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Scientific Office

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المكتب العلمي

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**Date: 15<sup>th</sup> Dec, 2012**

**Title: Wellbutrin<sup>®</sup> / Zyban<sup>®</sup> (Bupropion Safety Update – possible increased risk of some congenital cardiovascular malformations)**

Dear Healthcare Professional;

GSK has recently received the results of an epidemiology study investigating the risk of congenital cardiovascular malformations following bupropion exposure during the first trimester of pregnancy. Consideration of this additional data along with findings from other studies on the topic suggests a potential increased risk of some congenital cardiovascular malformations. Some data suggests a potential increased risk of ventricular septal defects and some data suggests a potential increased risk of left outflow tract heart defects but the findings are not consistent across the studies. No association was observed when all types of congenital cardiovascular malformations were considered as a group.

GSK is informing health care professionals of this potential risk.

#### **Therapeutic Indication**

1. Major depressive disorder (Wellbutrin<sup>®</sup> indication)
2. Smoking cessation (Zyban<sup>®</sup> indication)

#### **Key Messages**

- GSK is changing the pregnancy information in the labels for all of our bupropion containing products.
- This information is relevant to all women who are planning to become pregnant or who are pregnant.
- There is a potential increase in the risk of some congenital cardiovascular malformations when the mother is exposed to bupropion during the first trimester.
- Across the datasets that were assessed, congenital cardiovascular malformations were rare and the types of cardiovascular defects observed were inconsistent.
- GSK considers that Health Care Professionals should be aware of this potential risk, despite the inconsistent data.

### **Action required by Health Care Providers**

Health Care Providers should consider the new information relating to bupropion and the potential for some congenital cardiovascular malformations. The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant, and should only prescribe bupropion if the expected benefits are greater than the potential risks.

### **Revised Labeling**

Pregnancy section under "warnings and precaution" in the prescribing information for all GSK Bupropion containing products Wellbutrin<sup>®</sup> and Zyban<sup>®</sup> will be modified to reflect above safety information for Bupropion.

The changes are as follow:

Some epidemiological studies of pregnancy outcomes following maternal exposure to bupropion in the first trimester have reported an association with increased risk of some congenital cardiovascular malformations. These findings are not consistent across studies. The prescribing physician will need to weigh the option of alternative treatments in women who are pregnant or are planning to become pregnant, and should only prescribe WELLBUTRIN XL if the expected benefits are greater than the potential risks.

The prospectively observed proportion of cardiac birth defects in pregnancies with prenatal exposure to bupropion in the first trimester in the international Pregnancy Registry was 9/675 (1.3%). (*Bupropion Pregnancy Registry, 2008*)

In a retrospective, managed-care database study (n=7,005 infants), there was no greater proportion of congenital malformations (2.3%) or cardiovascular malformations (1.1%) associated with first trimester exposure to bupropion (n=1,213 infants) compared with the use of other antidepressants in the first trimester (n=4,743 infants; 2.3% and 1.1% for congenital and cardiovascular malformations, respectively) or bupropion use outside the first trimester (n=1,049: 2.2% and 1.0%, respectively). (*Cole et al., 2007*)

In a retrospective case-control analysis using data from the National Birth Defects Prevention Study, there were 12383 case infants and 5869 control infants. A statistically significant association was observed between the occurrence of a left outflow tract heart defect in the infant and self-reported maternal bupropion use in early pregnancy (n=10; adjusted OR=2.6; 95% CI 1.2, 5.7). No association was observed between maternal bupropion use and any other type of cardiac defect or with all categories of heart defects combined. (*Alwan et al., 2010*)

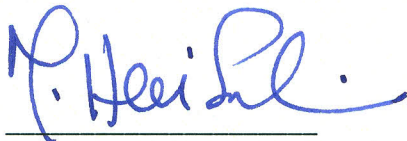
A further case-control analysis of data from the Slone Epidemiology Center Birth Defects Study included 7913 infant cases of cardiac defects and 8611 controls. This found no statistically significant increase of left outflow tract heart defects with maternal bupropion use (n=2; adjusted OR= 0.4; 95% CI 0.1, 1.6). However, a statistically significant association was observed for ventricular septal defects (n=17; adjusted OR=2.5; 95% CI 1.3, 5.0) following the use of bupropion alone during the first trimester. (*Slone Epidemiology Center, 2012*)

### **Further Information**

GlaxoSmithKline will continue to monitor the safety of Wellbutrin® and Zyban® and update SFDA of any serious adverse event for evaluation. You can assist us in monitoring the safety of Wellbutrin® and Zyban® by reporting adverse reactions to fax: [+96626536660](tel:+96626536660) or by email to GlaxoSmithKline safety email: [faisal.m.shujrah@gsk.com](mailto:faisal.m.shujrah@gsk.com) Or to national Pharmacovigilance and Drug Safety Center at Fax: [+966-1-2057662](tel:+966-1-2057662) or by email to: [npc.drug@sfd.gov.sa](mailto:npc.drug@sfd.gov.sa) .

If you have any question about the new information, please contact GSK medical information department at GlaxoSmithKline Saudi Arabia fax: [+96626536660](tel:+96626536660) or email: [mohammedatef.a.soliman@gsk.com](mailto:mohammedatef.a.soliman@gsk.com).

Best regards



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### **References**

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