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IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

GlaxoSmithKline (GSK) would like to advise you that it is **changing the Pregnancy subsection** of the PRECAUTIONS section in the labels for PAXIL® (paroxetine HCl) and PAXIL CR® (paroxetine HCl) Controlled-Release Tablets.

SUMMARY

- Paroxetine currently carries a Category C pregnancy precaution, indicating that there are no adequate and well-controlled studies in humans to determine the effect of paroxetine on the fetus. Labeling states that the drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The label also currently includes information related to possible nonteratogenic effects, including symptoms and complications observed in neonates exposed to paroxetine in the third trimester of pregnancy.

- GSK recently conducted a *retrospective* epidemiologic study of major congenital malformations in infants born to women taking antidepressants during the first trimester of pregnancy. Preliminary results suggest an increase in the risk of congenital malformations associated with the use of paroxetine as compared to other antidepressants. The types of congenital malformations, which were most commonly cardiovascular, were reflective of those seen in the general population. The most common cardiovascular malformations observed in the study were ventricular septal defects.

- The preliminary results of this study and recent abstracts published by Alwan & Wogelius differ from previous epidemiologic studies, making it difficult to conclude whether a causal relationship exists. For example, data from the Swedish Medical Birth Registry, one of the largest available birth registries, have not provided evidence for an increased risk of major malformations with SSRI medications, including paroxetine.

- GSK believes it is important to draw your attention to these recent findings, and is voluntarily adding this information to the paroxetine label. GSK will post 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.

RECOMMENDATIONS

- As with all Pregnancy Category C drugs, health care providers are advised to carefully weigh the potential risks and benefits of using paroxetine therapy in women during pregnancy. It is recommended that health care providers discuss these latest findings, described in more detail below, as well as treatment alternatives, with their patients.
- 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.
- Paroxetine should be used during pregnancy only if the potential benefit justifies the potential risks to the fetus.

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

PAXIL CR:

PRECAUTIONS

Pregnancy: *Teratogenic Effects:* Pregnancy Category C.

There are no adequate and well controlled studies in pregnant women. A recent retrospective epidemiological study of 3,581 pregnant women exposed to paroxetine or other antidepressants during the 1st trimester suggested an increased risk of overall major congenital malformations for paroxetine compared to other antidepressants (OR 2.20; 95% confidence interval 1.34-3.63). There was also an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 2.08; 95% confidence interval 1.03-4.23); 10 out of 14 infants with cardiovascular malformations had ventricular septal defects. A separate study based on the Swedish Medical Birth Registry evaluated 4,291 infants exposed to SSRIs in early pregnancy. This study reported no increased risk for overall major malformations in 708 infants born to women with paroxetine exposure in early pregnancy.

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^2 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^2 basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. Paroxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

PAXIL:

PRECAUTIONS

Pregnancy: *Teratogenic Effects:* Pregnancy Category C.

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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^2 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^2) the MRHD for major depressive disorder, social anxiety disorder, GAD, and PTSD; and at 0.16 times (mg/m^2) the MRHD for OCD. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known. Paroxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

BACKGROUND

GSK conducted a *retrospective* epidemiologic study of major congenital malformations in infants born to women taking antidepressants during the first trimester of pregnancy. A preliminary analysis has recently been conducted which 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. The prevalences of congenital malformations as a whole and cardiovascular malformation alone were approximately 4% and 2%, respectively. Of the cardiovascular malformations reported in infants whose mothers were dispensed paroxetine, the majority were ventricular septal defects.

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).

Previous epidemiological studies of pregnancy outcome following first trimester exposure to selective serotonin reuptake inhibitors (SSRIs), including paroxetine, have not provided evidence for an increased risk of major malformations for SSRI medications. In the most recent publication based on the Swedish Medical Birth Registry (Hallberg 2005), 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 of 3.5% among unexposed infants. Of 708 exposures to paroxetine in this registry, the prevalence of malformations was 3.4%.

In addition to the data by Hallberg et al, 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; Unfred, 2001; Diav-Citrin, 2002). 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).

More recently, Alwan et al (2005) have reported data obtained from the National Birth Defects Prevention Study of infants delivered from 1997-2001. 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) (odds ratio [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).

A second abstract, from Wogelius et al, just presented at the 21st International Conference on Pharmacoepidemiology and Therapeutic Risk Management (August 21-24, 2005), reported an adjusted OR of 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) from 30 days before conception

to the end of the first trimester compared to women with no SSRI prescriptions during this period.

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, however GSK believes it is important to draw your attention to the most recent findings. GSK is conducting additional epidemiologic studies to more fully understand these preliminary findings.

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. You can find other useful information related to this issue as well as to clinical trials involving other GSK products at our Clinical Trial Registry website (http://ctr.gsk.co.uk/welcome.asp).

Sincerely,

Regional Medical Director
Worldwide Development
GlaxoSmithKline