**GSK Medicine: Bupropion**

**Study No.: WWE112917**

**Title:** GlaxoSmithKline International Bupropion Pregnancy Registry

**Rationale:** GlaxoSmithKline managed this Registry as part of a program in epidemiologic safety monitoring. Bupropion is not indicated for use in pregnancy; however, women who smoke or women with depression may require or be unintentionally exposed to bupropion during pregnancy.

The purpose of the Registry was to monitor for substantial increase in the frequency of major birth defects in pregnancies inadvertently or intentionally exposed to Wellbutrin®, Wellbutrin SR®, Wellbutrin XL® and Zyban® brands of bupropion. The large number of women of reproductive age with depression or attempting smoking cessation and the lack of data concerning outcomes following bupropion use during pregnancy made such a Registry an important component of the program of epidemiologic studies of the safety of bupropion. Additionally, the Registry provided data on the types and frequency of pregnancy outcomes following exposure to bupropion.

Data from the registry were reviewed and conclusions developed by an independent scientific advisory committee on a semi-annual basis. The report is published at [http://pregnancyregistry.gsk.com/index.html](http://pregnancyregistry.gsk.com/index.html) and has been made available to regulators and healthcare providers.

**Objectives:**
- a) to detect any major teratogenic effect following exposure to bupropion in pregnancy and
- b) to provide information on outcomes following pregnancy exposure to bupropion and
- c) to generate hypotheses concerning potential associations with specific defect types, to be tested through appropriately designed studies.

**Indication:** Smoking cessation, major depressive disorder, prevention of seasonal major depressive episodes in patients with a diagnosis of seasonal affective disorder.

**Study Investigators/Centers:** The Registry was managed by Kendle International Inc.

**Research Methods:**

**Data Source:** Primary data collection. 1 September 1997 – 31 March 2008

**Study Design:** International, observational, exposure-registration, follow-up study

**Study Population:** Women exposed to bupropion during pregnancy.

**Enrollment criteria:**
The minimum criteria required to enroll a subject were:
- Country of origin of the report
- Documentation that bupropion was taken during pregnancy,
- Sufficient information to determine whether the pregnancy is being prospectively or retrospectively registered
- Date the pregnancy was registered
- Source of the report (health care professional, subject)
- Whether the outcome of pregnancy was known at the time of the report
- Timing of the prenatal exposure to bupropion (no broader than trimester during which the exposure took place),
• Whether the subject was involved in a study in pregnancy at the time of the prenatal exposure
• Full reporter contact information to allow for follow-up (name, address, etc.)

Study Methods:
Healthcare professionals with patients exposed to bupropion during pregnancy were encouraged to prospectively enroll each patient in the registry. Reporting of exposed pregnancies was voluntary. To further reduce possible bias in reporting, the Registry asked health care providers to enroll their subjects as early in pregnancy as possible, preferably before any prenatal testing for defects was done.

Prospectively reported pregnancies are those reported during pregnancy, before the pregnancy outcome is known. Because the outcome of the pregnancy is unknown when the exposure is reported, follow-up to determine the outcome is required.

When a patient initiated contact with the Registry they were asked to provide permission, and sufficient contact information, for the Registry to follow-up with their health care professional for the purpose of ascertaining details of the birth outcome. To assure patient confidentiality the Registry assigned a Patient ID number, which was used as the reference ID for follow-up communication with the reporting health professional.

At enrolment, information on maternal socio-demographics (age, ethnicity), pregnancy (date of last menstrual period, prenatal testing and bupropion treatment (timing, dose, duration) was collected. Near the estimated date of delivery, follow-up was obtained through the healthcare provider including information on maternal risk factors, pregnancy outcome, and neonatal health. Data on exposure to bupropion and other medications during pregnancy were also reviewed. A report of an exposure was closed when clear information on the bupropion exposure and pregnancy outcome had been obtained. A report was closed as having the minimum requirements were not reported despite attempts to obtain the minimum data points. Reports of exposures were closed as lost to follow-up after the reporting health care professional had been repeatedly contacted for follow-up well beyond the expected delivery date or if the health care professional could no longer locate the patient. Up to six attempts were made to contact the healthcare provider before a case was closed.

While the Registry is limited to prospective reports, some pregnancy exposures will be reported after the pregnancy outcome has occurred (retrospective reports). Each retrospective report was reviewed although not included in the primary analysis. In general, retrospective notification of outcomes following exposure to drugs is biased toward reporting severe and unusual cases, and is not reflective of the general experience with the drug. Moreover, information about the total number of exposed persons is unknown. Therefore, rates of outcomes cannot be calculated from the retrospective reports. However, a series of reported birth defects can be evaluated to detect patterns of specific birth defects and can help identify early signals of new drug risks.

Data were reviewed and conclusions developed on a semi-annual basis by an independent Scientific Advisory Committee consisting of experts in psychiatry, maternal-fetal medicine, teratology, and epidemiology.

Study Outcomes:
The major interest of the Registry was to monitor bupropion exposures in pregnancy for major congenital malformations that may be attributable to the drug exposure. This Registry adopts for clarification the term birth defect for abnormalities usually referred to as congenital abnormality. For purposes of data reporting, pregnancy outcomes are categorized as one of the following: 1)
outcomes with birth defects, 2) outcomes without birth defects, and 3) spontaneous pregnancy losses. The first and second categories are further classified by: (a) live births, (b) fetal deaths, and (c) induced abortions.

This Registry adopted the following definition for a birth defect: any live or stillborn infant of 20 weeks or greater, or electively terminated fetus of any gestational age, with a structural or chromosomal abnormality diagnosed before the child is 6 years of age. However, most outcomes are reported during the first year of life. Because access to pediatric evaluations and records to obtain follow-up information about the presence of defects is beyond the scope of its methods, the Registry primarily monitors the frequency of major defects that are external, recognizable in the delivery room and/or symptomatic shortly after birth. Chromosomal abnormalities are not included in the numerator in risk analyses as there are no known instances of drugs being associated with genetic abnormalities in humans. Minor defects and those diagnosed on an out-patient basis, weeks to months after delivery, were not consistently ascertained.

For reference, the Committee adopts the list of birth defects recognized by the CDC. This 6-digit code list is available from the CDC web site at http://www.cdc.gov/ncbddd/bd/macdp_resources.htm (and click on the 3rd bullet). All birth defects were classified taking into consideration advice from members of the Advisory Committee. Infants with only transient or infectious conditions, or biochemical abnormalities, were classified as being without birth defects unless there was a possibility that the condition reflects an unrecognized birth defect. Detected and reported transient or infectious conditions or biochemical abnormalities in infants without birth defects and defects that are excluded by the CDC guidelines were noted separately.

Study Exposures:
Prospective reports of pregnancy exposures to bupropion with documented pregnancy outcomes were stratified by the earliest trimester of exposure. Gestational weeks are counted from the date of the last menstrual period, with the second trimester beginning at week 14, and the third trimester beginning at week 28, and by birth outcome [live birth, induced abortion, spontaneous loss (<20 weeks), and fetal loss (>20 weeks)].

Study comparator groups:
There is no internal control/comparator group as this is a single drug pregnancy registry.

Data Analysis Methods:
The percentage of infants with major birth defects and 95% confidence intervals (Wilson score method with continuity correction) are calculated by trimester of exposure to bupropion as:

\[
\text{the total number of outcomes with major birth defects} \div (\text{the number of outcomes with major birth defects} + \text{the number of live births without major birth defects}).
\]

All spontaneous pregnancy losses, as well as elective terminations and fetal deaths without reported defects and pregnancies lost to follow up, are excluded from the denominator due to the potential lack of systematic defect ascertainment in those situations.

The risk of major birth defects following first trimester exposure to bupropion is of primary interest as this represents the period of organogenesis.

As there was no within-study comparison group, the Registry uses other published data on frequency of major birth defects to assess whether there are substantial elevations in risk of major birth defects in the Registry. Possible reference data include the CDC's birth defects surveillance system, which reports a total prevalence of birth defects identified among births from 1968 through 2003 of 2.67% . Seventy-eight percent of these infants and fetuses had birth defects that were identified either prior to
birth or during the first week of life (Correa et al., 2007). Quantitative comparisons between studies are difficult to interpret as case ascertainment methods and classification methods are not identical. In addition, published literature on the expected frequency of birth defects in depressed women and in women smoking cigarettes is considered. Most major structural defects have their origins in the first trimester of pregnancy, the time of major organogenesis. All analyses are stratified by earliest trimester of exposure.

For each case the timing of the exposure relative to the known origins of the defect are reviewed, alternative causes (e.g., recognized genetic or chromosomal defect or exposure to a known teratogen) are assessed, and the uniqueness of the defect is assessed. In addition, the magnitude of the proportion with birth defects is compared to the reference population, and the spectrum of defects are reviewed for common etiology.

All sources of data, on pregnancy exposures to bupropion including retrospective reports and published literature, were reviewed, but not included in the primary analysis.

Limitations:
As reporting of pregnancies was totally voluntary, it is possible that even in prospectively reported pregnancies there could be bias in type of pregnancies enrolled. Also, it is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Despite this, the Registry is intended both to supplement animal toxicology studies and other structured epidemiologic studies and clinical trial data, and to assist clinicians in weighing the risks and benefits of treatment for individual patients and circumstances.

The calculation of risk, which excludes voluntary terminations and fetal deaths without reported birth defects and all spontaneous pregnancy losses, may introduce some bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or birth defects. The data collection form attempts to obtain information on birth defects detected at the time of the outcome, but in all likelihood, the reporting physician may not always know the condition of the aborted fetus.

Study Results:
Through 31 March 2008:
Total No. prospectively registered pregnancies            1597
No. closed with known outcome                                     994 pregnancies, 1005 outcomes (9 sets of twins and 1 set of triplets)
No. pending                                                                    31
No. lost-to-follow-up                                                        572

For a breakdown of pregnancies by country please refer to the complete registry report at http://pregnancyregistry.gsk.com/index.html

Indication
Depression                                                                    683
Smoking cessation                                                        174
Both depression and smoking cessation                          26
Bipolar affective disorder                                                 14
Other                                                                                39
Unspecified                                                                      58

Outcomes by earliest trimester of exposure (1 September 1997 - 31 March 2008)

<table>
<thead>
<tr>
<th>Earliest Trimester of Exposure</th>
<th>Birth Defects</th>
<th>Induced Abortion</th>
<th>No Birth Defects Reported</th>
<th>Spontaneous Pregnancy Loss</th>
<th>Total Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live Birth</td>
<td>Live Birth</td>
<td>Fetal Death</td>
<td>Live Birth</td>
<td>Fetal Death</td>
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<tr>
<td>Fetal Death</td>
<td>Induced Abortion</td>
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<td>Induced Abortion</td>
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</tbody>
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* Some outcomes are not included in the primary analysis.
### Data Summary

#### Risk of major birth defects (MBDs) by earliest trimester of exposure

First trimester: 24 MBDs among 675 outcomes: 3.6% (95% CI 2.3% - 5.3%)

#### Risk of MBDs in general population surveillance programs

MACDP from 1968 through 2003: 2.67%

### Description of major birth defects by earliest trimester of exposure

#### First Trimester Bupropion Exposures

- Bilateral clubfeet
- Abnormal aortic valve thickening with secondary mild aortic insufficiency
- Klinefelter’s Syndrome with no physical abnormalities diagnosed by amniocentesis
- Ventricular septal defect
- Trivial valvular pulmonic stenosis and tiny atrial septal defect
- Evidence of Down Syndrome on a prenatal test
- Congenital heart defect (coarctation) and ventricular septal defect
- Thickened heart muscle
- Pulmonary stenosis
- Coarctation of the aorta
- Congenital pulmonary lymphangiectasis in one lung, secundum atrial septal defect, cleft palate, protuberant maxilla, low set ears, flattened pinnae, left pinna malformed, pectus excavatum, and kyphosis
- Trisomy 21
- Trisomy 18
- Down Syndrome
- Trisomy 14
- Ultrasound diagnosis of a left diaphragmatic hernia with intestine in the thorax, "stocky"hands and presence of karyotype 46,XX,t(15;15)/46,XX,t(15)
- Bilateral kidney dilation from reflux diagnosed prenatally and double ureters
- Jeune’s syndrome (thoracic dysplasia with short limbs) diagnosed prenatally
- Hypospadias and cleft right ear lobe
- Anencephaly
- Bilateral club feet
- Mixed superficial and deep hemangioma, left eyelid, requiring laser photocoagulation
- Atrial septal defect with patent ductus arteriosis and patent foramen ovale
- Duplicate left renal pelvis
Second Trimester Bupropion Exposures
Bilateral club feet; hemangioma on forehead x 2
Improving torticollis and oral neoplasm that spontaneously resolved
Cri-du-chat syndrome, 5p deletion
A descriptive of all retrospectively reported major birth defects can be found in the complete registry report at
http://pregnancyregistry.gsk.com/index.html

Conclusion: The observed proportion of major birth defects in pregnancies with prenatal exposure in the first trimester is 24/675 (3.6%, 95% CI 2.3% - 5.3%). This proportion includes 651 live births without birth defects, 18 live births with birth defects, 1 fetal death with a birth defect, and 5 induced abortions with birth defects. The overall proportion of major birth defects in metropolitan Atlanta reported by the MACDP from 1968 through 2003 was 2.67% (Correa et al, 2007).

Following the publication of a retrospective cohort study (Cole JA 2007) the Committee reviewed continuation of the Registry. Given this larger dataset and ten years of surveillance for the Registry, the Committee supported the termination of this Registry.

After reviewing the 1005 prospectively reported pregnancy outcomes the Bupropion Pregnancy Registry Advisory Committee concluded that the Registry has successfully met its primary purpose which was to exclude a major teratogenic effect in pregnancies inadvertently or intentionally exposed to any formulation of bupropion. The Registry was not designed to exclude moderate increases in the risk of specific defects.

Publications:

