June 4, 2003

GlaxoSmithKline

Siddika Mithani
Director, Bureau of Cardiology, Allergy and Neurological Sciences
c/o Submission & Information Policy Division
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Ottawa, ON K1A 1B9

GlaxoSmithKline Inc.
7333, Mississauga Road North
Mississauga, Ontario
Canada L5N 6L4

Tel Redacted
Fax
www.gsk.com

Re: **N/C: PAXIL® (paroxetine hydrochloride) Tablets**
File No.: 9427-G0838-42

Dear Dr. Mithani:

We are pleased to submit a Notifiable Change (NC) for PAXIL®, to update the Product Monograph with new safety information. Studies have now been conducted with PAXIL® in pediatrics. Therefore, the purpose of this submission is to update Product Monograph with new safety information regarding pediatric use. In addition to the new pediatric safety information, the drug interaction information within the Precautions section has also been update to include risperidone.

In the EU, a CTD has been prepared in support of the use of PAXIL in Obsessive Compulsive Disorder (OCD) and Social Anxiety Disorder (SAD). Since the safety data to support the proposed changes to the Product Monograph is contained within this CTD, it was agreed with Dr. Cathy Petersen, Manager of the CNS, Division, that the complete CTD would be provided, which includes both safety and efficacy summaries, as well as copies of the full study reports. This CTD contains the following Modules:

Module 1: 2 Volumes (Volume 1 in duplicate)
Module 2: 1 Volume (in duplicate)
Module 5: 25 Volumes

For further details regarding the format of this submission, please see the Note to Reviewer in the beginning of Module 1.

Please note that Modules 1 and 2 are singled sided, and Module 5 is double-sided. This was previously discussed with and agreed with Hieu Vu and Dr. Cathy Petersen.

This submission is confidential and the property of the GlaxoSmithKline group of companies. It contains proprietary information and trade secrets and is submitted to the regulatory authority for the sole purpose of licensing the identified product. Reproduction, disclosure or use of the submission or information contained therein in whole or part otherwise than for the said purpose is forbidden unless at the express request or with the written consent of the applicant.

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Please contact me at (905) 819-3328 or via fax at (905) 819-3339, should you require additional information.

Sincerely,
GlaxoSmithKline Inc.

Mark Braham, B.Sc.
Regulatory Affairs, Manager

Encl.

** PAXIL® is a registered trademark, used under license by GlaxoSmithKline Inc.*

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IMPORTANT DRUG SAFETY INFORMATION
Until further information is available,
PAXIL® (paroxetine hydrochloride) should
not be used in children and adolescents under 18 years of age

Dear Health Care Professional:

GlaxoSmithKline Inc., following discussions with Health Canada, is alerting you to important emerging safety information regarding reports of possible suicide-related adverse events in pediatric patients treated with PAXIL®. The following information will be incorporated into the Product Monograph:

Until further information is available, PAXIL® (paroxetine hydrochloride) should not be used in children and adolescents under 18 years of age (ie. pediatric patients), due to a possible increased risk of suicide-related adverse events in this patient population.

In pediatric patients with Major Depressive Disorder (MDD), PAXIL® is contraindicated, due to additional evidence of lack of efficacy.

There is new evidence from three pediatric placebo-controlled trials in MDD of an increased risk of suicidal thinking, suicide attempts or self-harm. The incidence of these events in the PAXIL® group as compared to the placebo group was: 5.3% (20/378) versus 2.8% (8/285), respectively. Some of these events occurred during the tapering-off period of the studies. The three trials also demonstrated that PAXIL® failed to show greater efficacy than placebo in MDD.

Placebo-controlled data from patients with Social Anxiety Disorder (Social Phobia, SAD) also may suggest an increased risk of possible suicide-related adverse events in patients treated with PAXIL®: 2.4% (4/165) versus 0% (0/157) with placebo. Suicide-related adverse events were also reported in the open label enrichment phase of a study in Obsessive Compulsive Disorder (OCD). In view of the well-established comorbidity between depression and other psychiatric disorders, further information is required before the safe use of PAXIL® can be established in SAD or OCD in pediatrics.

In the pediatric clinical trial programme, which included more than 1,000 patients treated with PAXIL®, there were no completed suicides.

Patients currently taking PAXIL® should not discontinue treatment abruptly, due to risk of discontinuation symptoms. A gradual reduction in dose under medical supervision is recommended.

Both the UK Department of Health and the FDA recently issued statements regarding the new evidence from placebo-controlled trials of a possible increased risk of suicidal thinking and suicide attempts in children and adolescents under the age of 18 being treated with the drug PAXIL® for depression.

Although PAXIL® is not indicated for use in patients under 18 years of age in Canada, Health Canada is aware of off-label use of this drug in the pediatric population.

After consulting with independent experts in child and adolescent psychiatry, and in conjunction with Health Canada, the following guidance is offered in treating patients under 18 years of age:

- PAXIL® should not be prescribed as new therapy for patients under 18 years of age.
- If your patient is being successfully treated with PAXIL®, then the completion of the planned treatment course should be considered as an option in the management of the illness.
- In all other cases, change of treatment should be considered. If the medical decision is made to stop treatment with PAXIL®, **it is very important that the drug not be discontinued abruptly due to risk of discontinuation symptoms.** A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment dose titration should be managed on the basis of the patient's clinical response. Patients should be monitored when discontinuing treatment, regardless of the indication for which PAXIL® is being prescribed.

This new safety information regarding the use of PAXIL® in children and adolescents under the age of 18 years, does not affect the use of PAXIL® in adults at this time.

GlaxoSmithKline Inc. continues to work closely with Health Canada to monitor adverse event reporting and to ensure that up-to-date information regarding the use of PAXIL® is available.

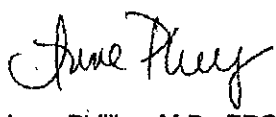
The identification, characterization and management of drug-related adverse events are dependent on the active participation of health care professionals in adverse drug reaction reporting programmes. Health care professionals are asked to report any suspected adverse reactions in patients receiving PAXIL® (paroxetine hydrochloride) directly to GlaxoSmithKline Inc. or the Marketed Health Products Directorate.

GlaxoSmithKline Inc.
7333 Mississauga Road North
Mississauga, Ontario
L5N 6L4
Tel: Redacted

Your professional commitment in this regard has an important role in protecting the well-being of your patients by contributing to early signal detection and informed drug use.

Any questions from health care professionals may be directed to Medical Information via GlaxoSmithKline Customer service at Redacted

Sincerely,



Anne Phillips, M.D., FRCPC
Vice-President, Research & Development and Chief Medical Officer
GlaxoSmithKline Inc.

Any suspected adverse reactions can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0201C2
OTTAWA, Ontario, K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free for consumers and health professionals:
Tel: 866 234-2345, Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the TPD web site or in The Canadian Compendium of Pharmaceuticals and Specialties.

IMPORTANT SAFETY INFORMATION
REGARDING PAXIL® IN PEDIATRIC PATIENTS

PAXIL® (paroxetine hydrochloride) should not be given to children and adolescents under 18 years of age due to a possible increased risk of suicide-related adverse events

MISSISSAUGA, Ontario (July 15, 2003) — GlaxoSmithKline Inc., following discussions with Health Canada, is alerting patients, their parents or guardians, and healthcare professionals that until further information is available Paxil should not be given to pediatric patients (children and adolescents under 18 years of age), due to concerns of a possible increased risk of suicidal thinking, suicide attempts or self-harm. Paxil must not be used in pediatric patients with major depressive disorder, due to the additional fact that studies have failed to show that Paxil was effective in this patient population.

Paxil is a drug prescribed by doctors to relieve symptoms of depression and anxiety disorders. These new safety concerns for patients under 18 years of age do not affect the use of Paxil in adults. Paxil is not approved in Canada for use in children and adolescents under 18 years of age.

It is very important that Paxil not be discontinued abruptly. Parents or guardians of pediatric patients or adolescents who are being treated with Paxil should consult with their doctors before discontinuing their medication. A doctor may decide to continue treatment with Paxil if the patient is responding well. Should the decision be made to stop treatment with Paxil, a gradual reduction in the dose under medical supervision is recommended due to the risk of discontinuation symptoms.

There is new evidence from pediatric clinical trials in major depressive disorder of an increased risk of suicidal thinking, suicide attempts or self-harm in patients treated with Paxil, compared to those treated with placebo (sugar pill). Reports of suicidal thinking and self-harm in Paxil-treated patients were also seen in pediatric trials in social anxiety disorder. Overall, the rate of such adverse events was higher in the Paxil-treated pediatric patients compared to placebo-treated patients. There were no suicides in the pediatric clinical trial program, which included more than 1,000 patients treated with the medication.

The study results also did not show that Paxil is effective in treating depression in pediatric patients. In view of this set of findings, and because depression may occur at the same time as anxiety disorders, such as obsessive compulsive disorder or social anxiety disorder, Paxil should not be given to children and adolescents under 18 for any indication, until further information is available.

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GlaxoSmithKline has sent a letter to healthcare professionals informing them of the new safety information. This information may be obtained on the Canadian website of GlaxoSmithKline (http://www.gsk.ca) or on the website of the Therapeutic Products Directorate of Health Canada (http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_public_e.html). The company is working with Health Canada to revise the Canadian prescribing information for Paxil. If patients have questions regarding their current Paxil prescription, they are asked to contact their doctor or pharmacist.

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For media inquires, please contact Alison Steeves or Jill McKinlay, (905) 819-3363.

Paxil® is a registered trademark, used under license by GlaxoSmithKline Inc.

Any suspected adverse reactions can also be reported to:
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0201C2
OTTAWA, Ontario, K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
Toll free for consumers and health professionals:
Tel: (866) 234-2345, Fax: (866) 678-6789
cadrmp@hc-sc.gc.ca
The AR Reporting Form and the AR Guidelines can be found on the TPD web site or in The Canadian Compendium of Pharmaceuticals and Specialties.