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**GlaxoSmithKline**
**Pharmaceuticals**
Stonemasons Way
Rathfarnham
Dublin 16
Ireland

Tel. +353-1-495 5000
Fax. +353-1-495 5105
www.gsk.com

## IMPORTANT SAFETY INFORMATION

Dear Healthcare Professional:

Following discussion with EU regulatory agencies including the Irish Medicines Board, GlaxoSmithKline (GSK) would like to inform you of **changes to the Pregnancy subsection** of the product information (Summary of Product Characteristics [SPC]) for **SEROXAT** (paroxetine hydrochloride).

**The amended text for the Pregnancy subsection of the product information is as follows (see Section 4.6 of the attached SPC for the complete Pregnancy wording);**

> Some epidemiological studies suggest a small increased risk of cardiovascular malformation (e.g. ventricular (majority) and atrial septum defects) associated with the use of paroxetine during the first trimester. The mechanism is unknown. The data suggests that the risk of having an infant with a cardiovascular defect following maternal paroxetine exposure is less than 2/100 compared with an expected rate for such defects of approximately 1/100 in the general population. Available data do not suggest an increase of the overall rate of congenital malformation.
>
> Paroxetine should only be used during pregnancy when strictly indicated. The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant. Abrupt discontinuation should be avoided during pregnancy (see "Withdrawal Symptoms Seen on Discontinuation of Paroxetine", section 4.2 Posology and Method of Administration).

## SUMMARY

- The current product information states that Paroxetine should be used during pregnancy only when strictly indicated. The product information also includes information related to possible nonteratogenic effects, including symptoms and complications observed in neonates exposed to Paroxetine in the third trimester of pregnancy.

**GlaxoSmithKline (Ireland) Ltd.**

**Registered in Ireland No. 15513**
**Registered office:** Stonemasons Way, Rathfarnham, Dublin 16, Ireland

**Directors:** **A.J. Lynch**
**T.A. Tordoff (GB)**
**D.S. Redfern (GB)**

- A recent GSK-sponsored, retrospective, U.S. epidemiological study of major malformations following maternal exposure to antidepressants in the first trimester showed a trend towards an 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 (VSD). This study showed a statistically significant increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) in infants exposed to paroxetine compared to other antidepressants. However, the point estimates for all antidepressants investigated in this study and the corresponding confidence intervals show a large overlap. 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 separate 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 an increased risk of cardiac defects (mainly VSD and atrial septal defects [ASD]) in infants exposed to paroxetine, compared with the general population. Unlike the U.S. epidemiological 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, 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. The mechanism for such effects is currently unknown. However to date, the available data indicate that the individual risk of a mother having an infant with a cardiac defect following maternal paroxetine exposure is less than 2/100, compared with an expected rate for such defects of approximately 1/100 infants in the general population. Some infants born with VSD or ASD defects will have no symptoms and the defect may correct itself spontaneously; in other infants, however, these defects may be more serious and require surgical intervention.

- GSK believes it is important to draw your attention to these recent findings, which are summarized in more detail at Annex 1.

**RECOMMENDATIONS**

- Health care providers are advised to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant, and should only prescribe paroxetine if the potential benefit outweighs the potential risk. It is recommended that health care providers discuss these latest findings with their patients.

- If you choose to discontinue paroxetine in a pregnant patient, please refer to the "Withdrawal Symptoms Seen on Discontinuation of Paroxetine", section

4.2 Posology and Method of Administration of the SPC for further information.

Any suspected adverse reactions should be notified to the company and /or the Irish Medicines Board in the usual way.

If you have any further questions or wish to discuss this letter, please contact GlaxoSmithKline on 1800 244 255.

Yours sincerely,

Martina Dempsey

Martina Dempsey PhD
Director of Medical and Regulatory Affairs
GlaxoSmithKline (Ireland) Limited

**Annex 1**

GSK has conducted aretrospective cohort study, which used U.S. United Health Care data, comprising 5,956 infants born to 5,791 women dispensed antidepressants during the first trimester. The study 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 1.82; 95% confidence interval 1.17-2.82). The prevalence of all congenital malformations was 3.8% for paroxetine vs. 2.1% 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 prevalence data should 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 1% for cardiovascular malformations alone and approximately 3% for any malformation (Honein et al, 1999).

A separate 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 found no evidence for an increased overall risk of major malformations with maternal exposure to SSRI medications, including paroxetine (Hallberg & Sjoblom, 2005; Ericson et al, 1999). In this latest study, the population that was investigated comprised 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 2.3%, compared with 1.3% in the general population.

In addition to the above, an abstract presented at the 33$^{rd}$ Annual Conference of the European Teratology Society (3$^{rd}$-7$^{th}$ 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 et al, 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.

In a further abstract, Alwan et al (2005) have reported data obtained from the National Birth Defects Prevention Study (US) 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).

Finally, an abstract from Wogelius et al, 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.

In addition to these recently-reported epidemiologic studies, there are three previous reports of small, epidemiologic studies based on prospectively gathered data in women exposed to paroxetine during their first trimester (Kulin et al, 1998; Unfred et al, 2001; Diav-Citrin et al, 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 et al, 2003).

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