Review and Evaluation of Clinical Data

Drugs, NDAs, sponsors, and date of submissions:

1. Wellbutrin (Bupropion), NDA 18-644, GlaxoSmithKline, submissions dated 11/04/03, 4/15/04, 5/18/04
2. Remeron (mirtazapine), NDA 20-415, Organon, submissions dated 11/10/03 & 4/15/04
3. Luvox (fluvoxamine), NDA 21-519, Solvay, submissions dated 11/10/03 & 4/13/04
4. Effexor and Effexor XR (venlafaxine), NDAs 20-151 and 20-699, Wyeth, submissions dated 11/19/03 & 5/14/04
5. Zoloft (sertraline), NDA 19-839, Pfizer, submissions dated 11/21/03 & 4/15/04
6. Celexa (citalopram), NDA 20-822, Forest, submissions dated 11/21/03 & 4/15/04
7. Paxil (paroxetine), NDA 20-031, GlaxoSmithKline, submissions dated 11/24/03, 4/15/04, & 5/17/04
8. Prozac (fluoxetine), NDA 18-936, Lilly, submissions dated 12/4/03 & 4/20/04
9. Serzone (nefazodone), NDA 20-152, Bristol Myers Squibb, submissions dated 1/14/04 & 4/20/04

Subject: Relationship between psychotropic drugs and pediatric suicidality
Reviewer: Tarek A. Hammad, M.D., Ph.D., M.Sc., M.S.
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This document analyzes and evaluates data submitted by sponsors of several psychotropic drugs in response to FDA requests regarding data pertinent to pediatric suicidality.

Several hyperlinks (seen underlined in blue color) were put in place to facilitate navigating through the document.

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1 Background

On May 22, 2003, GlaxoSmithKline submitted an analysis of suicide-related[1] adverse events in pediatric trials of paroxetine. This analysis showed a statistically significant increase in such behavior with paroxetine treatment, compared to placebo. In order to provide a meaningful comparison to the paroxetine findings, the Division of Neuropharmacological Drug Products (DNDP) requested that the sponsors of eight other psychotropic drugs tested in children and adolescents conduct searches of their databases similar to the search performed by GlaxoSmithKline. The initial letters requesting these searches were issued on 7/22/03. Follow up requests to obtain additional information were issued on 11/24/03 & 12/9/03 (Appendix I). The latter requests were issued in part to cast an even broader net for events, since there was concern that event-finding by sponsors may not have been complete.[2]

Based on our initial assessments of the responses to our 7/22/03 letters, we decided that it may be useful to obtain patient-level datasets to permit an exploration for covariates to assess for possible imbalances among treatment groups. Requests for these data sets were issued on 10/3/03 & 10/28/03 (Appendix II).

Because of a very wide diversity in the events the sponsors had subsumed under the broad category of "possibly suicide-related," concerns were raised within the Division that not all captured events could be considered to reasonably represent suicidal thinking and behavior. At a joint meeting of the Psychopharmacological Drug Products Advisory Committee and Pediatric Subcommittee of the Infectious Diseases Advisory Committee held on February 2, 2004[3], the Division presented these concerns publicly, and proposed a plan for outsourcing a blinded review of the adverse events of interest to an expert group of suicidologists. Subsequently, all adverse events (AEs) identified by the sponsors as being suicide-related, as well as all serious AEs, all accidental injuries, and all accidental overdoses were independently blindly adjudicated by a group of ten suicidology experts assembled by Columbia University. The adjudication process was applied to the additional AEs mentioned above to provide reassurance that all suicide-related AEs had been identified.

On 3/17/04, while the AEs were being classified, DNDP requested additional data (Appendix III) on treatment-emergent suicidality among study patients as measured by the suicidality item(s) in various depression questionnaires (the questionnaires are provided in Appendix IV).

The purpose of this document is to evaluate and to analyze the suicide-related adverse

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[1] The sponsor used an algorithm based on selected preferred terms to identify "suicide-related" adverse events.

[2] See Dr. Thomas P. Laughren memo to the PDAC meeting held on February 2, 2004. The memo was dated December 30, 2003.

[3] http://www.fda.gov/cder/drug/antidepressants/default.htm; http://cdernet.cder.fda.gov/ACS/Flash%20Minutes/Psychopharmacologic/psycho-Minutes_Quick_feb2.pdf

Note that there are large differences between the patterns of hazard in various placebo groups suggesting some heterogeneity in the background rates of suicidality among MDD pediatric patient populations recruited in various trials. Interestingly, the rate in some of the placebo groups, for example with Prozac, was higher than some of the drug groups, for example with Paxil.

When the data from all SSRIs in MDD trials were pooled, the resulting hazard curves showed consistent elevation of hazard in the drug group for most of the follow up period. Note, that the two curves crossed at around 65 days. However, the 95% CIs are very wide at this section of the curves reflecting a greater level of uncertainty because it relies only on only four events, one event in the drug group and three events in the placebo group.

The "hazard ratio" (HR) is a comparative measure of survival experience over the entire trial period, whereas the RR (which will be presented in the next section) is a comparative measure of event occurrence at the end of the trial. For example, a hazard ratio of two for "drug" means that at any given time during the study, the hazard of the event of interest for the drug group is twice that of placebo group.

For most drugs, the resulting overall HR did not differ meaningfully from the overall RR for each drug except for Zoloft where the former was higher than the latter (2.54 vs. 1.48, respectively). When the data from SSRIs in MDD trials were pooled the HR was 1.45 (0.85, 2.48). Compare this to the overall RR for SSRIs in MDD trials, which was 1.41 (0.84, 2.37).

Caution should be exercised in the interpretation of the HR because the basic assumption behind the calculation is that the hazards in the drug and the placebo groups are proportional over the entire period of the trial. This did not appear to be totally fulfilled for Celexa, Prozac, and the overall pooled analysis as depicted in the graphs referenced earlier in Appendix XIV.

5.10 Meta-analysis

Pooling of trials is often performed when investigating infrequently occurring adverse events observed in drug development programs as it provides a more robust point estimate of the risk associated with drug use. Single trials are almost invariably insufficiently powered for detecting signals for uncommon events. As such, this part of the review evaluates data pools to generate an overall estimate of various drug effects. To accomplish this pooling, a weighted average of treatment effects from individual trials was calculated by drug and by indication.

Two options were available for weighting the results of individual trials prior to generating an overall risk estimate, fixed-effect or random-effects models. In the fixed-effect approach, the premise is that the real effect that we are trying to estimate is fixed, and the observed variations between trials are by chance. In the random-effects approach, the premise is that the real effect varies around an average within a distribution reflected in the differences observed between trials.