DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-031/S-046
NDA 20-936/S-021

GlaxoSmithKline
Attention: James Murray
Director Regulatory Affairs
One Franklin Plaza
PO Box 7929
Philadelphia, PA 19101-7929

Dear Mr. Murray:

We acknowledge receipt of your supplemental new drug applications dated and received November 30, 2004 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil (paroxetine hydrochloride) Immediate Release Tablets (NDA 20-031), and Controlled Release Tablets (NDA 20-936).

These applications, submitted as "Changes Being Effected" supplements, provide for the following revisions to product labeling:

1. PRECAUTIONS/General/Discontinuation of Treatment with Paxil
   At the end of this section, a reference is added to the Pediatric Use section for information on adverse events reported upon Paxil discontinuation in pediatric patients.

2. PRECAUTIONS/General/Akathisia
   This new section is added and states: "The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment."

3. PRECAUTIONS/General/Serotonin Syndrome
   This new section states: "The development of a serotonin syndrome may occur in association with treatment with paroxetine, particularly with concomitant use of serotonergic drugs and with drugs which may have impaired metabolism of paroxetine. Symptoms have included agitation, confusion, diaphoresis, hallucinations, hyperreflexia, myoclonus, shivering, tachycardia, and tremor. The concomitant use of PAXIL with serotonin precursors (such as tryptophan) is not recommended (see WARNINGS, Potential for Interaction with Monoamine Oxidase Inhibitors and PRECAUTIONS, Drug Interactions)."

4. PRECAUTIONS/Drug Interactions/Tryptophan
   A reference to the new section regarding serotonin syndrome is added to the end of this section.

5. PRECAUTIONS/Drug Interactions/Serotonergic Drugs
   This new section states: "Based on the mechanism of action of paroxetine and the potential for serotonin syndrome, caution is advised when PAXIL is coadministered with other drugs or agents that may affect the serotonergic neurotransmitter systems, such as tryptophan, triptans, serotonin reuptake inhibitors, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see Serotonin Syndrome)."

6. PRECAUTIONS/Drug Interactions/Triptans
   The current section entitled "Sumatriptan" has been retitled "Triptans" and the existing statement has been expanded to apply to the concomitant use of any triptan with an SSRI instead of just sumatriptan. A reference to the new section regarding serotonin syndrome has been added at the end.

7. PRECAUTIONS/Drug Interactions/Lithium
   The current section is revised to delete the last phrase which indicates that the co-administration of paroxetine and lithium should be undertaken with caution since there is little experience with this combination. In its place, caution is advised when paroxetine is co-administered with lithium due to the potential for serotonin syndrome.

8. PRECAUTIONS/Pregnancy/Nonteratogenic Effects
   A statement has been added to indicate that there have been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRI's. We note that this subsection has now been moved to the WARNINGS section as noted in the Agency action letter dated February 6, 2006.

9. PRECAUTIONS/Pediatric Use
   The statement indicating that the safety and effectiveness in the pediatric population have not been established is retained. The following text is added to this statement: "Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with PAXIL and the data were not sufficient to support an indication for use in pediatric patients.

   In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with PAXIL and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

   Events reported upon discontinuation of treatment with PAXIL in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received PAXIL and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see Discontinuation of Treatment With PAXIL)."

10. ADVERSE REACTIONS/Postmarketing Reports
    The current information about postmarketing reports of serotonin syndrome, to include its association with the concomitant use of serotonergic drugs and drugs which impaired Paxil metabolism as well as the specific symptoms reported, has been deleted and replaced by the simple term "serotonin syndrome."

We have completed the review of your submission, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in your November 30, 2004 labeling. Accordingly, these applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Dr. Renmeet Gujral, Regulatory Project Manager, at (301) 796-1080.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
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