Questions posed for the November 3, 1999 Psychopharmacological Drugs Advisory Committee Fluoxetine for Premenstrual Dysphoric Disorder (PMDD)

The topic for this meeting is an application for fluoxetine in the treatment of Premenstrual Dysphoric Disorder (PMDD). As you are aware, there are as yet no drugs approved for this indication in the US. Since there are no regulatory precedents in this area, we would welcome any comments or discussion regarding PMDD as a new indication and the development of drug treatments for this indication. This kind of advice would be useful not only for this specific application, but also to help us in our evaluation of subsequent development programs for this indication. In addition, there are specific issues pertinent to this application. Finally, we will ask you to vote on the usual questions regarding the efficacy and safety of fluoxetine for PMDD.

A GENERAL QUESTIONS/ISSUES REGARDING PMDD AS A NEW INDICATION:

1. Although PMDD is discussed in DSM-IV and diagnostic criteria are provided, it is still reasonable to ask how widely recognized and accepted this entity is, and how well-defined it is as an independent clinical entity.

2. The diagnostic criteria for PMDD are included in an appendix section of DSM-IV intended to assist in the further research of proposed indications. Should this tentative status in DSM-IV influence the regulatory decision about this proposed indication?

3. Given that the clinical features of PMDD are predominantly affective, can PMDD be considered independent of the depressive disorders, in particular, major depressive disorder?

4. What is the relationship of PMDD to premenstrual syndrome (PMS)?

   Can PMDD be considered a subtype of PMS, i.e., severe PMS?

B. **SPECIFIC QUESTIONS/ISSUES REGARDING THE NDA FOR FLUOXETINE IN THE TREATMENT OF PMDD**:

1. The primary outcomes for the trials in support of a new indication for fluoxetine in the treatment of PMDD focused on affective symptom subsets of PMDD instruments (i.e., VAS Mood-3 for study 019 and VAS Mood-4 for study 022).

   1a. Are these appropriate outcomes?

   1b. Should this focus on affective symptom subsets of more general PMDD assessment instruments influence the indication, e.g., affective symptoms of PMDD rather than the full syndrome?

1. The trials in support of a new indication for fluoxetine in the treatment of PMDD involved continuous dosing with fluoxetine, rather than more limited dosing during the luteal phase, as has been the case with some published reports on studies of other SSRIs in PMDD trials.

   Given the goal of limiting treatment to whatever exposure interval is needed to achieve an optimal response, should the fact that these studies do not address the issue of more limited exposure intervals influence the regulatory judgement about the adequacy of these data regarding a new claim for PMDD?

2. Patients taking oral contraceptives were excluded from the trials in support of a new indication for fluoxetine in the treatment of PMDD.

   a. How important an omission is this in regard to the population likely to be candidates for treatment of PMDD?

   b. Should this fact influence the regulatory judgement about the adequacy of these data regarding a new claim for PMDD?

1. A relatively small number of patients participated in the 3 trials submitted in support of a new indication for fluoxetine in the treatment of PMDD. Thus, a judgement about the safety of fluoxetine in the PMDD population requires a reliance on the safety experience with other populations exposed to this drug.

   Is this a reasonable extrapolation?

2. One of the 2 positive trials submitted in support of this new claim, i.e., study 022, utilized a crossover design. Since this design is not ordinarily utilized in studies of chronic psychiatric disorders, it would be useful to have some discussion of the appropriateness of this design for this disorder. FDA?s statistical reviewer, Dr. Chen, performed tests for period effect and treatment-by-period interaction, both yielding nonsignificant results. However, these tests have limited power for detecting these effects.

   Is the crossover design acceptable in studies of PMDD?

C. OTHER QUESTIONS/ISSUES:

This is not by any means an exhaustive list of questions and issues that may benefit from discussion at the November 3rd meeting, and we hope you will bring up and discuss any other questions or issues that you feel are pertinent to this specific application or more generally to the development of drug products for this new indication. A meeting of the PDAC on an application for an indication for which there are no previous approvals takes on added importance since, in a sense, it sets precedents for future development programs and applications for that indication.

D. <u>QUESTIONS REQUIRING A VOTE OF THE PDAC</u>:

As usual, when all of the pertinent issues have been discussed, we will ask you to vote on specific questions pertinent to the efficacy and safety of Fluoxetine in the treatment of PMDD.

1. Has the sponsor provided evidence from more than one adequate and well controlled clinical investigation that supports the conclusion that Fluoxetine is effective for the treatment of Premenstrual Dysphoric Disorder (PMDD)?

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