September 29, 2005

GlaxoSmithKline Inc.
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NEW SAFETY INFORMATION REGARDING PAROXETINE:
FINDINGS SUGGEST INCREASED RISK OVER OTHER ANTIDEPRESSANTS, OF CONGENITAL MALFORMATIONS, FOLLOWING FIRST TRIMESTER EXPOSURE TO PAROXETINE

Dear Health Care Professional:

GlaxoSmithKline Inc. (GSK), following discussions with Health Canada, would like to inform you of important new safety information regarding the use of paroxetine during the first trimester of pregnancy.

- The preliminary report of a retrospective epidemiological study of 3,581 pregnant women exposed to paroxetine or other anti-depressants during the first trimester indicates an increased risk for paroxetine compared to other antidepressants, of:
  - Overall major congenital malformations (2 fold increase), and
  - Cardiovascular malformations (2 fold increase) with ventricular septal defects being the most frequent type of cardiovascular defect reported in the paroxetine-exposed group.
  - The prevalence of major congenital defects, and of cardiovascular defects, in paroxetine-exposed pregnancies were 4% and 2% respectively in the study, as compared to 3% and 1% respectively in one estimate of the overall prevalence in the US general population (i.e. inclusive of all births, regardless of drug treatment) (Honein, 1999[1]).
- Other independent studies of pregnancy outcome following first trimester exposure to antidepressants, including paroxetine, provide conflicting evidence regarding rate of birth defects.
- As currently stated in the Product Monographs, paroxetine should be used during pregnancy only if the potential benefit justifies the potential risks to the fetus. Prescribers should carefully evaluate this new information when considering the use of paroxetine in women who are pregnant or planning pregnancy. This information should be discussed with the patient.
- Due to the potential for discontinuation symptoms, 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.
- GSK, has posted the results of this study to its Clinical Trial Website where it can be read by anyone with Internet access. The website is http://ctr.gsk.co.uk/welcome.asp.

BACKGROUND

GSK initiated a retrospective epidemiologic study of major congenital malformations in infants born to women taking antidepressants during the first trimester of pregnancy from January 1995 to June 2003. The study was conducted in 3,581 pregnant women. A preliminary analysis has recently been conducted which has shown a 2.2 fold increase [adjusted odds ratios of 2.20 (95% CI: 1.34-3.63)] for congenital malformations as a whole, and a 2.08 fold increase [2.08 OR (95% CI: 1.03-4.23)] for cardiovascular malformations alone, for paroxetine as compared to the other antidepressants in the database. The prevalences of congenital malformations as a whole and cardiovascular malformation alone were approximately 4% and 2%, respectively. Preliminary counts of the types of cardiovascular malformations suggest that of the 14 paroxetine-exposed infants with cardiovascular malformations, 10 included ventricular septal defects (i.e. 71%) in comparison to 17/ 37 (46%) for the other antidepressants combined. Exposure to paroxetine in the mothers of these 14 infants may or may not have been accompanied by co-exposure to other antidepressants in the database.

It is important to note that because the GSK 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 be viewed within the context of the overall prevalence of congenital malformations in the general population, which is estimated in the US to be approximately 3% for any malformation and approximately 1% for cardiovascular malformations alone (Honein 1999).

Findings from other epidemiological studies

Other epidemiological studies of pregnancy outcome following first trimester exposure to selective serotonin reuptake inhibitors (SSRIs) including paroxetine, provide conflicting evidence regarding the possibility of increased risk of major malformations with SSRI medications.

Most recently, Alwan et al (2005)[2] have reported data obtained from the National Birth Defects Prevention Study of infants delivered from 1997-2001. This is an ongoing case control study of birth defect risk factors utilising cases ascertained from birth defects surveillance systems in eight US states. Infants with selected major birth defects, either isolated or multiple, (n=5357) and normal controls (n=3366) were studied. Adjusted analyses showed that women who took an SSRI were more likely than those who were not exposed to have an infant with omphalocele (n=161) (OR 3.0, CI 1.4-6.1). The strongest effect was reported to be with paroxetine, which accounted for 36% of all SSRI exposures (OR 6.3, CI 2.0-19.6). The authors also found an association of exposure to any SSRI and having an infant with craniosynostosis (n=372) (OR 1.8, CI 1.0-3.2).

In the most recent publication from the Swedish Medical Birth Registry (Hallberg & Sjoblom, 2005[3]), which unlike the GSK study above, included a comparison to infants not exposed to antidepressants, data on 4,291 infants born to mothers exposed to SSRIs in early pregnancy demonstrated an overall prevalence of 2.9% for congenital malformations, which the authors concluded did not differ from the expected rate (3.5%) among unexposed infants. Of 708 exposures to paroxetine in this registry, the prevalence of malformations was 3.4%.

In another recent study, Wogelius et al (2005)[4] reported on a population-based cohort study in four Danish counties. To study the risk of congenital malformations, pregnancy outcome in women who redeemed a prescription for SSRIs from 30 days before conception to the end of the first trimester (1054 women) was compared with women with no SSRI prescriptions during this period (150,908 women). The adjusted OR was 1.4 (CI 1.1-1.9) for congenital malformations overall and 1.6 (CI 1.0-2.6) for congenital cardiac malformations in women who redeemed a prescription for SSRIs (paroxetine-specific data were not presented).

In addition to these epidemiological studies, there are three published reports of small, epidemiologic case-control studies based on prospectively gathered data in women exposed to paroxetine during their first trimester (Kulin, 1998[5]; Unfred, 2001[6]; Diav-Citrin, 2002[7]). The number of paroxetine-exposed pregnancies reported in the three studies ranged from 89 to 97, and all studies found no major teratogenic risk. A small study (19 paroxetine-exposed pregnancies) based on medical records review found congenital anomaly rates in accord with the general population (Hendrick, 2003[8]). However, these studies are too small to allow firm conclusions about paroxetine as an individual drug (i.e. < 100 paroxetine-exposures per study).

Although the differences in the results from the available studies and the diversity in type of abnormalities recently reported makes it difficult to definitively conclude a causal relationship for any particular congenital abnormality with paroxetine, GSK considers that it is important to draw your attention to these most recent reports. GSK is conducting additional epidemiologic studies to more fully understand these preliminary findings. GSK, in discussion with Health Canada, will be adding information about the above GSK-sponsored study to the PAXIL® and PAXIL CR™ Product Monographs. GSK has voluntarily posted the results of this study to its Clinical Trial Website where it can be read by anyone with Internet access. The website is http://ctr.gsk.co.uk/welcome.asp

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: (613) 957-0337 or Fax: (613) 957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: 866 234-2345
Fax: 866 678-6789
cadrmp@hc-sc.gc.ca

For other inquiries: please refer to the contact information:

Bureau of Cardiology, Allergy and Neurological Sciences
BCANS_Enquiries@hc-sc.gc.ca
Tel: (613) 941-1499
Fax: (613) 941-1668

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/hpfb-dgpsa/tpd-dpt/adverse_e.html
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/adr_guideline_e.html

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.

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