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

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From: Anne Trontell, M.D., M.P.H., Deputy Director
Office of Drug Safety, HFD-400

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

SUBJECT: Office of Drug Safety Cover Memorandum
Follow-up Consult to 9-4-03 consult by Andrew Mosholder on Suicidality in pediatric clinical trials with paroxetine and other antidepressant drugs:

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

Dr. Mosholder has concluded from his composite analysis of preliminary data from the randomized clinical trials (RCTs) of selective serotonin reuptake inhibitors (SSRIs) in pediatric psychiatric conditions, that short-term use of these drugs is associated with a statistically and clinically significant elevation in the risk of self-injurious events over placebo. He found the short-term excess risk of SSRIs relative to placebo to be statistically significant in trials of major depressive disorder (MDD), but not in those for nonMDD indications. Based on these findings and the limited number of SSRI trials showing efficacy in pediatric MDD, Dr. Mosholder advocates discouraging antidepressant drugs outside their labeled efficacy indications. Specifically, he notes that only fluoxetine has demonstrated efficacy in pediatric MDD, and that the point estimate of its relative risk for suicide-related events of 0.88 (95% CI 0.34-2.30) "appears most favorable."

Dr. Mosholder's conclusions are based upon thoughtful consideration of what are, at this point, preliminary data. Systematic data collection and coding have not been assured, and unblinded analyses by Dr. Mosholder were not possible. Dr. Mosholder notes these deficiencies, but expresses his belief that only systematic bias could explain away his findings, and so "interim risk management" around labeled efficacy should be done pending definitive analyses.

As Dr. Mosholder's supervisors, Dr. Avigan and I disagree with his proposed interim risk management which implies making treatment recommendations about off-label use for SSRIs in pediatric psychiatric illness. In particular, we disagree that the data are sufficiently robust to advocate preferential use of fluoxetine in pediatric MDD. We note that the point estimate suggesting a modest protective effect in serious suicide-related events was not statistically significant, and that the 95% confidence interval could not rule out a doubling of the risk. We share Dr. Mosholder's concern about the potential excess risk of self-injurious behavior in pediatric patients treated with SSRIs, and agree that these potential concerns should be transmitted widely to physicians, patients, and parents when these drugs are used. Such information-sharing should reinforce prudent use and close patient follow-up in initiating therapy with SSRIs, particularly among patients being treated for MDD. We support additional adjudicated analyses being done by Columbia University, and once they are complete, recommend their comparison to Dr.

Mosholder's preliminary findings with due consideration and appropriate sensitivity analyses around indeterminate cases of self-injury.

Like Dr. Avigan, I believe the current safety data from pediatric SSRI RCTs are insufficiently characterized to assure they are free from nonrandom sources of error that may lead to erroneous conclusions. In particular, I believe they do not warrant making treatment recommendations at this time addressing labeled or unlabeled uses, particularly to suggest relative safety for one product over another.

I agree with Dr. Avigan's comments that the studies as analyzed by Dr. Mosholder may not be sufficiently homogeneous to support their composite analysis. Additional examination of the clinical trial data, along with additional statistical testing for homogeneity should be done to determine if making conclusions based on the combined data is valid. Dr. Avigan notes that differences in the selection of patient populations among the different trials may have led to individual differences in the self-injury risk of patients. This concern is supported by the observation of differences among the placebo rates of suicide-related events among the different trials, as well as the differential rates and relative risk of self-injurious behaviors across individual drug trials. Dr. Mosholder himself notes that the post-hoc ascertainment methods for suicide-related events were different among the sponsors of different drug trials. He does not mention the possibility that ascertainment differences may also have influenced data collection during the RCTs themselves, since self-injurious behaviors were not elicited prospectively or systematically. Investigator practices in eliciting, recording, or coding these events were not likely to have been done in a consistent fashion.

In addition to inconsistent ascertainment of self-injurious adverse events, Dr. Mosholder's analyses do not describe imbalances in individual treatment times (e.g. time-adjusted survival analyses) that may have occurred due to differential dropout rates of placebo patients relative to treated patients. The common side-effect profile of SSRIs (including akathesia) may have led to the loss of true blinding by either the investigator, patient, or both, and so influenced decision-making about continuing participation in the trial. Such a scenario would allow for the possibility that more severely ill patients (perhaps at higher risk of self-injurious behavior) might have been preferentially retained in active treatment.

In conclusion, Division and Office management within the Office of Drug Safety support Dr. Mosholder's concerns that pediatric patients being treated for MDD with SSRIs may experience an increase in self-injurious behaviors that may in turn, place them at greater risk of suicidal behaviors. We disagree as to the conclusiveness of this finding for making of psychiatric treatment recommendations such as the preferential use of fluoxetine in pediatric MDD. We instead advocate widespread information-sharing with clinicians, patients, and parents addressing the potential emergence of self-injurious behavior in the initial treatment of pediatric psychiatric illness, and urge attentive patient follow-up by all parties. We support the timely completion of adjudicated data analyses by Columbia University, and a reexamination of the data and consideration of clinical treatment recommendations when the Joint FDA Pediatric and Neurological Advisory Committee is reconvened later in 2004.