M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID# D030341

DATE: March 6, 2004

From: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation, HFD-430

TO: Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Suicidality in pediatric clinical trials with paroxetine and other antidepressant drugs: Follow-up to 9-4-03 consult

Drugs: paroxetine, sertraline, venlafaxine, fluoxetine, fluvoxamine, citalopram, nefazodone, mirtazapine, and bupropion

The attached memorandum from Andrew D. Mosholder, M.D., M.P.H., an epidemiologist in the Division of Drug Risk Evaluation/Office of Drug Safety, contains an analysis of suicidality in pediatric clinical trials with paroxetine and other antidepressant drugs and recommendations for a plan of action. An emphasis has been placed in suicide-related outcomes in the *composite* of randomized controlled trials of each pediatric drug development program. In Dr. Mosholder's analysis, for most but not all drugs of this class, there is a trend towards an increased attributable risk of suicide-related events linked to randomization to active drug, compared to placebo. Moreover, a meta-analysis of Major Depressive Disorder(MDD) studies across all drug programs reveals that the active treatment arm is associated with an increased risk for these events.

This meta-analysis raises critical concerns that must be addressed to optimize pharmacotherapy of pediatric MDD and other psychiatric illness(es). As Director of the Division of Drug Risk Evaluation, I have reviewed this document and support the analyses and conclusions that it contains, with the following exceptions and/or additions:

- Based on limitations in the data-set that has been made available, the meta-analysis that has been performed does not justify a recommendation for a labeled contraindication for use in 'all pediatric patients' of any of the reviewed drugs, at this time.

- As pointed out in Dr. Laughren's review[1], between individual trials, for each drug, there are inconsistencies of results of suicidality. This observation beckons for a more rigorous analysis of similarities and differences between the trials in their design and implementation.

[1] Thomas P. Laughren; Background on Suicidality Associated with Antidepressant treatment; submitted January 5, 2004; presented at Psychopharmacologic Drugs Advisory Committee and Pediatric Subcommittee of the Anti-Infectives Advisory Committee, February 2, 2004

In reviewing the clinical trial database to understand differences in suicidality between trials the following elements should be elucidated:

- *enrollment criteria (patient characteristics)*
- *classification criteria for including/excuding suicidality events*
- *protocols for following and assessing patients before, during and after treatment*

- Reasons for absence of efficacy for different agents in pediatric trials remain unclear. Whether differences in trial results are related to inherent differences in pharmacological properties between agents, or in trial characteristics (enrollment, powering, efficacy measures, etc.) has not yet been elucidated. Thus, at this time, differential labeling of fluoxetine to imply more a more favorable benefit/risk profile should be approached with caution.

- Although the rates of severe agitation and completed suicides have been reported in pediatric patients treated with anti-depressants, other events, including 'possible' and even 'serious' suicide-related events, appear to be much more common. Further information to understand the predictive relationship between these outcomes is critical in the interpretation of safety events associated with clinical trials.

- Dr. Mosholder's recommendation to discourage initiation of 'off-label' treatment of pediatric patients is based on a justifiable concern that in this age group, with the exception of fluoxetine, efficacy to treat MDD has not been demonstrated. Although off-label treatment is not directly discourages, the FDA Public Health Advisory issued on October 27, 2003 states:

  ..'FDA emphasizes that, for the 7 drugs evaluated in pediatric major depressive disorder (MDD), data reviewed by FDA were adequate to establish effectiveness in MDD for only one of these drugs, Prozac (fluoxetine). Failure to show effectiveness in any particular study in pediatric MDD, however, is not definitive evidence that the drug is not effective since trials may fail for many reasons, FDA recognizes that pediatric MDD is a serious condition for which there are few established options, and that clinicians often must make choices among treatments available for adult MDD.'

  'FDA emphasizes that these drugs must be used with caution. ....'

  At this time, because of lack of information, I do not support an explicit labeled instruction to avoid all 'off-label' treatment. Rather, an interim plan should be implemented to comprehensively inform physicians, patients and their families of the possible serious risks attached to treatment (in addition to their underlying psychiatric condition) suggested by some spontaneous reports that the agency has received. As part of this effort, explicit labeling about the association of antidepressant treatment with an increase in agitation, akathisia, aggression, depression, etc., that has been observed in some cases should be adopted. In addition, strategies to effectively communicate this information, in order to enhance vigilance of patients and their families and promote appropriate physician follow-up, should be developed.