The Bupropion Pregnancy Registry

Final Report

1 September 1997 through 31 March 2008

Issued: August 2008

A Project Conducted By GlaxoSmithKline

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BUPROPION PREGNANCY REGISTRY

FINAL REPORT

1 SEPTEMBER 1997 – 31 MARCH 2008

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FOREWORD

This Report describes the experience of the study of prospectively reported pregnancy outcomes in the Bupropion Pregnancy Registry through 31 March 2008.

Bupropion is available by prescription for the treatment of depression (under the brand names Wellbutrin®, Wellbutrin SR®, and Wellbutrin XL®) and for smoking cessation (under the brand name Zyban®). The medical division of GlaxoSmithKline established a program in postmarketing epidemiologic surveillance because of the potential for exposure in the first trimester of pregnancy and the potential risks for any new chemical entity. Through the Registry, patients exposed to any formulation of bupropion during pregnancy, for any indication, were registered by health care providers, the pregnancies were followed, and the outcomes were ascertained through follow-up.

The intent of the Registry was to provide an early signal of potential risks in advance of results from formal epidemiologic studies. Registry data are provided to supplement animal toxicology studies and to assist clinicians in weighing the potential risks and benefits of treatment for individual patients.

An Advisory Committee was established to review data, encourage referral of exposures, and disseminate information. Members of this Committee are listed below *in alphabetical order:*

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BUPROPION PREGNANCY REGISTRY - FINAL REPORT
1 SEPTEMBER 1997 THROUGH 31 MARCH 2008

REGISTRY CLOSURE INFORMATION

The Registry closed to new enrollments 1 November 2007 and follow-up continued on existing cases through 31 March 2008.

COMMITTEE CONSENSUS

"After reviewing the 1005 prospectively reported pregnancy outcomes, the Bupropion Pregnancy Registry Advisory Committee concludes 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 an increase in the risk of specific defects."

Source: Bupropion Pregnancy Registry Final Report, Issue Date: August 2008. See Page 13 for the complete Committee Consensus.

EXECUTIVE SUMMARY

Although there is no evidence of teratogenicity from preclinical studies of bupropion, the medical division of GlaxoSmithKline managed a program in epidemiologic safety monitoring. Women with depression or attempting smoking cessation may require or be unintentionally exposed to bupropion during pregnancy. This program was considered essential because of the potential for exposure in the first trimester of pregnancy and the unknown risks in pregnancy for any new chemical entity.

Studies have shown the risk of spontaneous abortion is high early in pregnancy and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 14-22% overall (Kline *et al*, 1989). Although the Advisory Committee carefully reviewed each pregnancy outcome, calculation of risk of spontaneous pregnancy losses overall should not be attempted and cannot be compared to background rates because pregnancies in this Registry were reported at variable and, at times, imprecise times. For example, if a pregnancy was registered at 10 weeks, only a spontaneous loss after this time could have been detected and included in the prospective reports. Similarly, pregnancy losses occurring early in gestation may not have been recognized and/or reported.

The Registry collected and followed only prospective reports of prenatal bupropion exposure. However, Interim Reports and this Final Report also include the following information as it became available to the Registry: cases found in medical literature, summaries of other studies involving prenatal bupropion exposure, and retrospective (spontaneous) reports of prenatal exposure collected through the GlaxoSmithKline product surveillance department. A report is considered retrospective when the pregnancy outcome is known at the time of reporting. Retrospective reports can be biased toward the reporting of more unusual and severe outcomes and are less likely to be representative of the general population experience. Therefore, the inclusion of such reports for calculation

of the proportion of birth defects is inappropriate. The purpose of reviewing retrospective reports is to detect unusual patterns that may exist among the reported birth defects.

The Registry closed to new enrollments 1 November 2007 and continued to follow existing cases through 31 March 2008. As of 31 March 2008, 1597 pregnancies involving exposure to bupropion have been prospectively registered. From those 1597 pregnancies, 31 were pending delivery, 572 cases are lost to follow-up, and 994 cases with 1005 outcomes were obtained (including 9 sets of twins and 1 set of triplets). As of 31 March 2008, the 31 pending cases will remain pending and no further follow-up will be conducted. Of these 1005 pregnancy outcomes, 806 involved earliest bupropion exposure in the first trimester, 147 involved earliest bupropion exposure in the second trimester, and 52 involved earliest bupropion exposure in the third trimester. Of the 806 pregnancy outcomes following earliest prenatal exposure in the first trimester, there were no reported birth defects in 651 live births, 33 induced abortions, and 2 fetal deaths. There were 18 infants born alive with birth defects, 5 induced abortions with a birth defect, and 1 fetal death with a birth defect. In addition, there were 96 spontaneous pregnancy losses with 1 defect detected (excluded from the analysis). Of the 147 pregnancy outcomes with the earliest bupropion exposure in the second trimester there were no reported birth defects in 142 live births and 1 induced abortion. There were 3 infants born alive with a birth defect. In addition, there was 1 spontaneous pregnancy loss. Of the 52 pregnancy outcomes with the earliest exposure in the third trimester, there were 51 live births without reported birth defects and 1 fetal death without a reported birth defect. See Table 4 for a description of the reported birth defects.

Among prospective pregnancy outcomes with a first trimester exposure, there were 651 live births without a reported birth defect and 24 outcomes which involved birth defects (total = 675): 1) a live infant with bilateral clubfeet, 2) a live infant with abnormal aortic valve thickening with secondary mild aortic insufficiency, 3) a live infant with Klinefelter's Syndrome with no physical abnormalities, 4) a live infant with ventricular septal defect, 5) a live infant with trivial valvular pulmonic stenosis and tiny atrial septal defect, 6) an induced abortion with evidence of Down Syndrome on a prenatal test, 7) a live infant with a congenital heart defect (coarctation) and ventricular septal defect, 8) a live infant born prematurely with a thickened heart muscle, 9) a live infant with pulmonary stenosis, 10) a live infant with coarctation of the aorta, 11) a fetal death with 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, 12) a live infant with Trisomy 21, 13) a live infant with Trisomy 18, 14) an induced abortion with Down Syndrome, 15) an induced abortion with 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,r(15), 16) a live infant with bilateral kidney dilation from reflux diagnosed prenatally and "double ureters", 17) an induced abortion with Jeune's syndrome and thoracic dysplasia with short limbs diagnosed prenatally, 18) a live infant with hypospadias and cleft right ear lobe, 19) an induced abortion with anencephaly, 20) a live infant with bilateral club feet, 21) a live infant with mixed superficial and deep hemangioma, left eyelid, requiring laser photocoagulation, 22) a live infant with atrial septal defect with patent ductus arteriosis and patent foramen ovale, 23) a live infant with duplicate left renal pelvis, and 24) a live infant with a left hand with misshapen thumb, index, middle, and ring fingers. There was also a spontaneous abortion with Trisomy 14, which was excluded from the analysis. The observed proportion of birth defects in pregnancies with prenatal exposure in the first trimester is 24/675 (3.6%, 95% Confidence Interval: 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.

Among prospective pregnancy outcomes with a second trimester exposure, there were 142 live births without a reported birth defect and 3 outcomes with a birth defect (total = 145): 1) a live infant with bilateral club feet; hemangioma on forehead x 2, 2) a live infant with improving torticollis and oral neoplasm that resolved, and 3) a live infant with Cri-du-chat syndrome, 5p deletion. The observed proportion of birth defects in pregnancies with prenatal exposure in the second trimester is 3/145 (2.1%, 95% Confidence Interval: 0.5-6.4%). This proportion includes 142 live births without birth defects and 3 live births with birth defects.

Among the 28 retrospectively reported birth defects, there were 12 reports of cardiac defects: 1) a live infant with hypoplastic left heart and other non-cardiac defects, 2) a live infant with hypoplastic right heart, left transposition of the great vessels, atrial septal defect, ventricular septal defect, and pulmonary atresia, 3) a live infant with unspecified cardiac defects, 4) a spontaneous abortion with an unspecified congenital heart defect, 5) a live infant with a hole in the heart (which resolved) and a heart murmur persists, 6) a live infant with dyspmorphic pulmonary valve leaflets, with severe pulmonary regurgitation, 7) an induced abortion with atrial/ventricular septal defect, unbalanced, with single right ventricle, double outlet right ventricle, and mildly hypoplastic aorta, 8) a live infant with a ventricular septal defect, 9) a live infant with a hypoplastic right heart and fetal tricuspid atresia diagnosed at 20 weeks gestation; normal chromosomes, 10) a live infant with a tiny ventricular septal defect, 11) a live infant with transposition of the great arteries, and 12) a live infant with Tetralogy of Fallot. It should be noted that no rate calculations from retrospective reports are appropriate because the denominator is unknown and because of the inherent bias in reporting of cases after the outcome is known.

The Committee commented on the retrospective reports of cardiac defects, as well as the increased number of prospective reports of birth defects involving the heart and great vessels. Given the relatively small sample size, the potential bias from the large percentage of cases lost to follow-up, and the incomplete descriptions of the reported cardiovascular defects, it was not possible to determine whether these data reflected a potential effect of bupropion on the developing cardiovascular system. Further, the small sample size precluded definitive conclusions regarding absolute or relative risk of any specific birth defects in women using bupropion during pregnancy. For this reason, the Committee felt that it would be prudent to explore rapid and controlled methods of accumulating pregnancy outcome data on women exposed to bupropion so that any potential drug effect can be more quickly identified, characterized, and quantified. Toward this end, the Committee supported the initiative by GlaxoSmithKline to conduct a claims-based, retrospective cohort study.

Results from this study have now been published and did not confirm a consistent pattern of defects. For all congenital malformations, the prevalence associated with 1213 bupropion first trimester exposures was 23.1 per 1000 infants. The adjusted odds ratios were 0.95 (95% Confidence Interval: 0.62-1.45) and 1.00 (95% Confidence Interval: 0.57-1.73) in comparison to other antidepressants (prevalence 23.2 per 1000) and bupropion outside the first trimester (prevalence 21.9 per 1000), respectively. For cardiovascular malformations, the prevalence associated with bupropion first trimester was 10.7 per 1000 infants. The adjusted odds ratios were 0.97 (95% Confidence Interval: 0.52-1.80) and 1.07 (95% Confidence Interval: 0.48-2.40) in comparison to other antidepressants (prevalence 10.8 per 1000) and bupropion outside the first trimester (prevalence 9.5 per 1000), respectively (Cole *et al*, 2007). The Committee agrees with the conclusions of this study, although subsequent data has raised the issue of an increase in cardiovascular risk related

to certain of the comparator antidepressants (Louik *et al,* 2007) and the issue remains the subject of continuing enquiry.

With the publication of these new data the Committee reviewed continuation of the Registry. Given this larger data set and the ten years of surveillance for the Registry, the Committee supported the termination of this Registry. The Registry closed to new enrollments 1 November 2007 and continued to follow existing cases through 31 March 2008. From this point forward, all existing cases with a pending status will remain pending and no further follow-up will be conducted. Monitoring for an association with specific defects should continue through established studies and systems; anonymized aggregated healthcare databases are emerging as additional data sources in which to evaluate any subsequent signals.

In summary, given the sample size, lack of an appropriate comparison group, and the high lost to follow-up rate, while the Bupropion Pregnancy Registry did not detect a signal of a major problem with birth defects, the population exposed and monitored is only sufficient to detect major teratogenicity, and cannot detect an increase in the risk of specific defects. This drug should be used during pregnancy only if the potential benefit outweighs the potential unknown risk.

1. INTRODUCTION

The purpose of the Registry was to detect any major teratogenic effect in pregnancies inadvertently or intentionally exposed to any formulation of Wellbutrin®, Wellbutrin SR®, Wellbutrin XL® and Zyban® (bupropion), regardless of indication. The large number of women of reproductive age with depression or attempting smoking cessation and the lack of data concerning bupropion use during pregnancy made such a Registry an essential component of the ongoing program of epidemiologic studies of the safety of bupropion. This study was an observational, exposure-registration and follow-up study. This study was reviewed and approved by an institutional review board (IRB). The IRB approval included a waiver from requiring patient informed consent for participation based on the Registry's process for protecting patient anonymity. The IRB approval also included a HIPAA authorization waiver. Patient confidentiality was strictly upheld. The intent of the Registry was to prospectively collect data concerning exposure to bupropion during pregnancy, potential confounding factors (such as exposure to other antidepressant or smoking cessation medications) and information related to the outcome of the pregnancy.

The Bupropion Pregnancy Registry was managed by GlaxoSmithKline in collaboration with obstetric, epidemiology, and teratology specialists which form the Advisory Committee. This Committee provided independent review of the data for the Registry. The Registry began in September 1997. The Registry closed to new enrollments 1 November 2007 and continued to follow existing cases through 31 March 2008.

2. BACKGROUND

2.1 Animal Data

Initially developed and marketed as an antidepressant, bupropion (Wellbutrin® [bupropion hydrochloride] Tablets and Wellbutrin SR® [bupropion hydrochloride] Sustained-Release Tablets) was later developed as a non-nicotine aid to smoking cessation and is marketed under the brand name of Zyban® [bupropion hydrochloride] Sustained-Release Tablets.

Bupropion is a relatively weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine, and does not inhibit monoamine oxidase. While the mechanism of action of bupropion is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms. Bupropion is chemically unrelated to tricyclic, tetracyclic, selective serotonin re-uptake inhibitors or other known antidepressant agents.

Treatment durations are different for the two indications of bupropion. It is recognized that acute episodes of depression require several months or longer of antidepressant drug treatment.

Treatment with bupropion for smoking cessation is usually prescribed for a period of 7-12 weeks.

Although a micronucleus test (which can detect aneuploidy) was not conducted, studies of mutagenicity consistent with regulatory standards were completed, and the overall battery was extensive: 2 Ames tests as well as 2 in vitro mammalian cell assays plus another type of in vivo test (unscheduled DNA synthesis).

A fertility study in rats at doses up to 300 mg/kg of bupropion revealed no evidence of impaired fertility.

Tucker published a manuscript that provided an overview of the preclinical toxicology of bupropion (Tucker, 1983). In this review of 2 animal reproductive studies of bupropion, a dose-related maternal toxicity was reported that included clonic convulsions in New Zealand white rabbits dosed with 25, 100, and 150 mg/kg/day. One rabbit died of a convulsive death at the 150 mg/kg/day dose. This study found increased numbers of offspring with supernumerary 13th ribs associated with maternal toxicity and stress at all dose levels. At the 150 mg/kg/day dose, delayed ossification of the 5th phalanx was reported. Both of these defects were considered stress-related skeletal variants and not drug-related teratogenic effects. In another study, rats were given doses of 150, 300, and 450 mg/kg/day from 6 to 15 days of gestation. There were no teratogenic effects despite toxicity to dams. The skeletal variants seen in the rabbits were not observed in the rats.

Sparenborg (1998) published a brief review manuscript examining mortality in rat pups born to dams dosed with monoamine reuptake inhibitors (including bupropion) and serotonin reuptake inhibitors during gestation. All data reported in this manuscript were extracted from reviews of reproductive toxicity studies submitted to the FDA by sponsors of the corresponding drugs. At low, middle, and high doses of bupropion (100, 200, and 300 mg/kg body weight of dam, respectively), no effect was seen on survival or birth weight. The author cites the FDA when concluding that bupropion was not toxic to either pups or dams at high doses (Pharmacologist Review of NDA 18-644, FOI Office, FDA, Rockville, MD 20857).

The effect of bupropion on labor and delivery in humans is unknown.

2.2 Clinical Trial Prenatal Exposures Reported Prior to Establishment of Registry

There were 14 pregnancies occurring in clinical trials prior to establishment of the Bupropion Pregnancy Registry, for which a prenatal exposure to bupropion was reported. Because these pregnancies occurred prior to the formation of the Registry where bupropion prenatal exposure-specific data collection forms are used, there are insufficient data on the pregnancies and their subsequent outcomes to be included in the Registry. However, to fully account for all prenatal exposure information known to us, the following summary of

those pregnancies is provided.

Of the 14 pregnancies reported, it was subsequently determined that for 3, the last dose of bupropion was prior to the last menstrual period (or conception if last menstrual period was unknown), and 1 was lost to follow-up. Of the 10 remaining pregnancies, insufficient details on timing of the exposure relevant to timing of the pregnancy were provided, but prenatal exposure is assumed. Outcomes for these 10 pregnancies include 2 spontaneous pregnancy losses and 8 live infants without birth defects. In summary, there were no reports of birth defects for the 14 pregnancies occurring in clinical trials *prior to* establishment of the Bupropion Pregnancy Registry. Pregnancies occurring in clinical trials *after* the start of the Bupropion Pregnancy Registry (1 September 1997) are included in the Pregnancy Registry data.

3. PROSPECTIVE REGISTRY

3.1 New Data

An interim Report was issued semiannually following the Advisory Committee's review of new data. Each issue, containing historical information, as well as new data known to the Registry, replaced all previous Reports. The new information in this Final Report includes data from all cases closed between 1 September 2007 and 31 March 2008 (Table 1).

Table 1. New Data During Reporting Period

Status	Newly Registered Pregnancies	Previously Registered Pregnancies-Closed This Period	Total
Pending	12	N/A	12
Lost to follow-up	1	29	30
Closed	6	44	50
Number of Outcomes	6	44	50
No Birth Defects	6	39	45
Live Birth	6	37	43
Fetal Death	0	0	0
Induced Abortion	0	2	2
Birth Defects	0	2	2
Live Birth	0	2	2
Fetal Death	0	0	0
Induced Abortions	0	0	0
Spontaneous Loss	0	3	3

3.2 All Data

The Registry closed to new enrollments 1 November 2007 and continued to follow existing cases through 31 March 2008. Through 31 March 2008, there were 1597 prospectively registered pregnancies involving exposure to bupropion. Of these 1597, 31 pregnancies were pending delivery, 572 are lost to follow-up, and there have been 994 pregnancies with 1005 outcomes obtained including 9 sets of twins and 1 set of triplets (Table 3). As of 31 March 2008, all pending cases will remain pending and no further follow-up will be

conducted. The indication for use was depression in 683 patients, smoking cessation in 174 patients, both depression and smoking cessation in 26 patients, bipolar affective disorder in 14 patients, other (e.g. alertness, attention deficit hyperactivity disorder, bipolar depression, borderline personality disorder, chronic fatigue, intermittent explosive disorder, postpartum depression, post traumatic stress disorder, postural orthostatic tachycardia syndrome, and seasonal depression) in 39 patients, and unspecified for 58 patients. Of the 572 lost to follow-up cases, 47% were due to no response from the registering health care professional despite 6 attempts (4 letters and 2 telephone calls) by the Registry to obtain follow-up information, 30% were because the patient did not remain under the reporter's care, 10% because the reporter could not identify the patient at time of follow-up from information provided at time of enrollment, 9% due to the registering health care professional leaving the practice with no forwarding address, 1% due to lack of response from the patient who still may be under the reporter's care but has not returned to the reporter to date, and 3% because the patient refused the release of information. Cases lost to follow-up are of concern to the Registry, as outcome of these cases could have an impact on the birth defect rate.

The distribution by country (16 countries) of the 994 prospectively registered pregnancies with outcomes is presented in Table 2.

Table 2. Prospective Registry - Bupropion Exposure in Pregnancy by Country of Origin
1 September 1997 – 31 March 2008

Country	Number of Reported Pregnancies[a]
Australia	4
Belgium	8
Canada	50
Czech Republic	1
Estonia	1
France	41
Germany	1
Holland	1
Luxemburg	1
Namibia	1
New Zealand	2
South Africa	3
Spain	4
Sweden	1
United Kingdom	25
United States	850
TOTAL	**994**

[a] Includes only patients with known pregnancy outcomes

Table 3. Prospective Registry - Bupropion Exposure in Pregnancy by Earliest Trimester of Exposure and Outcome

1 September 1997 – 31 March 2008

All Bupropion Exposures

Earliest Trimester of Exposure	Birth Defect Reported[d]			No Birth Defects Reported[a]			Spontaneous Pregnancy Loss[b,h]	Total Outcomes
	Live Birth	Fetal Death[c]	Induced Abortion	Live Birth	Fetal Death[c]	Induced Abortion		
First	18[g]	1	5	651[e,g]	2	33	96	806
Second	3	0	0	142[f]	0	1	1	147
Third	0	0	0	51	1	0	0	52
Total	21	1	5	844	3	34	97	1005

[a] Birth defect not reported but cannot be ruled out
[b] Pregnancy loss occurring < 20 weeks gestation
[c] Pregnancy loss occurring ≥ 20 weeks gestation
[d] See Table 4 for list of defects
[e] Includes 6 sets of twins (3 sets female, 2 sets not specified, and 1 set female and male) and 1 set of triplets (not specified)
[f] Includes 2 sets of twins (female)
[g] Includes 1 of a set of twins (male)
[h] Includes defect and non-defect reports. Spontaneous pregnancy losses < 20 weeks gestation are excluded from the calculation of risk of birth defects.

Table 4. Prospective Registry - Bupropion Exposure in Pregnancy Summaries of Birth Defects by Earliest Trimester of Exposure

1 September 1997 – 31 March 2008

First Trimester Bupropion Exposures

1. Live infant with bilateral clubfeet.
2. Live infant with abnormal aortic valve thickening with secondary mild aortic insufficiency.
3. Live infant with Klinefelter's Syndrome with no physical abnormalities diagnosed by amniocentesis.
4. Live infant with ventricular septal defect.
5. Live infant with trivial valvular pulmonic stenosis and tiny atrial septal defect.
6. Induced abortion with evidence of Down Syndrome on a prenatal test.
7. Live infant with congenital heart defect (coarctation) and ventricular septal defect.
8. Live infant born premature with a thickened heart muscle.
9. Live infant with pulmonary stenosis.
10. Live infant with coarctation of the aorta.
11. Fetal death with 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.
12. Live infant with Trisomy 21.
13. Live infant with Trisomy 18.
14. Induced abortion with Down Syndrome.
15.** Spontaneous abortion with Trisomy 14 *(excluded from analysis)*.
16. Induced abortion with 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,r(15).

Table 4. Prospective Registry - Bupropion Exposure in Pregnancy Summaries of Birth Defects by Earliest Trimester of Exposure (continued)

1 September 1997 – 31 March 2008

First Trimester Bupropion Exposures (continued)

17. Live infant with bilateral kidney dilation from reflux diagnosed prenatally and "double ureters".
18. Induced abortion with Jeune's syndrome (thoracic dysplasia with short limbs) diagnosed prenatally.
19. Live infant with hypospadias and cleft right ear lobe.
20. Induced abortion with anencephaly.
21. Live infant with bilateral club feet (patient's uncle and granduncle born with clubfoot).
22. Live infant with mixed superficial and deep hemangioma, left eyelid, requiring laser photocoagulation.
23. Live infant with atrial septal defect with patent ductus arteriosis and patent foramen ovale.
24. Live infant with duplicate left renal pelvis.
25.* Live infant with left hand with misshapen thumb, index, middle and ring fingers.

Second Trimester Bupropion Exposures

1. Live infant with bilateral club feet; hemangioma on forehead x 2.
2. Live infant with improving torticollis and oral "neoplasm" that spontaneously resolved.
3.* Live infant with Cri-du-chat syndrome, 5p deletion.

*Denotes new cases

**Spontaneous pregnancy losses < 20 weeks gestation, regardless of birth defect status, are excluded from the calculation of risk of birth defects.

Table 5. Prospective Registry - Gestational Age at Enrollment (weeks) – First Trimester

1 September 1997 – 31 March 2008

Number of Outcomes = 675				
	< 16 weeks	**16 – 20 weeks**	**> 20 weeks**	**Unknown**
Total	435 (64.4%)	60 (8.9%)	171 (25.3%)	9 (1.3%)
No Defect	417	60	165	9
Defect	18	0	6	0

4. RETROSPECTIVE REPORTS

Through its spontaneous reporting system, GlaxoSmithKline has received retrospective notification of bupropion-exposed pregnancies and their outcomes. Reports are considered retrospective when pregnancies involving bupropion exposure are reported after the pregnancy outcome is already known. Retrospective reports may be biased toward the reporting of more abnormal outcomes and are much less likely to be representative of the general population experience. These outcomes were reviewed because they may be helpful in detecting a possible pattern of birth defects suggestive of common etiology. Such reports are presented below.

Retrospective Health Care Provider Reports:

Through 31 March 2008, there have been 28 outcomes with birth defects retrospectively reported, with 25 involving the earliest maternal bupropion exposure in the first trimester, 1 in the second trimester, and 2 in the third trimester. The Registry follows the Centers for Disease Control and Prevention's (CDC) birth defect evaluation guidelines. A description of the 28 current birth defects follows:

Retrospective Health Care Provider Reports:

1. Live infant with one kidney, a bicornuate uterus, and double vagina with one opening to the outside.
2. Live infant with cardiac defects and omphalocele detected at an unspecified time during pregnancy.
3. Live infant with multiple cardiac defects including hypoplastic right heart, atrial septal defect, ventricular septal defect, pulmonary atresia, left transposition of the great vessels, and transverse heart. Cardiac abnormalities were detected by prenatal fetal echocardiogram.
4. Spontaneous abortion at 15 weeks gestation of a fetus with a congenital heart defect.
5. Live infant with multiple defects including hypoplastic left heart, diaphragmatic hernia, cleft lip and palate, absence of left radius, hemivertebrae, ear tags, microcephaly, and intrauterine growth retardation. Apparently, some of the defects were detected by prenatal ultrasound, but it is stated that the karyotype was normal by amniocentesis.
6. Live infant with gastroschisis requiring two laporatomies for repair.
7. Induced abortion at 19 weeks gestation due to transverse limb deficiencies, humero radioulnar, intercalary transverse meromelias bilateral, tibiofibular intercalary transverse meromelia of the lower limbs, missing digits of hands-bilateral, oligodactyly, imperforate anus, cleft palate, and short neck intra-abdominal calcifications on ultrasound. Chromosome studies were normal; study to look for centromere separation or puffing on c-binding was negative. Autopsy was refused.
8. Fetal death at 38 weeks gestation. The patient had an ultrasound, the result of which was a non-viable infant. Labor was induced. No autopsy was performed. Visual examination revealed the infant had hydrocephalus.
9. Spontaneous abortion at 12 weeks gestation of a fetus with disrupted cranium.
10. Live infant with tracheosophageal fistula.
11. Live infant with right ear microtia (absent canal).
12. Live infant with a hole in the heart (which resolved). A heart murmur persists.
13. Live infant with a small cleft lip – palate within normal limits.
14. Live infant with dysmorphic pulmonary valve, thickened valve leaflets, with severe pulmonary regurgitation.

Retrospective Health Care Provider Reports (continued):

15. Induced abortion at 20 weeks gestation with atrial/ventricular septal defect, unbalanced, with single right ventricle, double outlet right ventricle, and mildly hypoplastic aorta.

16. Live infant with bilateral club feet.

17. Live infant with a ventricular septal defect.

18. Live infant with a hypoplastic right heart and fetal tricuspid atresia diagnosed at 20 weeks gestation; normal chromosomes.

19. Live infant with a tiny ventricular septal defect.

20. Induced abortion with anencephaly.

21. Live infant with microphthalmia with coloboma. Bupropion started at 16 weeks gestation.

22. Live infant with mild form of late-onset adrenal hyperplasia.

23. Live infant with hypospadias.

24. Live infant with transposition of the great arteries.

25. Live infant with Down syndrome.

26. Induced abortion at 18 weeks due to Trisomy 18.

27. Live infant with Tetralogy of Fallot.

28. Live infant with cystic adenoid (presumably adenomatoid), malformation type 3, diagnosed by prenatal ultrasound.

*Denotes new cases

5. DATA FROM OTHER STUDIES

On an ongoing basis, the published medical literature and other data sources were reviewed for studies on outcomes of pregnancies exposed to bupropion.

Following the observation of a possible signal for cardiac malformations (specifically cardiac outflow tract obstructions), a retrospective cohort study from a large national managed care database was conducted. The study population included enrolled members of United Healthcare, with live births between January 1995 through June 2003. Rates of congenital malformations and rates of cardiac malformations were calculated for bupropion exposure in the first trimester versus other antidepressant exposure in the first trimester and for bupropion exposure in the first trimester versus bupropion exposure outside of the first trimester. The sample size for these results was insufficient to draw definitive conclusions, and so the study was extended. Results have been posted on the GlaxoSmithKline Clinical Trial Registry (http://ctr.gsk.co.uk/welcome.asp). The cases represented in this study may also have been captured in the Bupropion Pregnancy Registry. Final results from this study have now been published (Cole *et al,* 2007). The Committee agrees with the conclusions of this study, but subsequent data has raised the issue of an increase in cardiovascular risk

related to the use of antidepressants. Research continues to be ongoing to evaluate this concern.

The Motherisk Program in Toronto, Canada provides information and guidance to pregnant and lactating patients and their health care providers regarding the fetal risks associated with drug, chemical, infection, disease, and radiation exposure(s) during pregnancy. In addition to providing information, they collect data on prenatal exposures and pregnancy outcome. Researchers from the Motherisk Program conducted a study of 136 women exposed to bupropion in the first trimester of pregnancy. Among these 136 women, there were 105 live births; none had major malformations. The authors compared the bupropion-exposed group to control groups: 1) those exposed to other antidepressants during pregnancy, and 2) those who were not exposed to any teratogens. The authors reported no statistically significant differences between the groups with regard to major malformations. A limitation of this study is the small sample size, which was only sufficient to detect a 5-fold increase in the risk of malformations with 80% power and a type I error rate of 5%. Women in the Motherisk study were from Toronto, Canada, Farmington, Connecticut, and Southampton, United Kingdom (Chan *et al*, 2005). It is possible that some women included in this pregnancy Registry were also included in the Motherisk study. For more information about the Motherisk Program, contact them directly at 1-877-327-4636 or www.motherisk.org.

A surveillance study of Michigan Medicaid recipients examined data from 229,101 women with pregnancies completed between 1985 and 1992 (F. Rosa, personal communication, FDA, 1993). Among these pregnancies, 3 were live births with first trimester exposures to bupropion. No major birth defects were observed among these 3 infants.

6. DATA SUMMARY

The Committee reviewed the accumulated data for the 1005 prospectively reported pregnancy outcomes according to the criteria described under “Methods” in Appendix A.

Review of the composite data:

Of the 806 pregnancy outcomes following earliest prenatal exposure in the first trimester, there were no reported birth defects in 651 live births, 33 induced abortions, and 2 fetal deaths. There were 18 live born infants with birth defects: 1) bilateral club feet, 2) abnormal aortic valve thickening with secondary mild aortic insufficiency, 3) Klinefelter’s Syndrome with no physical abnormalities, 4) ventricular septal defect, 5) trivial valvular pulmonic stenosis, tiny atrial septal defect, 6) congenital heart defect (coarctation) and ventricular septal defect, 7) infant born premature with a thickened heart muscle, 8) pulmonary stenosis, 9) coarctation of the aorta, 10) Trisomy 21, 11) Trisomy 18, 12) bilateral kidney dilation from reflux diagnosed prenatally and “double ureters”, 13) hypospadias and cleft right ear lobe, 14) bilateral club feet, 15) mixed superficial and deep hemangioma, left eyelid, requiring laser photocoagulation, 16) atrial septal defect with patent ductus arteriosis and patent foramen ovale, 17) duplicate left renal pelvis, and 18) left hand with misshapen thumb, index, middle, and ring fingers. There were 5 induced abortions with birth defects: 1) evidence of Down Syndrome on a prenatal test, 2) Down Syndrome, 3) 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,r(15), 4) Jeune’s syndrome and thoracic dysplasia with short limbs diagnosed prenatally, and 5) anencephaly. There was 1 fetal death with 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. There were also 96 spontaneous abortions, 1 of which had a defect with Trisomy 14, which was excluded from the analysis as it was a spontaneous pregnancy loss < 20 weeks gestation.

Of the 147 pregnancy outcomes following earliest prenatal exposure in the second trimester, there were no reported birth defects in 142 live births and 1 induced abortion. There were 3 live born infants with a birth defect: 1) bilateral club feet; hemangioma on forehead x 2, 2) improving torticollis and oral neoplasm that resolved, and 3) Cri-du-chat syndrome, 5p deletion. There was also 1 spontaneous pregnancy loss. The outcomes for the 52 pregnancies with the earliest exposure in the third trimester were 51 live infants and 1 fetal death without reported birth defects.

The calculation of risk for birth defects is made by dividing the number of birth defects associated with any pregnancy outcome by the combined number of live births without birth defects and all outcomes involving birth defects. The observed proportion of birth defects in pregnancies with prenatal exposure in the first trimester is 24/675 (3.6%, 95% Confidence Interval: 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 observed proportion of birth defects in pregnancies with prenatal exposure in the second trimester is 3/145 (2.1%, 95% Confidence Interval: 0.5-6.4%). This proportion includes 142 live births without birth defects and 3 live births with birth defects.

7. COMMITTEE CONSENSUS – BUPROPION

Among prospective pregnancy outcomes with a first trimester exposure, there were 651 live births without a birth defect and 24 outcomes which involved birth defects (total = 675). The observed proportion of birth defects in pregnancies with prenatal exposure in the first trimester is 24/675 (3.6%, 95% Confidence Interval: 2.3-5.3%). This includes 18 live births with birth defects, 1 fetal death with a birth defect, and 5 induced abortions with birth defects (see Table 4).

The Registry uses the case definition of the Metropolitan Atlanta Congenital Defects Program (MACDP) for major birth defects, which includes chromosomal and genetic disorders, defects diagnosed solely by prenatal ultrasound, and those detected as incidental findings on postnatal diagnostic procedures. The overall frequency of major malformations in metropolitan Atlanta reported by the MACDP from 1968 through 2003 was 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). The prevalence of these “early diagnoses” is important for Registry comparisons since the majority of outcome reports are from clinicians who may have limited access to diagnoses made after the day of birth. Another study in a northeastern US hospital from a different time period (1972-1975 and 1979-1985), has reported a frequency of major malformations of 1.6%-2.2% at birth, depending on whether chromosomal anomalies and other genetic disorders are included (Nelson *et al*, 1989). In a study evaluating infants enrolled in the Tennessee Medicaid program, the rate of major malformations in 29,096 control subjects was 2.6% (Cooper *et al*, 2006).

Because of the international scope of the Bupropion Pregnancy Registry, the voluntary nature of recruitment and other methods used, there is no directly comparable group of unexposed pregnant women against whom to evaluate the observed prevalence of birth defects in the Registry.

For reference, the Committee adopts the list of birth defects utilized by MACDP. This 6-digit code list is available from the CDC web site at http://www.cdc.gov/ncbddd/bd/macdp_resources.htm.

Among prospective pregnancy outcomes with a second trimester exposure, there were 142 live births without birth defects, and there were 3 outcomes which involved a birth defect (total = 145). The observed proportion of birth defects in pregnancies with prenatal exposure in the second trimester is 3/145 (2.1%, 95% Confidence Interval: 0.5-6.4%). This proportion includes 142 live births without birth defects and 3 live births with birth defects. No birth defects were observed in pregnancies with prenatal exposure in the third trimester. Overall, the observed proportion of birth defects in pregnancies is 27/871 (3.1%, 95% Confidence Interval: 2.1-4.5%).

Among the 28 retrospectively reported birth defects, there were 12 reports of cardiac defects. It should be noted that no rate calculations from retrospective reports are appropriate because the denominator is unknown and because of the inherent bias in reporting of cases after the outcome is known.

The Committee has previously commented on the retrospective reports of cardiac defects, as well as the increased number of prospective reports with birth defects involving the heart and great vessels. Given the relatively small sample size to date, the potential bias from the large percentage of cases lost to follow-up, and the incomplete descriptions of the reported cardiovascular defects, it was not possible to determine whether these data reflected a potential effect of bupropion on the developing cardiovascular system. Further, the small sample size precluded definitive conclusions regarding absolute or relative risk of any specific birth defects in women using bupropion during pregnancy. Thus, the Committee agreed that it would be prudent to explore more rapid and controlled methods of accumulating pregnancy outcome data on women exposed to bupropion so that any potential drug effect can be more quickly identified, characterized, and quantified. Toward this end, the Committee supported the initiative by GlaxoSmithKline to conduct the proposed claims-based, retrospective cohort study using the United Healthcare database, entitled: “Bupropion in Pregnancy and the Risk of Cardiovascular and Overall Major Congenital Malformations”.

Results from this study have now been published and did not confirm a consistent pattern of defects. For all congenital malformations, the prevalence associated with 1213 bupropion first trimester exposures was 23.1 per 1000 infants. The adjusted odds ratios were 0.95 (95% Confidence Interval: 0.62-1.45) and 1.00 (95% Confidence Interval: 0.57-1.73) in comparison to other antidepressants (prevalence 23.2 per 1000) and bupropion outside the first trimester (prevalence 21.9 per 1000), respectively. For cardiovascular malformations, the prevalence associated with bupropion first trimester was 10.7 per 1000 infants. The adjusted odds ratios were 0.97 (95% Confidence Interval: 0.52-1.80) and 1.07 (95% Confidence Interval: 0.48-2.40) in comparison to other antidepressants (prevalence 10.8 per 1000) and bupropion outside the first trimester (prevalence 9.5 per 1000), respectively (Cole *et al*, 2006). The Committee agrees with the conclusions of this study, but subsequent data has raised the issue of an increase in cardiovascular risk related to antidepressants. Research continues to be ongoing to evaluate this concern.

With the publication of these new data the Committee reviewed continuation of the Registry. Given this larger dataset and the ten years of surveillance for the Registry the Committee supported the termination of this Registry. The Registry closed to new enrollments 1 November 2007 and continued to follow existing cases through 31 March 2008.

The genetic abnormalities from Table 4 merit clarification. Among 994 prospectively registered pregnancies with outcomes, there were no reported chromosomal anomalies among 4 fetal deaths, 2 cases of Trisomy 21 (Down's syndrome) among 39 induced abortions, 1 case of Trisomy 14 among 97 spontaneous abortions, and 5 chromosomal anomalies (1 case each of Trisomy 21, Trisomy 18, Klinefelter's syndrome, karyotype 47, XXY, and Cri-du-chat syndrome, 5p deletion) among 865 live births. Genetic abnormalities occur pre-conception or peri-conception during meiosis of gametes, and there are no known instances of drugs being associated with genetic abnormalities in humans. Four of the cases were exposed pre-conception among 994 prospectively registered pregnancies with outcomes. Although the number of fetal deaths and abortions that were karyotyped is unknown, the number of trisomy cases (3, including 2 cases of Trisomy 21) would not seem remarkable for the number of abortions registered, nor was the observation of 2 trisomy cases among 865 live births, recognizing among these trisomies that Trisomy 21 was the most common, as true for the general population (Moore *et al*, 1993).

The Advisory Committee notes the high lost to follow-up rate for the Registry. It is unclear whether the women for whom outcome information was not received differ from those for whom the outcome was known. Although the final Registry findings do not indicate a major problem with overall birth defects that would occur with major teratogenicity, given the sample size, lack of an appropriate comparison group, and the high lost to follow-up rate the Registry was unable to reach definitive conclusions regarding the possible risk of bupropion for specific defects because of their low expected prevalence in the general population.

Monitoring for an association with such specific defects should continue through established systems and studies including the ongoing case control surveillance through the National Birth Defects Prevention Study (Yoon *et al*, 2001). Anonymized aggregated healthcare databases (Oberlander *et al,* 2008, Cole *et al,* 2006, Cooper *et al,* 2006, HMO Research Network, Blue Cross and Blue Shield HealthCore database) are emerging as alternative data sources in which to evaluate any emerging signals.

After reviewing the 1005 prospectively reported pregnancy outcomes, the Bupropion Pregnancy Registry Advisory Committee concludes 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 an increase in the risk of specific defects.

This Final Report was issued following the independent review of data. This Report includes the historical information as well as new data known to the Registry and, therefore, replaces all previous Interim Reports. If your current Report is older than seven months, please request the updated Final Report from your local GlaxoSmithKline Company, or directly from the GlaxoSmithKline Drug Safety Group at (888) 825-5249.

REFERENCES

Centers for Disease Control and Prevention: Metropolitan Atlanta Congenital Defects Program Procedure Manual. July 1989 (Revised January 1998); A1-B11. To access a copy of the MACDP defect code, please go to http://www.cdc.gov/ncbddd/bd/macdp_resources.htm and click on the link to the .pdf file.

Centers for Disease Control and Prevention. Update on overall prevalence of major birth defects - Atlanta, Georgia, 1978-2005. MMWR 2008;57:1-5. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm

Chun-Fai-Chan B, Koren G, Fayez I, Kalra S, Voyer-Lavigne S, Boshier A, Shakir S, Einarson A. Pregnancy outcome of women exposed to bupropion during pregnancy: A prospective comparative study. *American Journal of Obstetrics and Gynecology* 2005;192:932-6.

Chung CS, Myrianthopoulos NC. Factors affecting risks of congenital malformations; reports from the Collaborative Perinatal Project. Series: Birth Defects Original Article Series 1975;11(10).

Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. *Pharmacoepidemiology and Drug Safety* 2007;16:474-484 (available to journal subscribers at www.interscience.wiley.com).

Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer S, Gideon PS, Hall K, Ray WA. Major congenital malformations after first-trimester exposure to ACE inhibitors. *New Engl J Med* 2006;(Vol. 354, No. 24):43-51.

Correa-Villasenor A, Cragan J, Kucik J, O'Leary L, Siffel C, Williams L. The Metropolitan Atlanta Congenital Defects Program: 35 years of birth defects surveillance at the Centers for Disease Control and Prevention. *Birth Defects Research (Part A)* 2003;67:617-624.

Correa A, Cragan J, Kucik J, *et al*. Metropolitan Atlanta Congenital Defects Program 40th Anniversary Edition Surveillance Report: Reporting Birth Defects Surveillance Data 1968-2003. *Birth Defects Research (Part A)* 2007;79:65-93.

Covington DL, Tilson H, Elder J, Doi PA, APR Steering Committee. Assessing teratogenicity of antiretroviral drugs: Monitoring and analysis plan of the Antiretroviral Pregnancy Registry. *Pharmacoepidemiology and Drug Safety* 2004;13:537-545.

Fleiss JL. Statistical Methods for Rates and Proportions. New York: John Wiley; 1981;14-15.

Food and Drug Administration. Guidance for Industry: Establishing pregnancy exposure registries. Rockville (MD): US Department of Health and Human Services, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research; 2002. Available from URL: http://www.fda.gov/cber/gdlns/pregnancy.pdf.

Honein MA, Paulozzi LJ, Cragan JD, Correa A. Evaluation of selected characteristics of pregnancy drug registries. *Teratology* 1999;60:356-364.

Kline J, Stein Z, Susser M. Conception to birth: Epidemiology of prenatal development. New York: Oxford University Press; 1989;43-68.

Louik C, Lin AE, Werler MM, Hernandez-Diaz S, Mitchell AA. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *New Engl J Med* 2007;(Vol. 326, No. 26):2675-2683.

REFERENCES (continued)

Moore KL, Persaud TVN. The Developing Human, 5th Ed., WB Saunders Co., Philadelphia, 1993;146.

Nelson K, Holmes LB. Malformations due to presumed spontaneous mutations in newborn infants. *New Engl J Med* 1989;(320):19-23.

Oberlander TF, Warburton W, Misri S, Riggs W, Aghajanian J, Hertzman C. Major congenital malformation following prenatal exposure to serotonin reuptake inhibitors and benzodiazepines using population-based health data. *Birth Defects Research (Part B)* 2008:(83):68-76.

Rosa F. Personal Communication, 1993. Cited in: Briggs GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 6th ed. Baltimore, MD: Williams & Wilkins, 2002;155-157.

Sparenborg S. Mortality in neonatal rats is increased by moderate prenatal exposure to some monoamine reuptake inhibitors. A brief review. *Ann NY Acad Sci* 1998;846:423-426.

Tucker WE Jr. Preclinical toxicology of bupropion: an overview. *J Clin Psychiatry* 1983;44:5 (Part 2):60-62.

Yoon PW, Rasmussen SA, Lynberg MC, *et al*. The National Birth Defects Prevention Study, *Public Health Rep.* 2001;116(1 Suppl): 32-40.

Appendix A: Methods

Registration and Follow-up

Registration data was collected by the Registry from the treating health care provider through telephone interview or by completing a short registration form. Minimum data points required to register a pregnancy included country of origin of report, documentation that the Registry drug was taken during pregnancy, enough information to determine whether the pregnancy was being prospectively or retrospectively registered, the date the pregnancy was registered, whether the report was made by a patient or medical professional, whether the pregnancy outcome was already known or was still pending delivery, the timing of the prenatal exposure to bupropion (no broader than during which trimester the exposure took place), whether the patient was involved in a study at the time of the prenatal exposure, and full reporter contact information to allow for follow-up (name, address, etc.). The patient's identity was kept confidential and a Patient (Log) ID number was assigned for the purpose of communicating with the reporting health care professional. Near the estimated date of delivery, follow-up was obtained through a short follow-up form sent to the health care professional who provided information on maternal risk factors, pregnancy outcome, and neonatal health.

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 "not valid" when the minimum requirements were not reported, however attempts were made 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. Only data from "closed" reports of exposed pregnancies with known outcomes are summarized in this Report. Patient identifiers were initially retained in the Registry database to allow for contact and confirmation of the patients and their data. However, after a confidential Registry number had been assigned to the reporting health care professional, this information was removed. In addition, the database link between patient and health care provider was severed.

Independent review by specialists in epidemiology, obstetrics, and teratology from the CDC and academic centers provided ongoing interpretation of the data and provided strategies for the dissemination of information regarding the Registry.

Institutional Review Board (IRB) Review

In accordance with the FDA Guidance to Industry: Establishing Pregnancy Exposure Registries, (FDA 2002), the Registry sought and obtained IRB approval from Western IRB (WIRB®) in August 2001. With the IRB approval of the protocol, the Registry was granted a waiver from having to obtain patient informed consent. The IRB reviewed the Registry protocol annually.

HIPAA Privacy Rule: Protecting Personal Health Information in Research

The HIPAA Privacy Rule allows covered entities (e.g., health care providers) to disclose protected health information (PHI) without subject authorization if the covered entity obtains documentation that an IRB has waived the requirement for authorization.

On 10 June 2003, WIRB® approved a request for a waiver of authorization for use and

disclosure of PHI. WIRB® determined that documentation received from this Registry satisfies the requirements for a waiver of authorization (*Standards for Privacy of Individually Identifiable Health Information* CRF 45, Part 160, Part 164 A-E, http://www.hhs.gov/ocr/hipaa; *Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule,* http://privacyruleandresearch.nih.gov.).

Classification of Outcomes

The major interest of the Registry was to monitor bupropion exposures in pregnancy for adverse outcomes to the fetus that may be have been attributable to the drug exposure. This Registry adopted for clarification the term "birth defect" for abnormalities usually referred to as "congenital abnormality". For purposes of data reporting, pregnancy outcomes were categorized as one of the following: 1) outcomes with birth defects, 2) outcomes without birth defects, and 3) spontaneous pregnancy losses. The second category was 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 infant is 6 years of age. However, most outcomes were reported during the first year of life. For reference, the Committee adopted the list of birth defects recognized by the CDC (Centers for Disease Control and Prevention, 1989; Correa-Villasenor *et al*, 2003, Correa *et al*, 2007). 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 reflected an unrecognized birth defect. Detected and reported transient or infectious conditions or biochemical abnormalities in infants without birth defects and defects that were excluded by the CDC guidelines are noted in Appendix B of this Report.

Exclusions

For this Registry, enrollment was limited to ongoing pregnancies involving bupropion exposure registered prior to any knowledge of the pregnancy outcome. However, GlaxoSmithKline encouraged reporting of all known prenatal exposures to bupropion. Pregnancies included in the data analysis were those prospectively registered by health care providers. Data from other sources, such as studies involving prenatal bupropion use, cases found in medical literature, and retrospective reports received by GlaxoSmithKline, were summarized in each Interim Report and in this Final Report. Occasionally the Registry received notification of prenatal exposures and pregnancy outcomes from patients, but without verification by a health care provider. Though the Committee also reviewed these outcomes, the reports were not included in the data analysis but are summarized in Appendix C.

Analysis

An important aspect of the Registry was the Advisory Committee which was formed to oversee the process and results. The Committee was composed of representatives from GlaxoSmithKline, epidemiology, obstetric, and teratology specialists, who reviewed all the Registry data on an ongoing basis, and who met twice a year to review the aggregate data. Members of the Committee agreed on an interpretation of the data, and provided strategies for the dissemination of information regarding the Registry. An Interim Report was prepared after each meeting to summarize these aggregate data. Since the Reports

contained historical information as well as the new data, each Report completely replaced all previous Reports. Interim Reports were available to health care providers who treat this specialized population. This Final Report now replaces all previous Interim Reports.

Pregnancy outcomes were stratified by the earliest trimester of exposure. Gestational weeks were counted from the date of the last menstrual period, the second trimester as beginning at week 14, and the third trimester as beginning at week 28.

The calculation of risk for birth defects was made by dividing the number of live births, fetal deaths, and induced abortions with reported birth defects by the combined number of live births without birth defects and the outcomes involving birth defects. Fetal deaths and induced abortions without reported birth defects were excluded from this calculation. Due to the likelihood of misclassification bias in spontaneous pregnancy losses < 20 weeks gestation, these cases were also excluded from the calculation regardless of birth defect status. However, birth defects occurring in spontaneous pregnancy losses are listed on Table 4. A 95% confidence interval was calculated using the Fleiss method (Fleiss, 1981). Fundamental to the assessment process the Committee used to review data, were the following concepts: the overall frequency of major malformations in metropolitan Atlanta reported by the MACDP from 1968 through 2003 was 2.67%. (Correa *et al*, 2007). The estimated risk quoted in the literature may vary due to differences in case definition, population sampled, and ascertainment methods. The Collaborative Perinatal Project, using a broader case definition and prospective ascertainment, reported a frequency of 5%-7% (Chung *et al*, 1975). The baseline risk of individual birth defects is thought to be considerably lower, generally less than 1 per 1000 live births. Most major structural birth defects have their origins in the first trimester of pregnancy, the time of major organogenesis. For such birth defects, exposures occurring in the second or third trimester are not likely to be causally associated. However, for the sake of completeness, and to enable the Committee to assess possible increases in the frequency of birth defects, all defects meeting the CDC criteria were included in the Registry Report.

The basic criteria used in review of each specific case were: was the timing of the exposure to bupropion relevant to the origins of the birth defect; was there another known or likely cause (e.g., recognized genetic or chromosomal defect or exposure to a known teratogen); was the birth defect totally unknown or a previously unseen event; was there a unique combination of birth defects; in review of the composite data, was there a deviation from the baseline expectation of birth defects indicating an increase in the overall frequency of birth defects; was there a deviation from the baseline of specific birth defects; in the review of all the reported birth defects, was there diversity in the birth defects, suggesting no apparent single cause, or was there uniqueness (e.g., a pattern) of the birth defects that might suggest a common etiology. The Data Summary section of this Report (page 12) describes the Committee's assessment of the data according to these criteria.

Studies have shown the risk of spontaneous abortion is high early in pregnancy and decreases substantially from week 8 to week 28, yielding a cumulative estimated risk of 14%-22% overall (Kline *et al*, 1989). Although the Advisory Committee carefully reviewed each pregnancy outcome, calculation of risk of spontaneous pregnancy losses overall should not be attempted and cannot be compared to background rates because pregnancies in this Registry were reported at variable and, at times, imprecise times.

For example, if a pregnancy was registered at 10 weeks, only a spontaneous loss after this time could have been detected and included in the prospective reports. Similarly, pregnancy losses occurring early in gestation may not have been recognized and/or reported.

While the Registry was limited to prospective reports, some pregnancy exposures were reported only following pregnancy outcome (retrospective reports). GlaxoSmithKline also carefully reviewed each retrospective report. In general, retrospective notification of outcomes following exposures to drugs is biased toward reporting the 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 these data. However, a series of reported birth defects can be evaluated to detect patterns of specific birth defects and can identify early signals of new drug risks.

Potential Biases

As reporting of pregnancies was totally voluntary, it is possible that even in prospectively reported pregnancies there could be bias in type of pregnancies reported. For example, high-risk pregnancies or low-risk pregnancies may be more likely to be reported. Also, it is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Despite this, the Registry was 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. Moreover, accrual of additional patient experience over time provided more definitive information regarding risks, if any, of exposure to bupropion during pregnancy.

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 attempted 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. While the Registry was limited to prospective reports, some pregnancy exposures were reported after the pregnancy outcome had occurred (retrospective reports). GlaxoSmithKline carefully reviewed each retrospective report. In general, retrospective notification of outcomes following exposure to drugs is biased toward reporting the 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 identify early signals of new drug risks. A separate section describes all abnormal outcomes of retrospectively reported cases.

Appendix B: Minor Birth Defects or Other Conditions Reported at the Outcome of Pregnancy

Infants with only transient or infectious conditions, biochemical abnormalities, or minor birth defects were classified as being without birth defects unless there is 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 infants with minor birth defects are noted in the following tables of reports of infants with conditions other than birth defects.

Prospective Registry

1st Trimester Exposure

1. Live infant born premature, reason unknown.
2. Live infant with episodes of apnea and bradycardia.
3. Live infant with a 2 vessel umbilical cord.
4. Live infant with nevus simplex-forehead and occiput. Placental pathology normal.
5. Live infant with jaundice that cleared, also colicky for approximately 2 months.
6. Live infant had to be briefly intubated, also had neurologic problems that resolved.
7. Live infant with cystic fibrosis and meconium ileus.
8. Live infant with stork bite on forehead – superficial laceration on right elbow.
9. Live infant with cord wrapped around neck.
10. Live infant with small patent ductus arteriosus which closed spontaneously.
11. Live infant with atopic dermatitis and asthma (strong family history, genetic).
12. Live infant with low baseline heart rate 1-2 weeks prior to delivery and for a couple of days after birth.
13. Live infant with respiratory problems, cord around neck, and swallowed amniotic fluid.
14. Live infant with acrocyanosis.
15. Live infant with tachypnea.
16. Live infant with necrotizing endocolotis.
17. Live infant with both 5th fingers crooked/bent.
18. Live infant born mildly premature with feeding difficulties which resolved.
19. Live infant with pilonidal cyst.
20. Live infant was born early with jaundice and fluid in lungs.
21. Live infant with paralyzed vocal cord – already resolving – no surgery planned.
22. Live infant with pulmonary hypertension requiring neonatal intensive care for a few days.
23. Stillbirth with mild to moderate micrognathia, no cleft palate. Chromosomes 46, XX. Premature rupture of membranes occurred with acute funisitis, chorioamnionitis, and a somewhat small placenta noted at delivery.
24. Live infant with intraventricular hemorrhage with mild ventricular asymmetry.

Appendix B: Minor Birth Defects or Other Conditions Reported at the Outcome of Pregnancy (continued)

1st Trimester Exposure (continued)

25. Live infant with laryngomalacia, symptoms include stridor. Also diagnosed with failure to thrive.
26. Live infant with jaundice.
27. Live infant with apnea.
28. Live infant with tremulous legs periodically.
29. Live infant with apnea.
30. Live infant with mild colic.
31. Live infant slow to breast feed.
32. Live infant with two vessel cord.
33. Live infant with abnormal placenta and meconium stained amniotic fluid.
34. Live infant with high bilirubin count.
35. Live infant in Neonatal Intensive Care Unit due to early gestational age at birth.
36. Live infant crying out more than usual, possibly bupropion withdrawal.
37. Induced abortion due to intrauterine fetal demise.
38. Live infant with inadequate weight gain.
39. Live infant with intolerability to breast milk and formula the first 2 days after delivery.
40. Live infant with inguinal hernia requiring surgical repair.
41. Live infant with acid reflux.
42. Live infant one week overdue and in Neonatal Intensive Care Unit due to undiagnosed etiology.
43. Live infant swallowed meconium during delivery.
44. Live infant with eating problem and lack of weight gain.
45. Live infant delivered one month early.
46. Live infant with not enough foreskin to circumcise.
47. Live infant in Neonatal Intensive Care Unit due to early gestational age at birth, was intubated for respiratory distress.
48.* Live infant with hypoxic ischemic encephalopathy.

2nd Trimester Exposure

1. Live infant with mild respiratory distress secondary to umbilical cord around neck.
2. Live infant seizured at delivery, cause of the seizure is unknown.
3. Live infant died of sudden infant death syndrome.
4. Live infant with anal fissure with passage of blood in meconium. The infant also required intensive care due to sepsis.
5. Live infant initially failed left hearing screen, but recheck was normal.

3rd Trimester Exposure

1. Live infant with respiratory distress due to immaturity of the lungs.
2. Live infant with ventriculomegaly with no sequela.

*Denotes new cases

Appendix C: Patient Reported Prenatal Bupropion Exposures

Patient Reported Prenatal Bupropion Exposures

Criteria for inclusion in the prospective Registry required registration and follow-up by a health care provider. However, the Registry accepted reports of exposures from patients without confirmation by the health care provider. These reports are not included in the prospective Registry data analysis or prospective data section of the Final Report unless confirmed by the patient's health care provider. All patient-reported prenatal exposures, including those reported prior to establishment of the Registry, are accounted for here in Appendix C.

Patient reported pregnancies *prior to establishment* of Registry:

Prior to 1 September 1997, there were 2 prospective prenatal bupropion exposures reported by patients. Of these 2, 1 was lost to follow-up and the other involved the birth of an infant without birth defects.

Patient reported pregnancies *enrolled following establishment* of Registry:

The Registry closed to new enrollments 1 November 2007 and continued to follow up on existing cases through 31 March 2008. As of 31 March 2008, there were 112 prospective reports made to the Registry by patients concerning prenatal exposure to bupropion. There were 8 retrospective reports made to the Registry by patients. Birth defects were noted in 2 retrospective cases reported by patients: 1) one large and four small ventricular septal defects and 2) ventricular septal defect, but the Registry was unable to confirm the cases with the health care providers.