Questions for the July 19, 2000
Psychopharmacological Drugs Advisory Committee
Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland

NDA 20-825: Zeldox(ziprasidone hydrochloride capsules, Pfizer)

A. Issues to be considered:

Principles Considered in Regulating QTc Prolonging Drugs
-Indication/Available Treatments
-Observed QTc Effect
-Other evidence suggestive of a serious outcome associated with a drug's QTc effect
-Metabolic Problem

Indication/Available Treatments
- -How serious is it?
- -How effective are available treatments?
- -How many alternative treatments are available?
- -How does new treatment compare regarding efficacy?
- -How does new treatment compare regarding safety?

Observed QTc Effect
- -Absolute size of mean QTc effect in dose range proposed?
- -Proportion of outliers on QTc effect?
  - -having a change from baseline of 75 msec
  - -going over some threshhold, such as 500 msec

Other Evidence Suggestive of a Serious Outcome Associated with a Drug's QTc Effect
- -Excess overall mortality or SUDs
  - -NDA database
  - -Other experience
- -Actual cases of TDP or other serious arrhythmia
- -Excess syncopal episodes

Metabolic Problem
- -Vulnerability to increased plasma levels
  - -In presence of inhibitor
  - -In subpopulation with compromised metabolic capacity (e.g., 2D6 poor metabolizers)

B: General Questions for Committee

1. Has the sponsor provided evidence from more than one adequate and well-controlled clinical investigation that supports the conclusion that ziprasidone is effective for the treatment of schizophrenia?

2. Has the sponsor provided evidence that ziprasidone is safe when used in the treatment of schizophrenia?

If the committee responds positively to the 2 general questions, there are some additional questions and issues that we would like you to consider in your discussions.

3. Do you think that ziprasidone's risk of serious ventricular arrhythmias and SUD is greater than that of most other drugs in this class (even if that excess risk cannot be quantified)?

4. If you believe there is some excess risk, albeit unquantified, of serious ventricular arrhythmias and SUD associated with the use of ziprasidone, and you, nevertheless, conclude that ziprasidone should be approved, how should this excess risk be managed in labeling?

-First line vs second line status?

-What prominence should the risk be given in labeling?
- -Black box warning
- -Lesser warning statement

-Should there be a medication guide for patients to alert them to the risks of using ziprasidone?

5. Should the sponsor be required to conduct additional studies for ziprasidone, and when should these studies be conducted relative to any approval decisions regarding this application?

-Large comparative trial to estimate (or rule out at some level) the risk of excess SUD in association with the use of ziprasidone

-Study to demonstrate superior efficacy for ziprasidone, e.g., in patients demonstrated to be refractory to standard therapy