



The Bupropion Pregnancy Registry

Interim Report

1 September 1997 through 28 February 2007

Issued: June 2007

For policy on presentation/quotation of data, please see inside cover.

A Project Conducted By GlaxoSmithKline

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POLICY FOR ORAL PRESENTATION OF DATA

The sponsor encourages the responsible sharing of the information contained in this Report with health care professionals who might benefit. In an attempt to standardize dissemination and interpretation of the data, the following guidelines have been developed for oral presentation (no written document may include the data in this document without permission of GlaxoSmithKline):

1. The data contained in this Report will become out-of-date within 7 months of the Report's publication. Please contact the Bupropion Pregnancy Registry ((800) 336-2176 or (910) 256-0549 for international calls) to ensure you have obtained the most recently published Report.
2. The data in Table 2 (Prospective Registry – Bupropion Exposure in Pregnancy by Earliest Trimester of Exposure) are the most appropriate for presentation. Presentation of results stratified by earliest trimester of exposure is imperative.
3. A statement regarding the Committee Consensus must be referenced in any presentation of these data, including emphasis on the limitations of voluntary prenatal drug exposure registries such as this one. Include the following statement in the sample slide below in any presentation of results:

COMMITTEE CONSENSUS

“After reviewing the 909 prospectively reported pregnancy outcomes, the Bupropion Pregnancy Registry Advisory Committee concludes that while the Registry to date has not detected a signal of a major problem with birth defects, the population exposed and monitored to date is only sufficient to detect major teratogenicity, and cannot detect an increase in the risk of relatively rare defects at this time.”

Source: Bupropion Pregnancy Registry Interim Report, Issue Date: June 2007.
See Page 13 for the complete Committee Consensus.

4. When presenting data from the Pregnancy Registry, please remind the audience that the success of the study depends on reporting of exposures by health care providers. Registry contact information should be presented, as outlined in the sample slide below:

REGISTRY CONTACT INFORMATION

Pregnancies should be enrolled into the Bupropion Pregnancy Registry as early in the pregnancy as possible. Please contact the GlaxoSmithKline Pregnancy Registries to enroll a pregnancy exposure at:

US & Canada:	Phone: (800) 336-2176 (toll free)
	FAX: (800) 800-1052

International:	Phone: (910) 256-0549 (call collect)
	FAX: (910) 256-0549

To maximize validity of the data, exposed pregnancies should be enrolled into the Pregnancy Registry as early in the pregnancy as possible.

Please contact the Bupropion Pregnancy Registry to enroll pregnancy exposures or if you have any questions at:

- (800) 336-2176 (toll free)
- (910) 256-0549 (call collect)

Data forms are available at: <http://www.kendle.com/registries/>

BUPROPION PREGNANCY REGISTRY

INTERIM REPORT

1 SEPTEMBER 1997 – 28 FEBRUARY 2007

PROJECT OFFICE

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FOREWORD

This Report describes the experience of the ongoing study of prospectively reported pregnancy outcomes in the Bupropion Pregnancy Registry through 28 February 2007.

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 an ongoing 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, are registered by health care providers, the pregnancies are followed, and the outcomes are ascertained through follow-up.

The Registry is intended to provide an early signal of potential risks in advance of results from formal epidemiologic studies. Registry data will be 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*:

John Ascher, MD
Neurosciences MDC
GlaxoSmithKline

Hugh Tilson, MD, DrPH
University of North Carolina at Chapel Hill
School of Public Health

Janet Cragan, MD
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The *Bupropion Pregnancy Registry* encourages reporting of all known exposures. Such referrals should be directed to the Bupropion Pregnancy Registry, Kendle International Inc., Research Park, 1011 Ashes Drive, Wilmington, NC 28405, U.S.A., telephone (910) 256-0549 (call collect) or (800) 336-2176 or FAX (800) 800-1052 (toll free within the U.S.) or (910) 256-0637 for all international faxes. The Registry operations manager is Paige Churchill. GlaxoSmithKline contact: Katherine Firth, Information Manager, telephone: (44) 1279-646951.

BUPROPION PREGNANCY REGISTRY - INTERIM REPORT

1 SEPTEMBER 1997 THROUGH 28 FEBRUARY 2007

EXECUTIVE SUMMARY

Although there is no evidence of teratogenicity from preclinical studies of bupropion, the medical division of GlaxoSmithKline manages an ongoing program in epidemiologic safety monitoring. Women with depression or attempting smoking cessation may require or be unintentionally exposed to bupropion during pregnancy. This program is 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 reviews 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 are reported at variable and, at times, imprecise times. For example, if a pregnancy is registered at 10 weeks, only a spontaneous loss after this time can be detected and included in the prospective reports. Similarly, pregnancy losses occurring early in gestation may not be recognized and/or reported.

The Registry collects and follows only prospective reports of prenatal bupropion exposure. However, Interim Reports will also include the following information as it becomes 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.

As of 28 February 2007, 1513 pregnancies involving exposure to bupropion have been prospectively registered. From those 1513 pregnancies, 96 are pending delivery, 519 cases are lost to follow-up, and 898 cases with 909 outcomes were obtained (including 9 sets of twins and 1 set of triplets). Of these 909 pregnancy outcomes, 724 involved earliest bupropion exposure in the first trimester, 134 involved earliest bupropion exposure in the second trimester, and 51 involved earliest bupropion exposure in the third trimester. Of the 724 pregnancy outcomes following earliest prenatal exposure in the first trimester, there were no reported birth defects in 579 live births, 30 induced abortions, and 2 fetal deaths. There were 17 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 90 spontaneous pregnancy losses with 1 defect detected (excluded from the analysis). Of the 134 pregnancy outcomes with the earliest bupropion exposure in the second trimester there were no reported birth defects in 130 live births and 1 induced abortion. There were 2 infants born alive with a birth defect. In addition, there was 1 spontaneous pregnancy loss. Of the 51 pregnancy outcomes with the earliest exposure in the third trimester, there were 50 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 579 live births without a reported birth defect and 23 outcomes which involved birth defects (total = 602): 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 arteriosus and patent foramen ovale, and 23) a live infant with duplicate left renal pelvis. 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 23/602 (3.8%, 95% Confidence Interval: 2.5-5.8%). This proportion includes 579 live births without birth defects, 17 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 130 live births without a reported birth defect and 2 outcomes with a birth defect (total = 132): 1) a live infant with bilateral club feet; hemangioma on forehead x 2, and 2) a live infant with improving torticollis and oral neoplasm that resolved. The observed proportion of birth defects in pregnancies with prenatal exposure in the second trimester is 2/132 (1.5%, 95% Confidence Interval: 0.3-5.9%). This proportion includes 130 live births without birth defects and 2 live births with birth defects.

Among the 24 retrospectively reported birth defects, there were 11 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 dysmorphic 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, and 11) a live infant with transposition of the great arteries. 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 of 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 is not currently possible to determine whether these data reflect a potential effect of bupropion on the developing cardiovascular system. Further, the current small sample size precludes 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% CI 0.62-1.45) and 1.00 (95% CI 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% CI 0.52-1.80) and 1.07 (95% CI 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.

With the publication of this new data the Committee has reviewed continuation of the Registry. The Committee recommends planned termination of this Registry around a level of reassurance for overall birth defects and the more frequent classes of birth defects. With current recruitment this goal would be reached within the next year, provided no new signals emerge. Monitoring for an association with specific defects should continue through established systems; anonymized aggregated healthcare databases are emerging as 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 has not detected a signal of a major problem with birth defects, the population exposed and monitored to date is only sufficient to detect major teratogenicity, and cannot detect an increase in the risk of specific defects at this time. This drug should be used during pregnancy only if the potential benefit outweighs the potential unknown risk.

1. INTRODUCTION

The purpose of the Registry is 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 make such a Registry an essential component of the ongoing program of epidemiologic studies of the safety of bupropion. This study is an observational, exposure-registration and follow-up study. This study has been 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 is strictly upheld. The intent of the Registry is 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 is managed by GlaxoSmithKline in collaboration with obstetric, epidemiology, and teratology specialists which form the Advisory Committee. This Committee provides independent review of the data for the Registry. The Registry began in September 1997.

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.

Bupropion produced a positive response (two to three times control mutation rate) in two of five strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in one of three in vivo rat bone marrow cytogenetic studies.

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

This Interim Report is 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, replaces all previous Reports. The new information in this Report includes data from all cases closed between 1 September 2006 and 28 February 2007 (Table 1).

Table 1. New Data During Reporting Period

Status	Newly Registered Pregnancies	Previously Registered Pregnancies-Closed This Period	Total
Pending	58	N/A	58
Lost to follow-up	2	34	36
Closed	12	60	72
Number of Outcomes	13*	63**	76
No Birth Defects	10	55	65
<i>Live Birth</i>	9	54	63
<i>Fetal Death</i>	0	0	0
<i>Induced Abortion</i>	1	1	2
Birth Defects	0	2	2
<i>Live Birth</i>	0	2	2
<i>Fetal Death</i>	0	0	0
<i>Induced Abortions</i>	0	0	0
Spontaneous Loss	3	6	9

*Includes 1 set of twins, ** includes 1 set of triplets

3.2 All Data

Through 28 February 2007, there have been 1513 prospectively registered pregnancies involving exposure to bupropion. Of these 1513, 96 pregnancies are pending delivery, 519 are lost to follow-up, and there have been 898 pregnancies with 909 outcomes obtained including 9 sets of twins and 1 set of triplets (Table 3). The indication for use was depression in 610 patients, smoking cessation in 173 patients, both depression and smoking cessation in 26 patients, bipolar affective disorder in 9 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 25 patients, and unspecified for 55 patients. Of the 519 lost to follow-up cases, 46% 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, 31% 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 (15 countries) of the 898 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 – 28 February 2007

Country	Number of Reported Pregnancies ^a
Australia	4
Belgium	8
Canada	49
Czech Republic	1
Estonia	1
France	40
Germany	1
Holland	1
Luxemburg	1
New Zealand	2
South Africa	3
Spain	4
Sweden	1
United Kingdom	25
United States	757
TOTAL	898

^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 – 28 February 2007

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	17 ^g	1	5	579 ^{a,g}	2	30	90	724
Second	2	0	0	130	0	1	1	134
Third	0	0	0	50	1	0	0	51
Total	19	1	5	759	3	31	91	909

^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. Due to the likelihood of misclassification, 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 – 28 February 2007

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).
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 arteriosus and patent foramen ovale.

24.* Live infant with duplicate left renal pelvis.

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.

*Denotes new cases

** Due to the likelihood of misclassification, 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 – 28 February 2007

Number of Outcomes = 602				
	< 16 weeks	16 – 20 weeks	> 20 weeks	Unknown
Total	386 (64.1%)	52 (8.6%)	156 (25.9%)	8 (1.3%)
No Defect	369	52	150	8
Defect	17	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 are 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 28 February 2007, there have been 24 outcomes with birth defects retrospectively reported, with 22 involving the earliest maternal bupropion exposure in the first trimester, 1 in the second trimester, and 1 in the third trimester. The Registry follows the Centers for Disease Control and Prevention’s (CDC) birth defect evaluation guidelines. A description of the 24 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.

Retrospective Health Care Provider Reports (continued):

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.
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.

Retrospective Health Care Provider Reports (continued):

- 23.* Live infant with hypospadias.
- 24.* Live infant with transposition of the great arteries.

*Denotes new cases

5. DATA FROM OTHER STUDIES

On an ongoing basis, the published medical literature and other data sources are 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. Preliminary 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 be captured in the Bupropion Pregnancy Registry. Final results from this study have now been published (See Committee Consensus for results).

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 909 prospectively reported pregnancy outcomes according to the criteria described under “Methods” in Appendix A.

Review of the composite data:

Of the 724 pregnancy outcomes following earliest prenatal exposure in the first trimester, there were no reported birth defects in 579 live births, 30 induced abortions, and 2 fetal deaths. There were 17 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 arteriosus and patent foramen ovale, and 17) duplicate left renal pelvis. 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 90 spontaneous abortions, 1 of which had a defect with Trisomy 14, which was excluded from the analysis due to the likelihood of misclassification bias among spontaneous pregnancy losses < 20 weeks gestation.

Of the 134 pregnancy outcomes following earliest prenatal exposure in the second trimester, there were no reported birth defects in 130 live births and 1 induced abortion. There were 2 live born infants with a birth defect: 1) bilateral club feet; hemangioma on forehead x 2, and 2) improving torticollis and oral neoplasm that resolved. There was also 1 spontaneous pregnancy loss. The outcomes for the 51 pregnancies with the earliest exposure in the third trimester were 50 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 23/602 (3.8%, 95% Confidence Interval: 2.5-5.8%). This proportion includes 579 live births without birth defects, 17 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 2/132 (1.5%, 95% Confidence Interval: 0.3-5.9%). This proportion includes 130 live births without birth defects and 2 live births with birth defects.

7. COMMITTEE CONSENSUS – BUPROPION

Among prospective pregnancy outcomes with a first trimester exposure, there were 579 live births without a birth defect and 23 outcomes which involved birth defects (total = 602): 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 arteriosus and patent foramen ovale, and 23) a live infant with duplicate left renal pelvis. There was also a spontaneous abortion with Trisomy 14 which was excluded from the analysis due to the likelihood of misclassification bias in spontaneous pregnancy losses < 20 weeks gestation. The observed proportion of birth defects in pregnancies with prenatal exposure in the first trimester is 23/602 (3.8%, 95% Confidence Interval: 2.5-5.8%). This proportion includes 579 live births without birth defects, 17 live births with birth defects, 1 fetal death with a birth defect, and 5 induced abortions with birth defects.

The international nature of the Bupropion Pregnancy Registry means there is no direct comparator. The MACDP covers the same time period and has the same case definitions. The overall frequency of major malformations in metropolitan Atlanta reported by the MACDP from 1991 through 1995 was 3.1% (95% Confidence Interval: 3.1-3.2%), and the prevalence of birth defects identified either prior to birth or during the first day of life was 2.2% (95% Confidence Interval: 2.1-2.2%) (Honein *et al*,1999). The prevalence of "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.

Among prospective pregnancy outcomes with a second trimester exposure, there were 130 live births without birth defects, and there were 2 outcomes which involved a birth defect (total = 132): a live infant with bilateral club feet; hemangioma on forehead x 2, and 2) a live infant with improving torticollis and oral neoplasm that resolved. The observed proportion of birth defects in pregnancies with prenatal exposure in the second trimester is 2/132 (1.5%, 95% Confidence Interval: 0.3-5.9%). This proportion includes 130 live births without birth defects and 2 live births with birth defects.

Among the 24 retrospectively reported birth defects, there were 11 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 dysplastic 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, and 11) a live infant with transposition of the great arteries. 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 is not currently possible to determine whether these data reflect a potential effect of bupropion on the developing cardiovascular system. Further, the current small sample size precludes 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% CI 0.62-1.45) and 1.00 (95% CI 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% CI 0.52-1.80) and 1.07 (95% CI 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.

With the publication of this new data the Committee has reviewed continuation of the Registry. Given this larger dataset and the ten years of surveillance for the Registry the Committee recommends planned termination of this Registry around a level of reassurance for overall birth defects and the more frequent classes of birth defects. With current recruitment this goal would be reached within the next year, provided no new signals emerge. The expected 700 first trimester exposures would be able to detect a risk of 1.6 for overall birth defects and from 2.2 (heart and circulation) to 2.8 (nervous system) for the more frequent classes of defects (Covington, *et al*, 2004). Monitoring for an association with specific defects should continue through established systems including the ongoing case control surveillance through the National Birth Defects Prevention Study (Yoon *et al*, 2001).

Anonymized aggregated healthcare databases (HMO Research Network, Blue Cross and Blue Shield HealthCore database) are emerging as alternative data sources in which to evaluate any emerging signals.

The Advisory Committee notes the high lost to follow-up rate for the current Registry. It is unclear why this is occurring and whether the women for whom outcome information is not received differ from those for whom the outcome is known. The Advisory Committee strongly urges health care providers who initially report exposed pregnancies to provide follow-up information to the Registry to add to the validity of the data and usefulness of the Registry.

Given the sample size, lack of an appropriate comparison group, and the high lost to follow-up rate, the Bupropion Pregnancy Registry findings do not indicate a major problem with overall birth defects that would occur with major teratogenicity but is unable to reach definitive conclusions regarding the possible risk of bupropion for specific defects.

This Interim Report is issued semiannually following the independent review of new data. Each Report includes the historical information as well as new data known to the Registry and, therefore, replaces all previous Reports. If your current Report is older than seven months, please request the updated Interim Report from your local GlaxoSmithKline Company, or directly from the Registry.

8. REGISTRY ENROLLMENT

To avoid bias, it is important to enroll all known exposures to bupropion as early in the pregnancy as possible.

In this Registry, enrollment should take place as early in the pregnancy as possible, after an exposure has already occurred, but preferably before any prenatal testing is performed. A case registration approach only works with the continued participation of health care professionals who register patients and provide follow-up information postpartum. The assistance of health care professionals who have provided information to the Registry is greatly appreciated, and the help of others is eagerly sought.

The Bupropion Pregnancy Registry encourages reporting of all known exposures. Such referrals should be directed to the Bupropion Pregnancy Registry, Kendle International Inc., Research Park, 1011 Ashes Drive, Wilmington, NC 28405, U.S.A., telephone (910) 256-0549 (call collect), or (800) 336-2176 (toll-free), or FAX (800) 800-1052 or (910) 256-0637 for all international faxes (see Appendix D for enrollment forms).

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Appendix A: Methods

Registration and Follow-up

Reporting of exposed pregnancies is voluntary. Health care providers with patients exposed to bupropion during pregnancy are encouraged to enroll each patient in the Registry as early in the pregnancy as possible. When a patient initiates contact with the Registry they are asked to provide permission and sufficient contact information for the Registry to follow-up with their health care provider for the purpose of disseminating Registry data and completing the pregnancy registration process.

Enrollment in the Registry involves the prospective notification to the Registry of ongoing pregnancies exposed to bupropion, but without knowledge of the pregnancy outcome. Because the outcome of the pregnancy is unknown when the exposure is reported, follow-up to determine the outcome is required.

When the pregnancy is prospectively reported, registration data is collected by the Registry from the treating health care provider through telephone interview or by completing a short registration form. There are minimum data points required to register a pregnancy: country of origin of report, documentation that the Registry drug was taken during pregnancy, enough information to determine whether the pregnancy is 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 is already known or is 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 is confidential and a Patient (Log) ID number is assigned for the purpose of communicating with the reporting health care professional. Near the estimated date of delivery, follow-up is obtained through a short follow-up form sent to the health care professional who provides information on maternal risk factors, pregnancy outcome, and neonatal health.

A report of an exposure is closed when clear information on the bupropion exposure and pregnancy outcome has been obtained. A report will be closed as "not valid" when the minimum requirements are not reported, however attempts are made to obtain the minimum data points. Reports of exposures are closed as "lost to follow-up" after the reporting health care professional has been repeatedly contacted for follow-up well beyond the expected delivery date or if the health care professional can no longer locate the patient. Only data from "closed" reports of exposed pregnancies with known outcomes are summarized in this Report. Patient identifiers are initially retained in the Registry database to allow for contact and confirmation of the patients and their data. However, after a confidential Registry number has been assigned to the reporting health care professional, this information is removed. In addition, the database link between patient and health care provider is severed.

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

Institutional Review Board (IRB) Review

In accordance with the now published FDA Guidance to Industry: Establishing Pregnancy Exposure Registries, (FDA 2002), the Registry has 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 reviews the Registry protocol annually with quarterly interim status reports required.

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 June 10, 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 is to monitor bupropion exposures in pregnancy for adverse outcomes to the fetus 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 second category is further classified by: (a) live births, (b) fetal deaths, and (c) induced abortions. This Registry adopts 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 are reported during the first year of life. For reference, the Committee adopts the list of birth defects recognized by the CDC (Centers for Disease Control and Prevention, 1989; Correa-Villasenor *et al*, 2003). All birth defects are classified taking into consideration advice from members of the Advisory Committee.

Infants with only transient or infectious conditions, or biochemical abnormalities, are 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 defects that are excluded by the CDC guidelines will be noted in Appendix B of the Report.

Exclusions

For this Registry, enrollment is limited to ongoing pregnancies involving bupropion exposure registered prior to any knowledge of the pregnancy outcome. However, GlaxoSmithKline encourages reporting of all known prenatal exposures to bupropion. Pregnancies included in the data analysis are 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, will be summarized in the

Registry's full Interim Report. Occasionally the Registry receives notification of prenatal exposures and pregnancy outcomes from patients, but without verification by a health care provider. Though the Committee also reviews these outcomes, the reports are not included in the data analysis but are summarized in Appendix C.

Analysis

An important aspect of the Registry is the Advisory Committee formed to oversee the process and results. The Committee is composed of representatives from GlaxoSmithKline, epidemiology, obstetric, and teratology specialists, who review all the Registry data on an ongoing basis, and who meet twice a year to review the aggregate data. Members of the Committee agree on an interpretation of the data, and provide strategies for the dissemination of information regarding the Registry. An Interim Report is prepared after each meeting to summarize these aggregate data. Since the Report contains historical information as well as the new data, it completely replaces all previous Reports. This Report is available to health care providers who treat this specialized population.

Pregnancy outcomes are stratified by the earliest trimester of exposure. Gestational weeks are 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 is 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 are excluded from this calculation. Due to the likelihood of misclassification bias in spontaneous pregnancy losses < 20 weeks gestation, these cases are 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 is calculated using the Fleiss method (Fleiss, 1981). Fundamental to the assessment process the Committee uses to review data, are the following concepts: the baseline risk (in the general population) of all birth defects meeting the CDC criteria is 3.1% (95% Confidence Interval: 3.1-3.2%) of live births (Honein *et al*, 1999). 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 are included in the Registry Report.

The basic criteria used in review of each specific case are: 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 10) 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 reviews 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 are reported at variable and, at times, imprecise times. For example, if a pregnancy is registered at 10 weeks, only a spontaneous loss after this time can be detected and included in the prospective reports. Similarly, pregnancy losses occurring early in gestation may not be recognized and/or reported.

While the Registry is limited to prospective reports, some pregnancy exposures are reported only following pregnancy outcome (retrospective reports). GlaxoSmithKline also carefully reviews 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 is 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 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. Moreover, accrual of additional patient experience over time will provide 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 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. While the Registry is limited to prospective reports, some pregnancy exposures will be reported after the pregnancy outcome has occurred (retrospective reports). GlaxoSmithKline also carefully reviews 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 are 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 endocolitis.
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.

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

1st Trimester Exposure (continued)

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.
25. Live infant with laryngomalacia, symptoms include stridor. Also diagnosed with failure to thrive.
26. Live infant with apnea.
27. Live infant with tremulous legs periodically.
28. Live infant with apnea.
29. Live infant with mild colic.
30. Live infant slow to breast feed.
31. Live infant with two vessel cord.
32. Live infant with abnormal placenta and meconium stained amniotic fluid.
33. Live infant with high bilirubin count.
34. Live infant in Neonatal Intensive Care Unit due to early gestational age at birth.
35. Live infant crying out more than usual, possibly bupropion withdrawal.
36. Induced abortion due to intrauterine fetal demise.
- 37.* Live infant with inadequate weight gain.
- 38.* Live infant with intolerance to breast milk and formula the first 2 days after delivery.
- 39.* Live infant with inguinal hernia requiring surgical repair.
- 40.* Live infant with acid reflux.

2nd Trimester Exposure

1. Live infant with mild respiratory distress secondary to umbilical cord around neck.
2. Live infant seized 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 requires registration and follow-up by a health care provider. The Registry continues to accept 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 Interim 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:

As of 28 February 2007, there were 110 prospective reports made to the Registry by patients concerning prenatal exposure to bupropion. A birth defect was noted in one case reported by a patient (ventricular septal defect), but the Registry was unable to confirm the case with her health care provider. Two cases are pending outcome.

Appendix D: Registry Enrollment and Data Forms

Enrollment and Follow-up forms may be obtained from the Pregnancy Registry or may be copied from the included samples to prospectively report prenatal exposure to bupropion.

Instructions for completing forms:

Patient Anonymity and Patient Identifiers

In the past, the Registry has made efforts to assure patient confidentiality within the Registry. It is now felt that the Registry should make a further effort to assure patient anonymity in the Registry. Therefore, the Registry will NO LONGER COLLECT ANY IDENTIFIERS that might inadvertently compromise patient confidentiality. The patient identifier is now a **Registry assigned number** provided to the reporter at the time the patient is registered.

Patient IDs can be obtained by calling or faxing the Registry for a number (or a block of numbers, for providers who register patients on a regular basis). The Registry also provides a Patient Log ID as a possible way the reporter might cross-reference the patient with the Registry Patient ID number. Whatever method is used, the record should be kept in a secure place to assist in protecting patient confidentiality at your site.

Prospective Registration - (To be completed when notifying Registry of prenatal exposure while patient is still pregnant).

- Call or fax the Registry office for Patient ID
 - Track the Patient ID number with your own identification of the patient
 - Secure the tracking log to protect patient confidentiality
- Copy all pages of the Registration Form
- Fill in as much information as is available at the time of reporting
- Report as early as possible after the exposure is known to you

Return the form to the Registry. You will be sent a short Follow-up Form to report on the pregnancy outcome at or near the patient's estimated date of delivery.

Please notify the Registry of all prenatal exposures to bupropion at:

**Bupropion Pregnancy Registry
Kendle International Inc.
Research Park
1011 Ashes Drive
Wilmington, NC 28405**

OR Register via FAX transmittal by dialing: (800) 800-1052

or (910) 256-0637 for all international faxes.

or Register via phone by dialing: (910) 256-0549 (call collect)

or (800) 336-2176 (toll-free).

Bupropion Pregnancy Registry

FOR OFFICE USE ONLY

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of 2

Registration Form

Return by FAX to: 800-800-1052
910-256-0637 (All International Faxes)

Registry Patient ID _____ HCP ID _____

WSPSP ID _____ Country _____

Registry date of notification _____
Phone _____

Transcribed _____ day month year

MATERNAL DATA

Patient ID _____

Registry-assigned ID number. Call or Fax the Registry Office for a non-patient identifying number (Phone: 800-336-2176 US/Canada; 910-256-0549 International; Fax: 800-800-1052 US/Canada; 910-256-0637 International)

*Note: To help assure patient confidentiality, the Registry uses a Registry-assigned patient ID to refer to your patient to obtain follow-up and outcome information. A **patient log** will be sent to you, if this is your first registrant. The Log will help cross-reference this ID with your own identifier(s) for this patient. Keep the log in a secure place.*

Race: White Black Hispanic
 Asian Other

Patient Age _____

Is there evidence of a defect from a prenatal test?

Yes No

Last Menstrual Period _____
day month year

If yes, indicate which test(s) showed evidence of birth defect:

Ultrasound Amniocentesis
 MSAFP Other: _____

Estimated Date of Delivery _____
day month year

How was the Estimated Date of Delivery determined?

by Last Menstrual Period by Ultrasound

If yes, findings: _____

by Other Method: _____

ALL BUPROPION DOSES DURING THIS PREGNANCY INDICATION:

Smoking Cessation Major Depression Other, specify (e.g., bipolar depression, ADHD) _____

	Course Began (d/m/y)	Daily Dose (total mg/day)	Course Began* (gestation week from LMP)	Course Ended (gestation week from LMP)	If Ongoing (√)
Course 1	_____	_____	_____	_____	<input type="checkbox"/>
Course 2	_____	_____	_____	_____	<input type="checkbox"/>
Course 3	_____	_____	_____	_____	<input type="checkbox"/>

• If Course 1 began prior to conception, enter 0

HISTORY OF CIGARETTE SMOKING

Has patient smoked cigarettes within 1 month of conception or during this pregnancy? Yes No

Did patient quit smoking? Yes No If yes, when? _____ (gestation week)

Did patient resume smoking? Yes No If yes, when? _____ (gestation week)

OTHER INFORMATION

Is this pregnancy considered high risk (e.g. history of pregnancy complications, family history of malformations, major medical problems, or any other concern about potential complications or malformations)? Yes No

If Yes, describe: _____

HEALTH CARE PROVIDER INFORMATION

Name _____ Specialty _____

Address _____ Phone _____

Fax _____

Alternate Contact _____

Provider's Signature _____

Date _____
day month year

Bupropion Pregnancy Registry — Registration Form

Page 2 of 2

Return by FAX to: 800-800-1052 or 910-256-0637 (All International Faxes)

Registry Patient ID _____
(FOR OFFICE USE ONLY)

Patient ID _____ (Registry-assigned ID number)

OTHER ILLNESS / POTENTIAL RISK FACTORS

Yes (Ö) No (Ö)

Cancer.....	<input type="checkbox"/>	<input type="checkbox"/>
Epilepsy.....	<input type="checkbox"/>	<input type="checkbox"/>
Type I Diabetes Mellitus.....	<input type="checkbox"/>	<input type="checkbox"/>
Type II Diabetes Mellitus, poorly controlled during pregnancy.....	<input type="checkbox"/>	<input type="checkbox"/>
Gestational Diabetes, poorly controlled.....	<input type="checkbox"/>	<input type="checkbox"/>
Obesity.....	<input type="checkbox"/>	<input type="checkbox"/>
Alcohol use during pregnancy.....	<input type="checkbox"/>	<input type="checkbox"/>
Substance abuse during pregnancy.....	<input type="checkbox"/>	<input type="checkbox"/>

OTHER MEDICATIONS USED (to date) DURING PREGNANCY

	Prior to conception (Ö)	TRIMESTER OF PREGNANCY		
		First (Ö)	Second (Ö)	Third (Ö)
Antidepressants				
SSRIs (Selective Serotonin Reuptake Inhibitors) (e.g., citalopram [Celexa], escitalopram [Lexapro], fluoxetine [Prozac], fluvoxamine [Luvox], paroxetine [Paxil], sertraline [Zoloft])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SNRIs (Serotonin Norepinephrine Reuptake Inhibitors) (e.g., duloxetine [Cymbalta], venlafaxine [Effexor])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
TCAs (Tricyclics) (e.g., amitriptyline [Elavil, Endep], desipramine [Norpramine], doxepin [Adapin, Sinequan], imipramine [Tofranil], nortriptyline [Pamelor])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
MAOIs (Monoamine Oxidase Inhibitors) (e.g., isocarboxazid [Marplan], phenelzine [Nardil], tranlycypromine [Parnate])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Miscellaneous (e.g., mirtazapine [Remeron], trazodone [Desyrel])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mood Stabilizers or Anticonvulsants				
carbamazepine (Tegretol, Carbatrol)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
lithium (Eskalith, Lithobid)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
phenytoin (Dilantin)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
valproic acid (Depakote, Depakene)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (e.g., gabapentin [Neurotin], topiramate [Topomax], lamotrigine [Lamictal], phenobarbital, zonisamide [Zonegran], oxcarbazepine [Trileptal])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Antipsychotics (e.g., haloperidol [Haldol], fluphenazine [Prolixin], chlorpromazine [Thorazine], thioridazine [Mellaril], clozapine [Clozaril], olanzapine [Zyprexa], risperidone [Risperdal], quetiapine [Seroquel], ziprasidone [Geodon], aripiprazole [Abilify])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Medications - Please list all other prescription medications (<i>including non-psychiatric medications</i>) that the patient is taking or has taken.				
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Is the patient taking (or has the patient taken) any medication that you believe could cause or contribute to fetal problems or complications during pregnancy? Yes No
If Yes, describe: _____

Bupropion Pregnancy Registry Follow-Up Form Return by FAX to: 800-800-1052 910-256-0637 (All International Faxes)	FOR OFFICE USE ONLY Page 1 of 3
	Registry Patient ID _____ HCP ID _____
	WSPSP ID _____ Country _____
	Date case closed _____ <input type="checkbox"/> Phone day month year <input type="checkbox"/> Transcribed

MATERNAL DATA
Patient ID _____ (Registry-assigned ID number)

ALL BUPROPION DOSES DURING THIS PREGNANCY
INDICATION: Smoking Cessation
 Major Depression
 Other, specify (e.g., bipolar depression, ADHD) _____

	Course Began (d/m/y)	Daily Dose (total mg/day)	Course Began* (gestation week from LMP)	Course Ended (gestation week from LMP)	If Ongoing (√)
Course 1	_____	_____	_____	_____	<input type="checkbox"/>
Course 2	_____	_____	_____	_____	<input type="checkbox"/>
Course 3	_____	_____	_____	_____	<input type="checkbox"/>

* If Course 1 began prior to conception, enter 0

HISTORY OF CIGARETTE SMOKING
Has patient smoked cigarettes within 1 month of conception or during this pregnancy? Yes No
Did patient quit smoking? Yes No If yes, when? _____ (gestation week)
Did patient resume smoking? Yes No If yes, when? _____ (gestation week)

OTHER INFORMATION
Is this pregnancy considered high risk (e.g. history of pregnancy complications, family history of malformations, major medical problems or any other concern about potential complications or malformations)? Yes No
If Yes, describe: _____

OTHER ILLNESS / POTENTIAL RISK FACTORS
_____ Yes (0) No (0)

Cancer.....	<input type="checkbox"/>	<input type="checkbox"/>
Epilepsy.....	<input type="checkbox"/>	<input type="checkbox"/>
Type I Diabetes Mellitus.....	<input type="checkbox"/>	<input type="checkbox"/>
Type II Diabetes Mellitus, poorly controlled during pregnancy	<input type="checkbox"/>	<input type="checkbox"/>
Gestational Diabetes, poorly controlled.....	<input type="checkbox"/>	<input type="checkbox"/>
Obesity	<input type="checkbox"/>	<input type="checkbox"/>
Alcohol use during pregnancy.....	<input type="checkbox"/>	<input type="checkbox"/>
Substance abuse during pregnancy	<input type="checkbox"/>	<input type="checkbox"/>

Bupropion Pregnancy Registry — Follow-Up Form

Return by FAX to: 800-800-1052 or 910-256-0637 (All International Faxes)

Registry Patient ID _____
(FOR OFFICE USE ONLY)

Patient ID _____ (Registry-assigned ID number)

OTHER MEDICATIONS USED DURING PREGNANCY

	Prior to	TRIMESTER OF PREGNANCY		
	conception (0)	First (0)	Second (0)	Third (0)
Antidepressants				
SSRIs (Selective Serotonin Reuptake Inhibitors) (e.g., citalopram [Celexa], escitalopram [Lexapro], fluoxetine [Prozac], fluvoxamine [Luvox], paroxetine [Paxil], sertraline [Zoloft])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SNRIs (Serotonin Norepinephrine Reuptake Inhibitors) (e.g., duloxetine [Cymbalta], venlafaxine [Effexor])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
TCAs (Tricyclics) (e.g., amitriptyline [Elavil, Endep], desipramine [Norpramine], doxepin [Adapin, Sinequan], imipramine [Tofranil], nortriptyline [Pamelor])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
MAOIs (Monoamine Oxidase Inhibitors) (e.g., isocarboxazid [Marplan], phenelzine [Nardil], tranylcypromine [Parnate])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Miscellaneous (e.g., mirtazapine [Remeron], trazodone [Desyrel])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mood Stabilizers or Anticonvulsants				
carbamazepine (Tegretol, Carbatrol)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
lithium (Eskalith, Lithobid)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
phenytoin (Dilantin)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
valproic acid (Depakote, Depakene)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (e.g., gabapentin [Neurotin], topiramate [Topomax], lamotrigine [Lamictal], phenobarbital, zonisamide [Zonegran], oxcarbazepine [Trileptal])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Antipsychotics (e.g., haloperidol [Haldol], fluphenazine [Prolixin], chlorpromazine [Thorazine], thioridazine [Mellaril], clozapine [Clozaril], olanzapine [Zyprexa], risperidone [Risperdal], quetiapine [Seroquel], ziprasidone [Geodon], aripiprazole [Abilify])	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other Medications - Please list all other prescription medications (<i>including non-psychiatric medications</i>) that the patient is taking or has taken.				
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Is the patient taking (or has the patient taken) any medication that you believe could cause or contribute to fetal problems or complications during pregnancy? Yes No

If Yes, describe:
