



GlaxoSmithKline

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

**Health Canada Endorsed
Important Safety Information on Paroxetine**

December 16, 2005

Subject: New Safety Information Regarding Paroxetine: Second Large Study Shows an Increased Risk of Cardiac Defects, Over Other Antidepressants, Following First Trimester Exposure to Paroxetine

Dear Health Care Professional:

On September 29, 2005, GlaxoSmithKline (GSK), in discussions with Health Canada, wrote to you with important new safety information regarding the potential for an increased risk of cardiovascular malformations with maternal exposure to paroxetine, in response to preliminary data from a GSK-sponsored epidemiologic study. GSK is now providing an update on the use of paroxetine during pregnancy, on the basis of findings from a new analysis of data from the Swedish national registry data.

SUMMARY OF FINDINGS

- An independent epidemiological study of delivery outcome following maternal use of SSRI antidepressants in early pregnancy has been conducted utilizing the Swedish national registry data (n=5,123 women). The findings show an approximate 2-fold increased risk of cardiac malformations in infants exposed to paroxetine, compared with the total registry population (approximately 2% incidence vs. 1%, respectively).
- The above Swedish findings are similar to those from a GSK-sponsored, U.S. epidemiologic study (n=5,791 women): an approximate 1.5-fold increased risk of cardiovascular malformations in infants exposed to paroxetine, as compared to exposure to other antidepressants (approximately 1.5% incidence vs. 1%, respectively).
- The majority of paroxetine-associated cardiac malformations were ventricular septal defects (VSD) and atrial septal defects (ASD) in the Swedish study, and VSD in the US study. To date, the combined data from these epidemiological studies, which use different methodologies, suggest that the individual risk of a mother having an infant with a cardiac defect following maternal paroxetine exposure is approximately 1/50, compared with an expected rate for such defects of approximately 1/100 infants in the general population. In general, septal defects range from those that are symptomatic and may require surgery, to those that are asymptomatic, and may resolve spontaneously. Information about the severity of the septal defects reported in the above database is not currently available.

RECOMMENDATIONS

- If a patient becomes pregnant while taking paroxetine, she should be informed of the current estimate of increased risk to the fetus with paroxetine over other antidepressants. Examinations of additional databases, as well as updated analyses, may result in changes to the current risk estimates. Consideration should be given to switching to other treatment options, including another antidepressant or non-pharmaceutical treatment such as cognitive behavioral therapy. Paroxetine treatment should only be continued for an individual patient, if the potential benefits outweigh the potential risks.
- Due to the potential for discontinuation symptoms, doctors should inform patients that the drug should not be stopped without first discussing it with their doctor. If the decision is made to discontinue paroxetine in a patient, please refer to the Discontinuation of Treatment with PAXIL®/PAXIL CR™ subsection of the WARNINGS & PRECAUTIONS section in the Product Monograph for further information.
- For women who intend to become pregnant, or are in their first trimester of pregnancy, initiation of paroxetine should be considered only after other treatment options have been evaluated.

BACKGROUND

GSK recently wrote to healthcare professionals advising of findings from a retrospective, U.S. epidemiologic study of major congenital malformations in infants born to 3,581 women dispensed antidepressants during the first trimester of pregnancy. A preliminary analysis of these data yielded adjusted odds ratios of 2.20 (95% Confidence interval [CI]: 1.34-3.63) for congenital malformations as a whole, and 2.08 (CI: 1.03-4.23) for cardiovascular malformations alone, for paroxetine as compared to the other antidepressants in the database.

A new study of delivery outcome following maternal use of SSRI antidepressants in early pregnancy has been conducted utilizing the Swedish national registry data. Previous published studies utilizing these registry data, and cited in our previous letter of September 29, 2005, to Health Care Professionals, found no evidence for an increased overall risk of major malformations with maternal exposure to SSRI medications, including paroxetine (Hallberg 2005, Ericson 1999). In this latest study, the population that was investigated comprised 5,175 infants born during the period July 1, 1995 to December 31, 2003, to 5,123 women reporting the use of any SSRI in the first trimester. Among them, 815 (15.9%) women reported the use of paroxetine (third most commonly used) and they delivered 822 infants. Rates of malformations in these infants were compared with the general population experience. No increase in the overall rate of congenital malformations was observed in infants exposed to paroxetine (4.9%), compared with the general population rate (4.8%) (adjusted OR 1.03; 95% confidence interval 0.75-1.41). There was, however, an increased risk for cardiac defects in infants exposed to paroxetine (OR 1.78, 95% confidence interval 1.12-2.75), which was contributed mainly by an increased risk of VSD and ASD (OR 1.92; 95% confidence interval 1.12-3.10); 13 of 19 paroxetine-exposed infants with cardiac defects had a VSD or ASD. An increased risk of cardiac defects was not observed in infants whose mothers received an SSRI other than paroxetine (OR 0.92; 95% confidence interval 0.89-1.21). The rate of cardiac malformations in infants exposed to paroxetine was approximately 2% for paroxetine vs 1% in the general population.

The retrospective GSK-sponsored cohort study, which used U.S. United Health Care data, was recently updated to include an extended study population, now comprising 5,956 infants born during the period of January 1995 through September 2004 to 5,791 women dispensed antidepressants during the first trimester. Out of the 5956 infants in the database that were exposed to an antidepressant, 815 (13.7%) were exposed to paroxetine alone (third most commonly used alone). The updated analysis showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.54; 95% confidence interval 0.81-2.92), whereas the preliminary analysis showed a statistically significant increase in risk for cardiovascular malformations. In the update analysis; nine out of 12 infants with cardiovascular malformations born to mothers who were dispensed paroxetine (and no other antidepressants) had a VSD. The prevalence of cardiovascular malformations was 1.5% for paroxetine vs. 1% for other antidepressants. This study also showed a statistically significant increased overall risk of major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.8; 95% confidence interval 1.2-2.8). The prevalence of all congenital malformations was 4% for paroxetine vs. 2% for other antidepressants. Separate analyses were not done for any specific malformations other than cardiovascular. It is important to note that because this study was designed to evaluate the *relative* risk of congenital malformations in infants born to women exposed to antidepressants, the study did not include a comparison to infants who were not exposed to any antidepressant. Therefore, these data should also be viewed within the context of the overall prevalence of congenital malformations in the general population, which is estimated by one source to be, in the U.S. approximately 3% for any malformation and approximately 1% for cardiovascular malformations alone (Honein 1999). GSK has posted the results of this study to its Clinical Trial Register where it can be read by anyone with Internet access. The website is <http://ctr.gsk.co.uk/welcome.asp>.

In addition to the above, a recent abstract presented at the 33rd Annual Conference of the European Teratology Society (3rd-7th September 2005) reported a smaller study examining pregnancy outcomes in pregnant women exposed to paroxetine or fluoxetine who contacted two teratogen information services in Israel and Italy (Diav-Citrin 2005). There was a higher overall rate of major congenital malformations in infants exposed to paroxetine in the first trimester (13/257 [5.1%]) compared to infants in a control group with drug exposures not known to be teratogenic (28/1062 [2.6%]) (relative risk [RR] 1.92; 95% confidence interval 1.01-3.65). A higher rate of cardiovascular anomalies was also observed in the paroxetine group (5/257 [1.9%]) compared to the control group (6/1066 [0.6%]) (RR 3.46; 95% confidence interval 1.06-11.2). Similar trends were reported in the fluoxetine group, but did not reach statistical significance.

It is not clear if the findings from these studies represent a true causal association with maternal paroxetine exposure.

For information on other epidemiological studies of pregnancy outcome following first trimester exposure to SSRIs, including paroxetine, please refer to our September 29, 2005, Dear Health Care Professional Letter.

PAXIL® is indicated for the treatment of major depressive disorder, obsessive-compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder; PAXIL CR™ is indicated for the treatment of major depressive disorder, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder.

GSK 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® and PAXIL CR™ 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 programs. The reporting rates determined on the basis of spontaneously reported adverse events are generally presumed to underestimate the risks associated with drug treatments. Healthcare professionals are asked to report any suspected adverse reactions in patients receiving PAXIL® or PAXIL CR™ directly to GSK or Health Canada at the following addresses:

GlaxoSmithKline Inc.
7333 Mississauga Road North
Mississauga, Ontario L5N 6L4
Tel: 1-800-387-7374

Any suspected adverse reaction can also be reported to:

Canadian Adverse Drug Reaction Monitoring Program (CADRMP)

Marketed Health Products Directorate

HEALTH CANADA

Address Locator: 0701C

OTTAWA, Ontario, K1A 0K9

Tel: 1-613-957-0337 or Fax: 1-613-957-0335

To report an Adverse Reaction, consumers and health professionals may call toll free:

Tel: 1-866-234-2345

Fax: 1-866-678-6789

cadrmp@hc-sc.gc.ca

The [AR Reporting Form](#) and the [AR Guidelines](#) can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-ei_form_e.html

http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/guide/ar-ei_guide-ldir_e.html

For other inquiries related to this communication, please contact Health Canada at:

Bureau of Cardiology, Allergy and Neurological Sciences

BCANS_Enquiries@hc-sc.gc.ca

Tel: 1-613-941-1499

Fax: 1-613-941-1668

Your professional commitment in this regard is important to 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 GSK Customer service at 1-800-387-7374.

Sincerely,



Dr John A Dillon MB BCh MFPM
VP, Medical Division and Chief Medical Officer
GlaxoSmithKline Inc.

REFERENCES

Diav-Citrin O, Shechtman S, Weinbaum D, et al. Paroxetine and fluoxetine in pregnancy: a multicenter, prospective, controlled study [abstract]. *Reproductive Toxicology* 2005;20:459.

Ericson A, Kallen B, Wilholm BE. Delivery outcome after the use of antidepressants in early pregnancy. *European Journal Clinical Pharmacology* 1999;55:503-508.

Hallberg P & Sjoblom V. The use of selective serotonin reuptake inhibitors during pregnancy and breast-feeding: a review and clinical aspects. *Journal of Clinical Psychopharmacology* 2005;25(1):59-73.