DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-031/S-049/S-054/S-055
NDA 20-936/S-023/S-030/S-031
NDA 20-710/S-018/S-019

GlaxoSmithKline
Attention: Barbara E. Arning, M.D.
Senior Director
US Regulatory Affairs, Psychiatry
2301 Rennaissance Boulevard
PO Box 61540
King of Prussia, PA 19406-2772

Dear Dr. Arning:

We acknowledge receipt of your supplemental new drug applications dated May 8, 2006 (NDAs 20-031/S-054, 20-936/S-030, 20-710/S-018), and June 7, 2006 (NDAs 20-031/S-055, 20-936/S-031 and 20-710/S-019) submitted under section 505(b) of the Federal Food Drug and Cosmetic Act for Paxil (paroxetine hydrochloride) tablets (NDA 20-031), Paxil (paroxetine hydrochloride) CR tablets (NDA 20-936), and Paxil (paroxetine hydrochloride) suspension (NDA 20-710).

We additionally acknowledge receipt of your submission dated May 18, 2006 to NDAs 20-031/S-049 and 20-936/S-023. Your May 18, 2006 resubmission constituted a complete response to our March 21, 2006 action letter.

Reference is also made to an Agency letter dated May 9, 2006, requesting revisions to product labeling pertaining to persistent pulmonary hypertension of the newborn (PPHN) and concomitant use of SSRIs/SNRIs and triptans.

These supplemental applications provide for the following revisions to product labeling (double underline font denotes additions to the labeling and strike through font denotes deletions):

20-031/S-054
20-936/S-030
20-710/S-018

- **Usage in Pregnancy: Nonteratogenic Effects**

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case-

control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.
There have also been postmarketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.
When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

20-031/S-049
20-936/S-023

- A statement has been added under **WARNINGS** section, **Clinical Worsening and Suicide Risk** subsection:

  In addition, patients with a history of suicidal behavior or thoughts, those patients exhibiting a significant degree of suicidal ideation prior to commencement of treatment, and young adults, are at an increased risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

- The following language under the **PRECAUTIONS** section, "Discontinuation of Treatment with Paxil" subsection as underlined:

  Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety, confusion headache lethargy, emotional lability, insomnia, and hypomania.

- A drug interaction statement has been added under the **PRECAUTIONS** section, under a new heading " Fosamprenavir/Ritonavir"

  Fosamprenavir/ritonavir: Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

- A statement has been added under **ADVERSE REACTIONS**

Hallucination: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9089 receiving drug and 4 of 3187 patients receiving placebo.

20-031/S-055
20-936/S-031
20-710/S-019

These supplements provide for revisions to the package insert in the following sections:

WARNINGS/Serotonin Syndrome:
The development of a potentially life-threatening serotonin syndrome may occur with use of PAXIL, particularly with concomitant use of serotonergic drugs (including triptans) and with drugs which impair metabolism of serotonin (including MAOIs). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The concomitant use of PAXIL with MAOIs intended to treat depression is contraindicated (see CONTRAINDICATIONS and WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors). If concomitant use of PAXIL with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see PRECAUTIONS—Drug Interactions). The concomitant use of PAXIL with serotonin precursors (such as tryptophan) is not recommended (see PRECAUTIONS—Drug Interactions).

Information for Patients: PAXIL should not be chewed or crushed, and should be swallowed whole. Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of PAXIL and triptans, tramadol, or other serotonergic agents.

Drug Interactions/Serotonergic Drugs: Based on the mechanism of action of paroxetine hydrochloride 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 triptans, linezolid (an antibiotic which is a reversible non-selective MAOI)(b)(4)_____
(b)(4)_____
-------- ---------- - ---------- ----- use of PAXIL with other SSRIs, SNRIs or tryptophan is not recommended (see PRECAUTIONS— Drug Interactions, *Tryptophan*).(b)(4)_____).

Drug Interactions/*Triptans:* There have been rare postmarketing reports of serotonin syndrome
(b)(4)_____
(b)(4)_____ ---------- --
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(b)(4)_____(b)(4)_____ ----------
---------- d dose increases (see WARNINGS—

Serotonin Syndrome) -(b)(4) [redacted]

We have completed the review of these supplemental applications 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 labeling submitted on June 7, 2006. Accordingly, these supplemental applications are approved effective on the date of this letter.

(b)(4) [redacted]

[redacted]

- [redacted]

- [redacted] ≥ [redacted]

(b)(4)

[redacted]

- [redacted]

[redacted]

[redacted]

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 Renmeet Gujral, Pharm. D., 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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