DRAFT MEMORANDUM OF MEETING MINUTES

Teleconference Date: 05 May 2003

Time: 2:30PM

Application: NDA 21-520, Olanzapine plus Fluoxetine Combination

Meeting Recorder: Pat Burns

FDA Attendees:
Russell Katz
Paul Andreason
Judy Racoosin
Tarek Hammad
Doris Bates

Lilly Attendees:
Greg Brophy
Alan Breier (San Francisco)
Sara Corya
Patrizia Cavazzoni
Cherri Miner
Patrick Burns

Topic discussed during the teleconference

1. Potential warning for Diabetes Mellitus
2. Classification of response to approvable letter
3. Potential warning for CVA
4. Potential warning for Bleeding Risk
5. Orthostatic hypotension
6. Toxicology abuse potential study as a Phase 4 Commitment
7. DSI Inspection

1. Potential warning for Diabetes Mellitus
    - The FDA has received and is currently evaluating the data from the VA study.
    - The FDA stated that class labeling is a possibility but the final decision has not been made. [The FDA is leaning in the direction of class labeling]
    - The FDA considered the class to be all atypical agents.
    - Should the FDA institute class labeling they would attempt to get it out to all sponsors with to institute in the next label change.
    - The FDA acknowledge the "level playing ground" issues and would try to get all sponsors to change as close together as possible but that it was difficult to set a date. To help address the issue of differential timing of the addition to other sponsors PIs, the FDA suggested the possibility of issuing a "press release" or "public statement" stating that the wording would be added to all labels.
    - With regards to the specific wording for the proposed warning the FDA suggested that we leave that section of the PI blank and they would get back with us when they had wording developed. The wording will likely address the complexities of the drug/disease state interactions.
    - Within the discussion we asked the FDA what criteria they used for assigning an event a warning as opposed to a precaution. They responded that there were no hard and fast

rules. But in general if they consider the event to be of significant importance with a finite risk they would likely consider that for a warning over a precaution.

2. Re-classification of the Response
   - Lilly inquired if the FDA view the response as a Class 1 (2 month review) or a Class 2 (6 month review). The FDA (Dr. Katz) responded that because of the additional safety questions that were asked in the approvable letter and the need to have the inspections completed they considered it to be a Class 2 response.
   - When asked how they view a 6-month review for a priority application the FDA stated that they understood the concerns but the priority status refers to the initial response and did not carry through the post approvable review period.

3. CVA
   - When asked the FDA stated that this warning was being driven by the information submitted to the Zyprexa NDA.
   - When asked if the CVA warning is "class labeling" the FDA stated that this may not necessarily be class labeling. A hypothetical example cited was: If the data from 4 companies that studied dementia had a signal but 2 companies, with similar mechanisms of actions, did not study dementia they would likely get class labeling. However if all 6 companies studied dementia but there were differences in the signal rates then there may be differential labeling.

4. Bleeding Abnormalities
   - When we said that we were surprised to see this in the Symbyax label because we had not received anything for the Prozac label the FDA stated that "it's coming, you just haven't received it yet".
   - The possibility of differential labeling was mentioned similar to the hypothetical example cited above.

5. Orthostatic Hypotension (OH)
   - When asked about their concern they FDA cited the normal subjects in the in the original Zyprexa NDA, normal subjects in rapid acting application and those in the Symbyax NDA who experienced OH with decreases in heart rate.
   - They viewed bipolar patients to be more like the normal subjects and to be more sensitive to the hypotensive effects of antipsychotics.

6. Abuse liability as a Phase 4 commitment.

   - The FDA acknowledged that this came from the toxicology group rather than CSS and offered the opportunity to submit additional data to support not conducting the study.

** post teleconference Information**

- Per a follow up discussion with the FDA Project Manager any response to the this request (either agreement to conduct the study or submission of additional data to support not conducting the study will be consulted to the CSS group for comment.