DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-037

Glaxo SmithKline
Attention: Thomas Kline
Director, U.S. Regulatory Affairs
1250 S. Collegeville Road, P.O. Box 5089
Collegeville, PA 19426-0989

Dear Mr. Kline:

Please refer to your supplemental new drug application dated and received April 11, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil (paroxetine hydrochloride) Immediate Release Tablets.

We acknowledge receipt of your amendments dated July 3, and August 8, 2002.

This supplemental new drug application proposes the use of Paxil in the treatment of major depressive disorder (MDD) and obsessive compulsive disorder (OCD) in the pediatric population.

We have completed the review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to submit the following information and respond to the following issues:

Labeling

We agree that the results from Study 704 demonstrate the short-term efficacy of Paxil in pediatric patients with OCD, and that the results from Studies 329, 377, and 701 failed to demonstrate the efficacy of Paxil in pediatric patients with MDD. Given the fact that negative trials are frequently seen, even for antidepressant drugs that we know are effective, we agree that it would not be useful to describe these negative trials in labeling.

Accompanying this letter (Attachment) is the Agency's proposal for the labeling of Paxil in the treatment of pediatric OCD. We have used, as our base labeling, the most recently acceptable paroxetine labeling (see Agency letter dated October 2, 2002). Double underline font denotes additions to the labeling, and strikeout font denotes deletions to the labeling. Brackets [] embedded within the text that follows include comments and explanations concerning our proposed labeling. The Agency's revisions are based on the labeling changes proposed in your April 11, 2002 submission. For some sections, few changes were proposed, while others required extensive modification.

Request for Additional Information

1. As conveyed in an electronic communication to you dated August 30, 2002, we are requesting that you submit additional ECG analyses. The ECG QT interval data which you included for study 715 (pharmacokinetic study) was only summary data.
   The following raw data is requested:

   a) QTc interval and heart rate data for the studies in children and adolescents.
   b) Any complete (i.e., collected for an entire dosing interval) adult PK, QTc interval and heart rate data.

2. As conveyed in an electronic communication to you dated July 15, 2002, we noted that you did not provide any analysis of ECG interval data for the controlled studies. The results provided for studies 701 and 704 consisted of a count of the numbers of patients with ECG abnormalities. In study 329, ECG abnormalities were considered adverse events but were not otherwise analyzed.

   In order to complete our review of this application, we are requesting that you submit the typical kind of analyses conducted for these type of data; i.e., an analysis of mean change from baseline for measured ECG intervals, and a count of the numbers of patients on drug or placebo exceeding potentially clinically significant thresholds. We request that you use the ECG data from the placebo-controlled, parallel group trials that included pre-treatment and on-treatment ECGs (studies 329, 701 and 715).

3. Please provide the exposure (total number of patients and person-years) for placebo in all studies combined.

4. Please prepare a table showing the duration of exposure and mean daily dose for all paroxetine patients. In this table, the columns should represent mean daily dose and the rows should represent duration of exposure. Patients should be enumerated within each cell, and each patient should be counted in only one cell, according to the patient's duration of exposure and mean daily dose. We can provide an example of such a table if it would be helpful.

5. ISS tables 18.43 through 18.47 provide a listing of paroxetine patients with serious adverse events. Please provide a similar listing for placebo patients. It would also be helpful to provide a summary tabulation of these serious adverse events, similar to ISS table 4.1.2.

6. Please provide further information on the serious adverse events that occurred in study 676; at the time of this submission, the treatment assignments were still blinded.

7. Table 6.14 in the ISS listed paroxetine treated patients who experienced adverse events coded under the terms hostility, emotional lability or agitation. However, the table did not include placebo patients, nor did it include psychiatric adverse events that were coded under other terms. Please prepare an expanded version of this table, including all psychiatric and behavioral adverse events, and also those that occurred among placebo patients. In addition, it would be helpful if you could attach the narrative case summaries for those events that were either serious or resulted in premature discontinuation.

8. Please provide your rationale for coding suicide attempts and other forms of self-injurious behavior under the

WHOART term "emotional lability."

9. ISS table 4.2.6 provides a comparison of weight gain velocity between paroxetine and placebo in study 329; however, the comparison is shown only by age subgroups. Please provide a comparison pooling all paroxetine and placebo patients across ages.

10. Weight corrected clearance was shown to be significantly higher in male children than in female children. Although section 16 of the ISS described analyses of adverse events according to age and gender subgroups, you did not explore the effect of gender on adverse event incidences within age subgroups. Please conduct an appropriate analysis to address this issue.

11. Tables 11.14, 11.15, and 11.16 in the ISS present the mean change from baseline for vital signs (including height and weight), for all subjects combined, children alone, and adolescents alone. Please perform an appropriate statistical test for the differences between treatment groups on these parameters.

12. We note that your application did not contain any information on environmental impact as required under 21 CFR 25.15. Please submit either a claim for environmental exclusion under 21 CFR 25.30 or 21 CFR 25.31 or an environmental assessment under 21 CFR 25.40.

Safety Update

Our assessment of the safety of Paxil in the pediatric population is based on our review of all safety information provided in your original submission. Please provide a final serious events update to include serious adverse events up to a more recent cutoff date.

Regulatory Status Update

Please provide any new information on the regulatory status of Paxil in the pediatric population worldwide.

Worldwide Literature Update

Please provide an updated worldwide literature search for paroxetine.

Phase 4 Commitments

As requested in an Agency letter dated January 10, 2001 and as part of the Agency's pediatric initiative, we believe that additional studies in young animals will be needed to support a complete pediatric assessment. Therefore, we are requesting that you commit, as a Phase 4 commitment, to conduct juvenile animal studies.

Since there are no standard protocols in this area, we suggest that you design a study that would address drug effects in animals of an age range which is analogous to that of the proposed patient population. In addition to the usual toxicological parameters, such a study would presumably evaluate effects on growth and neurological, behavioral, and reproductive development.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment