MAY 18 1999

NDA 20-031
NDA 20-710

SmithKline Beecham Pharmaceuticals
Attention: Thomas F. Kline
Manager, U.S. Regulatory Affairs
1250 South Collegeville Road, P.O. Box 5089
Collegeville, Pennsylvania 19426-0989

Dear Mr. Kline:

Please refer to your New Drug Applications for Paxil (paroxetine hydrochloride) 10 mg, 20 mg, 30 mg, and 40 mg tablets (NDA 20-031) and 10 mg/5 ml oral suspension (NDA 20-710).

Reference is also made to your submissions dated August 27, and October 15, 1998, providing for a proposed pediatric study request.

We additionally refer to an Agency pediatric written request letter dated April 28, 1999.

We have the following comments regarding your specific pediatric proposal:

In your August 27, 1998 proposed pediatric study request for paroxetine, you proposed to submit the results from two double-blind, randomized, short-term, placebo-controlled trials of paroxetine in pediatric depression, i.e., studies 329 and 377. Study 329 describes a completed 8 week, double blind, placebo controlled study, with a 6 month extension study in adolescents aged 12-18; and Study 377 is a double-blind, placebo-controlled twelve week trial in patients aged 13-17 that we assume is now ongoing in Europe and Canada. These two protocols describe adequate and well-controlled clinical trials limited to adolescents with depression.

We have the following comments on your proposed pediatric depression program:

1. This program is deficient in that it does not address depression in school age children 7-11, as outlined in the April 28, 1999 letter. Your program must include at least one study that addresses depression in this younger age group.

2. Detailed statistical plans for both studies 329 & 377 are needed.

3. We note that you have designated 2 a priori primary outcomes for both of these trials. You should be advised that, in this situation, it would be customary to require both outcomes to be superior to placebo at a 0.05 level in order for either trial to be considered positive. Assuming the data from these trials have not yet been analyzed, we would

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recommend that you amend the protocols by designating change from baseline on the HAMD total score as the primary outcome for study 329 and change from baseline on the MADRS as the primary outcome for study 377, since these outcomes are closely linked to the diagnostic criteria for major depression.

Your October 15, 1998 proposed pediatric study request for paroxetine included Study 453, a 38-week study in pediatric OCD which included a 16 week open label phase followed by a 16 week, double-blind, placebo controlled relapse prevention phase. Although we have no objection to your conducting this study, and although it would provide data complementing those obtained in an acute efficacy trial, this study by itself would be insufficient to provide meaningful clinical information to establish the efficacy of paroxetine in the pediatric OCD population. Consequently, we ask that you amend your proposal regarding the pediatric OCD indication. This amendment should address recommendations included under the heading "General Advice for Developing a Drug for Pediatric Obsessive Compulsive Disorder (OCD)" in the pediatric written request letter of April 28, 1999, in particular, the conduct of an adequate and well-controlled acute efficacy study in pediatric OCD.

Finally, your proposal should provide more complete detail regarding how you will address questions on the safety and pharmacokinetics of paroxetine in pediatric patients.

If you have any questions, contact Paul A. David, Regulatory Project Manager, at (301) 594-5530.

Sincerely yours,

5/18/99

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

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