0

There was also some discussion about the dose range. Some members of the committee felt that there was not a striking difference between 5, 7.5 and 10.

2. Has the sponsor provided evidence that (olanzapine IM/ziprasidone IM) is safe when used in the treatment of agitation? (**The committee added the words – in the populations studied.**)

Yes=9

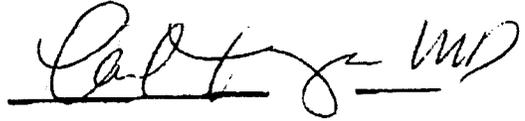
NO=0

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](http://www.fda.gov/ohrms/dockets/ac/acmenu.htm).

I certify that I attended the February 14, 2001 meeting of the Psychopharmacologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

 2/14/01

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



Carol Tamminga, M.D. Date
Chair, PDAC

Prepared on February 14, 2001
Sandra Titus, Ph.D.