

February 16, 1995

NOTE TO FILE

Dr. C. M. Beasley
Dr. J. C. Bloom
Ms. P. A. Bradley
Dr. J. T. Callaghan
Dr. M. A. Dorato
Dr. T. R. Franson
Dr. J. S. Kasher
Mr. J. C. Lancaster
Dr. J. C. Lechleiter

Dr. G. G. Long
Ms. V. Morris
Dr. A. H. Rampey
Dr. T. Sanger
Dr. W. G. Satterlee
Ms. V. L. Thompson
Dr. G. D. Tollefson
Dr. P. V. Tran
IND File

Re: IND 28,705 - Olanzapine

On Thursday, February 16, 1995 the pre-NDA meeting with FDA was held. It lasted approximately 1 hour and 45 minutes. The attached itinerary presents Lilly attendees; of the anticipated FDA attendees, Drs. Fitzgerald, Freed, and Baweja did not attend. Thus, there were no toxicologists present from FDA.

Dr. Tollefson presented an overview of olanzapine which included several issues for discussion (a hard copy of the three acetates which were presented is attached). There were no FDA comments.

Dr. Leber initiated discussion by asking what would be in our label (indication language). A lengthy debate ensued, but the bottom line is that he will be very conservative in regard to labeling. There was mention of an FDA meeting (presumably on March 23-24, 1995) that he thought might be of interest to us. The implied topic was the structure of clinical trials and their bearing on labeling.

The topic of what patient population we are studying came up (as had been predicted). Dr. Leber did not want to discuss this, he just wanted to stress that we make this clear in the NDA. Dr. Laughren bought up the point (again, predicted by pre-meeting comments from the CSO) that we were not planning a relapse prevention trial. Although we feel a blinded extension of our current trial provides comparable useful information, Neuropharm. management clearly disagreed. Extensive discussion of the idea of direct re-randomization to placebo resulted in no resolution of the disagreement. I think our group did not feel that a re-randomization study as defined by Dr. Leber was essential to potential approval of olanzapine, and Dr. Laughren stated it was not needed for approval.

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Furthermore, Dr. Laughren acknowledged that designs other than placebo rerandomization (i.e., multiple decreasing fixed dose rerandomization) could provide adequate data.

A discussion of pediatric issues related to olanzapine left the impression that, while theoretically the FDA encourages research in the field, information (safety/efficacy) obtained short of two pivotal trials was of little value with regard to labeling. It is hard to believe that at least some safety and pharmacokinetic information in adolescent patients placed in the Clinical Pharmacology Section of the package insert would not be seen as of value to either the FDA or the Advisory Committee.

Similarly, Dr. Leber was not enthusiastic about study HGAO (psychotic demented elderly) with respect to the indication for use, and extensive discussion did not resolve the disagreement. Dr. Leber felt that including the findings of HGAO in the package insert might imply an approval for such use. He was concerned, but not adamant that it would not be included. The writer feels identically regarding the FDA thinking about safety experience in elderly (as regarding pediatric). It seemed to me that Dr. Leber doubted whether the disease is the same in children, the elderly, and the remainder of the age distribution for psychosis schizophrenia.

Dr. Leber was also unenthusiastic about the expression "atypical" applied to antipsychotics. He was not encouraging about what information might be used to support the use of the designation. The Advisory Committee's views on this issue apparently have not been of influence.

In response to direct questions about the adequacy of our information package in regard to supporting safety and efficacy of olanzapine, both Dr. Leber and Dr. Laughren were of a positive inclination. Dr. Leber termed the form of the studies (seemingly) capable of demonstrating (safety and efficacy). Dr. Laughren referred to two studies that appear adequate and indicated that there was not concern regarding safety perspective or the extent of patient exposure. He said long-term data hadn't been a requirement (and wasn't for risperidone).

Todd Sanger discussed with Dr. Hoberman several issues of formatting and statistical analysis that were desired. Many of these were also requested for Dr. Hoberman's analysis of risperidone. I will ask Todd to write a note regarding this discussion.

Some general coaching evolved: don't overkill, or oversell the data; be certain index is excellent - bad index can cause RTF; don't skimp on detail of describing study population (e.g., - make clear who are patients in HGBD). Dr. Leber stated that brevity is desirable.

The FDA made reference to the need for and their interest in having an adequate metabolic package, including sufficient numbers of drug interaction trials.

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A discussion of requirements for CRFs was initiated (with the assistance of CSO Steve Hardeman whom I had enlisted). Despite the surprise of Charles Beasley, Patrice Bradley and myself, Dr. Laughren stated that he only needed CRFs for death and discontinuation due to an adverse event. This contracts the 1400 volumes of paper to only a small extent. They do not have the authority to give us permission not to submit paper CRFs. We made clear the problem of numbering these volumes at the last minute, and I gave CSO Steve Hardeman five sham volume covers (provided by Jeff Ramsey) to help present the issue of needed flexibility on this. There may be room for flexing. Steve said he would try to help us resolve the issue; I stressed the urgency. There was mention of multi-search capacity for the CD-ROM (of CRFs). However, we pointed out that the data browser provided this opportunity.

Dr. Leber asked about submission timing. He was told October 1. He stated the review time would be within the one-year called for in the User Fee guidelines.

J. Alan Webber
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Attachments

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