



December, 2005

## IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

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In September, 2005, GlaxoSmithKline (GSK) wrote to you regarding changes to the Pregnancy subsection of the PRECAUTIONS section in the labels for PAXIL<sup>®</sup> (paroxetine HCl) and PAXIL CR<sup>®</sup> (paroxetine HCl) Controlled-Release Tablets. These revisions were in response to preliminary data from a GSK-sponsored epidemiologic study of major congenital malformations in infants born to women taking antidepressants during the first trimester of pregnancy, which suggested an increased risk of congenital malformations with maternal exposure to paroxetine.

Updated analyses from this study (based on a larger cohort of pregnant women taking antidepressants), together with new data from another study utilizing a large medical birth registry, have now become available. On the basis of these new data, **GSK is making further revisions to the labels for PAXIL<sup>®</sup> and PAXIL CR<sup>®</sup>, including revision of the pregnancy precaution from Pregnancy Category C to Pregnancy Category D (indicative of positive evidence of human fetal risk) as well as placement of the usage in pregnancy language in the WARNINGS section of the label.**

### SUMMARY

- Updated data from a GSK-sponsored, retrospective, U.S. epidemiologic study of major malformations following maternal exposure to antidepressants in the first trimester showed a trend towards a 1.5-fold increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (whereas the preliminary analysis showed a statistically significant increase in risk for cardiovascular malformations). The most common cardiovascular malformations observed among paroxetine-exposed infants were ventricular septal defects. This study showed a statistically significant increased overall risk of major congenital malformations (inclusive of the cardiovascular defects) in infants exposed to paroxetine compared to other antidepressants. 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>
- A new study of delivery outcome following maternal use of SSRI antidepressants in early pregnancy has been conducted utilizing the Swedish national registry data. This study has reported a 2-fold increased risk of cardiac defects (contributed mainly by ventricular septal defects [VSD] and atrial septal defects [ASD]) in infants exposed to paroxetine, compared with the general population. Unlike the U.S. epidemiologic study mentioned above, this study found no increase in the risk of overall congenital malformations after maternal use of paroxetine -- an observation consistent with previous published analyses of these registry data (cited in the previous version of the Prescribing Information), which

found no evidence for an increased overall risk of major malformations with maternal exposure to SSRI medications, including paroxetine.

- It is not clear if the findings from these studies represent a true causal association with maternal paroxetine exposure. However, the data to date indicate 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 can range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously.
- GSK believes it is important to draw your attention to these recent findings, and is voluntarily adding details of these studies to the paroxetine label. On the basis of these data, it is considered appropriate at the current time to revise the pregnancy precaution to Pregnancy Category D.

## RECOMMENDATIONS

- If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant in these cases.
- If you choose to discontinue paroxetine in a patient, please refer to the Discontinuation of Treatment with PAXIL/PAXIL CR subsection of the PRECAUTIONS section in the labeling for further information.
- For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

**Please see below for the full text of the amended WARNINGS** (*new text has been underlined*). Complete copies of the revised package inserts for PAXIL and PAXIL CR are enclosed.

### PAXIL CR:

#### WARNINGS

##### Usage in Pregnancy: *Teratogenic Effects:*

Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential

harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see **PRECAUTIONS: Discontinuation of Treatment with PAXIL CR**). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

A study based on Swedish national registry data evaluated infants of 6, 896 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRIs; including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1-2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was approximately 2% vs. 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.

A separate retrospective cohort study using U.S. United Healthcare data evaluated 5,956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n=815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall 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 following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

**Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the MRHD on an mg/m<sup>2</sup> basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m<sup>2</sup> basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

**Nonteratogenic Effects:** Neonates exposed to PAXIL CR and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis,

apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors).

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 the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

## **PAXIL:**

### **WARNINGS**

#### **Usage in Pregnancy: *Teratogenic Effects:***

Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see **PRECAUTIONS: Discontinuation of Treatment with PAXIL CR**). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

A study based on Swedish national registry data evaluated infants of 6,896 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRIs; including n=815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1-2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was approximately 2% vs. 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.

A separate retrospective cohort study using U.S. United Healthcare data evaluated 5,956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n=815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8-2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with

cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall 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 following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

**Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are equivalent to 9.7 (rat) and 2.2 (rabbit) times the maximum recommended human dose (MRHD) for major depressive disorder, social anxiety disorder, GAD, and PTSD (50 mg) and 8.1 (rat) and 1.9 (rabbit) times the MRHD for OCD, on an mg/m<sup>2</sup> basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or 0.19 times (mg/m<sup>2</sup>) the MRHD for major depressive disorder, social anxiety disorder, GAD, and PTSD; and at 0.16 times (mg/m<sup>2</sup>) the MRHD for OCD. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

**Nonteratogenic Effects:** Neonates exposed to PAXIL and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS—Potential for Interaction With Monoamine Oxidase Inhibitors).

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 the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION).

## **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.

This retrospective 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 to 5,791 women dispensed antidepressants during the first trimester. 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); 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 suggested an increased risk of overall 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. 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 in the U.S. to be approximately 3% for any malformation and approximately 1% for cardiovascular malformations alone (Honein 1999).

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 the previous version of the paroxetine Prescribing Information, 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 infants of 6,896 women exposed to antidepressants in early pregnancy (including 5,175 infants born to 5,123 women reporting the use of any SSRI in the first trimester). Among them, 815 women reported the use of paroxetine 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.

In addition to the above, an abstract presented at the 33<sup>rd</sup> Annual Conference of the European Teratology Society (3<sup>rd</sup>-7<sup>th</sup> 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

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.

The medical community can further our understanding of PAXIL and PAXIL CR by reporting adverse events to GlaxoSmithKline at 1-888-825-5249 or to the FDA MEDWATCH program by phone at 1-800-FDA-1088, by FAX at 1-800-FDA-0178, by modem at 1-800-FDA-7737 or by mail:

MEDWATCH HF-2  
FDA  
5600 Fisher's Lane  
Rockville, MD 20857

GlaxoSmithKline encourages you to familiarize yourself with these revisions to labeling. If you have any questions about the new information, please contact our Customer Response Center at 1-888-825-5249.

Sincerely,



Jack Modell, MD  
Vice President  
Clinical Psychiatry – North America  
GlaxoSmithKline