The Lamotrigine Pregnancy Registry

Final Report

1 September 1992 through 31 March 2010

Issued: July 2010

REGISTRY CLOSURE INFORMATION

The Registry began in September 1992, closed to new prospective enrollments on June 3, 2009, and continued follow up on existing enrollments through March 31, 2010.

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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 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 written permission of GlaxoSmithKline):

1. The data in Table 4 (Prospective Registry - Lamotrigine Exposure in Pregnancy by Earliest Trimester of Exposure and Outcome) is the most appropriate for presentation. Presentation of results stratified by earliest trimester of exposure is imperative.
2. 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.

COMMITTEE CONSENSUS STATEMENT (from full consensus). The Committee notes that the Registry has considerably surpassed the milestone of enrolling 1000 prospective birth outcomes following first trimester exposure to lamotrigine monotherapy. At Registry closure, 1558 birth outcomes from first trimester exposures have been evaluated. The Registry was thus adequately powered to meet its primary objective, which was to determine whether the overall rate of major malformations was increased among the offspring of exposed women. The Registry has not detected an appreciable increase in the singular outcome of major birth defects overall. However, the population monitored was not powered to exclude increases in the rates of specific defects. Monitoring of the risk of specific birth defects following *in utero* lamotrigine exposure will continue through the EUROCAT network. The case control method will offer a more powerful approach to the study of specific birth defects.

Source: Lamotrigine Pregnancy Registry Final Report, Issue Date: July 2010.
See Page 44 for the complete Committee Consensus.

Despite the closure of the Lamotrigine Pregnancy Registry, patients in North America can continue to participate in the study of lamotrigine in pregnancy by enrolling in the North American AED Pregnancy Registry by calling (888) 233-2334 (call toll-free).

Outside of North American, patients can alert their healthcare provider to the possibility of participating in EURAP, an International Registry of Antiepileptic Drugs and Pregnancy. HCPs can learn about participating in this Registry by visiting http://www.eurapinternational.org/

For questions regarding lamotrigine, please contact GlaxoSmithKline's Customer Response Center at (888) 825-5249.

GlaxoSmithKline International

LAMOTRIGINE PREGNANCY REGISTRY

Final Report

1 September 1992 – 31 March 2010

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TABLE OF CONTENTS

FOREWORD

This Final Report describes the experience of an international study of prospectively and retrospectively reported pregnancy outcomes in the Lamotrigine Pregnancy Registry and covers the period 1 September 1992 through 31 March 2010. This Final Report replaces all previous reports.

Lamotrigine is a second generation anticonvulsant therapy. The medical division of GlaxoSmithKline established this Registry as part of an ongoing program in postmarketing epidemiologic surveillance because of the potential for exposure in the first trimester of pregnancy, the potential risks for any new chemical entity, the known teratogenicity of specific existing anticonvulsants, and the suspected increased risk of teratogenicity with polytherapy. Through this study, patients exposed to lamotrigine during pregnancy were registered by health professionals, 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.

While the Registry has failed to find evidence of a substantial increase in the risk of all major birth defects combined, the sample size makes it inappropriate to draw conclusions around the risk of specific defect types and potential dose response relationships.

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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LAMOTRIGINE PREGNANCY REGISTRY
1 SEPTEMBER 1992 THROUGH 31 MARCH 2010

REGISTRY CLOSURE INFORMATION

The Registry began in September 1992, closed to new prospective enrollments on June 3, 2009, and continued follow up on existing enrollments through March 31, 2010.

EXECUTIVE SUMMARY

Although there is no evidence of teratogenicity from preclinical studies of lamotrigine, the medical division of GlaxoSmithKline managed this Registry as part of an ongoing program in epidemiologic safety monitoring. Lamotrigine is not indicated for use in pregnancy; however, women with epilepsy may require or be unintentionally exposed to lamotrigine during pregnancy. This Registry was considered essential because of the potential for exposure in the first trimester of pregnancy, the unknown risks in pregnancy for any new chemical entity, the known teratogenicity of specific existing anticonvulsants, and the increased risk of teratogenicity with polytherapy.

The purpose of this Registry was two-fold: a) to monitor for any large risk of major malformations following exposure to lamotrigine in pregnancy and b) to provide information on outcomes following pregnancy exposure to lamotrigine so that patients and physicians can best determine how to manage pregnancies exposed to lamotrigine. Registry data supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients.

No data on a comparison group were collected by the Registry, but proportions of major birth defects in lamotrigine-exposed pregnancies were compared to proportions of major defects reported in the literature. Because lamotrigine is used to treat women with epilepsy, results from this Registry were compared with published data on women with epilepsy who did not take lamotrigine. However, many women with epilepsy in this Registry received one or more concomitant medications in addition to lamotrigine, some of which have been associated with an increased frequency of birth defects. For this reason, safety signals generated from this Registry should be interpreted with caution and in the context of the potential effects of any concomitant medications and types of epilepsy being treated.

This Registry Report contains a description of all prenatal exposures to lamotrigine voluntarily reported to the Registry. The intention of the Registry was to collect prospective registrations of pregnancies exposed to lamotrigine. Prospectively reported exposures are those reported before the pregnancy outcome is known. Because the reports are voluntary, they may be subject to selection biases and may not be representative of the target population. However, prospective reporting reduces ascertainment bias among the outcomes and permits estimation of the proportion of major birth defects among exposed pregnancies. This requires obtaining follow-up information to ascertain the pregnancy outcome.

The Registry also received and reviewed retrospective reports, defined as those for which the pregnancy outcome was known at the time of reporting. Retrospective reports of birth defects can be biased toward more unusual and severe outcomes and are less likely to be representative of the general population experience. Therefore, calculation of the proportion of major defects among retrospective reports is inappropriate and can be misleading. The purpose of summarizing the retrospective reports of major birth defects is to assist in the detection of any unusual patterns.

To provide consistency in the definition of major defects, this Registry utilized the Metropolitan Atlanta Congenital Defect Program (MACDP) list of birth defects. This 6-digit code list is available from the CDC web site at http://www.cdc.gov/ncbddd/bd/macdp resources.htm (and click on the 3rd bullet). Because access to pediatric evaluations and medical records to obtain follow-up information about the presence of defects was beyond the scope of its methods, the Registry primarily monitored the frequency of major defects that were external, recognizable in the delivery room and/or symptomatic shortly after birth. Minor defects and those diagnosed on an out-patient basis weeks to months after delivery were not consistently ascertained. Conditions not meeting the definition of a major malformation are listed in Appendix B as Minor Defects or Other Conditions Reported at Outcome of Pregnancy. As with retrospective reports, these were reviewed to detect any unusual patterns.

Studies have shown that the rate of spontaneous abortion is high early in pregnancy and decreases progressively and substantially from week 8 to week 28. The cumulative estimated rate is 14%-22% (Kline *et al*, 1989). However, because pregnancies were reported to the Registry at different and sometimes imprecise times during gestation, calculation of the prevalence rate (throughout the remainder of the document "prevalence rate" will be referred to as "rate") of spontaneous pregnancy loss from the Registry data was deemed inappropriate and could have led to erroneous conclusions.

The denominators in the following estimates included the number of live born infants with and without major birth defect(s) + the number of induced abortions and stillbirths with major birth defect(s), stratified by trimester of exposure.

The Registry began in September 1992, closed to new prospective enrollments on June 3, 2009, and continued follow up on existing enrollments through March 31, 2010. For those patients with pregnancy outcome information pending after Registry closure to new enrollments, multiple attempts were made to collect outcome information. Cases for which no outcome information was received by the Registry at close of the Registry (March 31, 2010) were deemed "lost to follow up."

Lamotrigine Monotherapy: There were 35 outcomes with major defects among 1558 outcomes (2.2%) involving a *first trimester* monotherapy exposure (95% Confidence Interval: 1.6%-3.1%) (Fleiss 1981). There were 4 outcomes with a major defect among 95 outcomes following a *second trimester* monotherapy exposure and 1 outcome with a major defect among the 18 outcomes following a *third trimester* monotherapy exposure.

Data, obtained using the same methods as this Registry, are not available for other antiepileptic drugs (AED). The most recent literature on the frequency of birth defects in women with epilepsy has reported average frequencies of malformations in cohorts of women using AED monotherapy ranging between 3.3% and 4.5% (Holmes *et al,*

2001, Morrow *et al,* 2001, Morrow *et al*, 2003, Morrow *et al*, 2006, Samren *et al,* 1999). The true rate of major malformations in women with epilepsy is not known, and may in fact be lower than 3.3%.

Polytherapy including Valproate: There were 16 outcomes with major defects among 150 total outcomes (10.7%) involving *first trimester* exposure to lamotrigine and valproate, with or without one or more additional antiepileptic drugs (95% Confidence Interval: 6.4%-17.0%) (Fleiss 1981). There was 1 outcome with a major defect among the 7 outcomes following a *second trimester* exposure to lamotrigine and valproate, with or without one or more additional antiepileptic drugs. This exposure group had the highest proportion with major defects observed among first trimester exposures in the Registry.

Polytherapy not including Valproate: There were 12 outcomes with major birth defects among 430 total outcomes (2.8%) involving *first trimester* exposure to lamotrigine and at least one other antiepileptic drug, excluding valproate (95% Confidence Interval: 1.5%-5.0%) (Fleiss 1981). There was 1 outcome with a major birth defect among the 3 total outcomes involving *third trimester* exposure to lamotrigine and at least one other antiepileptic drug, excluding valproate.

There was no consistent pattern among the major birth defects reported prospectively to the Registry. Refer to Table 5 for a summary of major defects by earliest trimester of exposure.

The Lamotrigine Pregnancy Registry Advisory Committee noted the higher frequency of major malformations within the group exposed to the combinations including lamotrigine and valproate compared with other polytherapies or compared with lamotrigine monotherapy. The observed frequency of major defects (2.8% in women exposed to lamotrigine and at least one other antiepileptic drug, excluding valproate, and 10.7% in women exposed to lamotrigine and at least one other antiepileptic drug including valproate) is consistent with published studies which report that women using valproate have experienced elevated rates of birth defects (Arpino *et al*, 2000, Artama *et al*, 2005, Morrow *et al,* 2006, Omtzigt *et al*, 1992, Thisted *et al*, 1993, Wyszynski *et al*, 2005). However, it was beyond the scope of this Registry to determine the contribution to the reported defect rates of any specific AED within polytherapy combinations.

Because Morrow *et al*, 2006 noted a positive dose-response effect for major congenital malformations with lamotrigine use, the Lamotrigine Pregnancy Registry Advisory Committee continuously examined the Registry data related to dose and included the data in this Report (Table 13). The Committee considered the data as reassuring, providing no evidence of a dose effect. The available data are insufficient to make a definitive conclusion, but they do suggest that any dose effect that might exist is likely to be small.

The Committee noted that the Registry has considerably passed the milestone of 1000 outcomes for prospective first trimester exposures to lamotrigine monotherapy and thus has met its primary objective, which was to determine whether the overall rate of malformations was increased among the offspring of exposed women. The Registry has not detected an appreciable increase in the overall risk of major birth defects. It was further noted by the Committee that with the sample size in excess of 1000 exposed subjects without the observation of an increase in the risk of major birth defects as a singular outcome (background rate of 2%-3%), the confidence

interval is sufficiently narrow to indicate that there is not an appreciable effect of the exposure on the risk of major birth defects overall. At the same time, the Committee recognized that as the Registry sample size is in excess of 1000 subjects, the likelihood of chance findings for specific defects (which may occur at baseline rates of 1/1000 or less) has increased, and the Committee agreed that other methods (e.g., various case-control approaches) are more appropriate and powerful to identify increases in the rate of specific defects. For these reasons, the Committee recommended termination of this Registry. Monitoring for an increase in specific defects will continue through various other observational approaches, specifically case control surveillance through the EUROCAT network.

1. INTRODUCTION

The purpose of this Registry was two-fold: a) to monitor for any large risk of major malformations following exposure to lamotrigine in pregnancy and b) to provide information on outcomes following pregnancy exposure to lamotrigine so that patients and physicians can best determine how to manage pregnancies exposed to lamotrigine.

The combination of the large number of women with epilepsy who are of reproductive capacity and the lack of data concerning lamotrigine use during pregnancy made such a Registry an essential component of the ongoing program of epidemiologic studies of the safety of lamotrigine. This study was an observational, exposure-registration, and follow-up study. Patient confidentiality was strictly upheld. Furthermore, the Registry initiated a registration process which protected patient anonymity at the Registry Office. The 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. The intent of the Registry was to prospectively collect data concerning exposure to lamotrigine during pregnancy, potential confounding factors (such as exposure to other antiepileptic medications, the number and severity of seizures occurring during pregnancy), and information related to the outcome of the pregnancy.

The Lamotrigine Pregnancy Registry was managed by GlaxoSmithKline considering the advice of external experts in epilepsy, pediatrics, obstetrics, birth defects and epidemiology These individuals provided independent review of the data as members of the Advisory Committee for the Registry. The Registry began in September 1992, closed to new prospective enrollments on June 3, 2009, and continued follow up on existing enrollments through March 31, 2010.

2. BACKGROUND

2.1 Animal Data

Lamotrigine is an antiepileptic medication indicated for oral use as adjunctive therapy in the control of partial seizures with or without generalized tonic-clonic seizures. It is also used as a monotherapy in a number of countries. Lamotrigine is a drug of the phenyltriazine class and is chemically unrelated to existing antiepileptic medications.

Teratology studies were conducted in mice, rats, and rabbits at oral doses up to 10, 3, and 4 times the upper human dose (500 mg/day or 7 mg/kg/day), respectively, and revealed no evidence of teratogenicity. However, maternal toxicity and secondary fetal toxicity, resulting in reduced fetal weight and/or delayed ossification, were seen in mice, rats, and rabbits treated orally at these doses. Teratology studies were also conducted using bolus intravenous (i.v.) administration of the isethionate salt of lamotrigine in multiples of the projected human dose. Intravenous lamotrigine resulted in convulsions or impaired coordination in rat and rabbit dams at 30 mg/kg and 15 mg/kg, respectively. In rat dams, the 30 mg/kg i.v. dose produced an increased incidence of intrauterine death without signs of teratogenicity. Thus, even at maternally toxic levels leading to fetal death, there was no evidence of teratogenicity. Lamotrigine decreases fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans. There are, however, no adequate or well-controlled studies in pregnant women. Clinical data indicate that lamotrigine has no effect on blood folate concentrations in adults; however, the effects of lamotrigine on fetal blood folate levels in utero are unknown. Animal reproduction studies are not always predictive of human response; therefore this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with lamotrigine.

Lamotrigine was not mutagenic in microbial (Ames test) or mammalian (mouse lymphoma) mutagenicity tests, with or without metabolic activation. Lamotrigine was not associated with an increased incidence of structural or numerical chromosomal abnormalities in cultured human lymphocytes exposed to lamotrigine concentrations up to 1000 µg/mL in the presence and absence of S9 metabolic activation. Lamotrigine was not associated with an increased incidence of structural or numerical chromosomal abnormalities in a rat *in vivo* cytogenetic test, in which rats were given oral doses up to 200 mg/kg.

A reproduction/fertility study was conducted in rats. No evidence of impairment of fertility was encountered at oral lamotrigine doses up to 20 mg/kg/day. The effect of lamotrigine on human fertility, if any, is unknown.

Evaluating the etiology of birth defects is difficult because numerous factors can influence pregnancy outcome. The difficulty in evaluating whether lamotrigine is teratogenic is compounded by the additional unique characteristics of the population with epilepsy included in this Registry. In this population, the same elements that influence the outcome of pregnancies in the general population are present, as are two additional factors: 1) other anticonvulsant medication exposures and 2) seizures during pregnancy.

The desire to continue treating a woman already receiving lamotrigine may lead physicians to prescribe lamotrigine to pregnant women. Inadvertent use of lamotrigine by pregnant women has also been reported. This Registry provided a mechanism to collect data concerning exposures to lamotrigine during pregnancy. Semiannual interim reports were distributed to the medical community on the outcomes of those pregnancies. This Registry supplements animal toxicology studies and the continuing lamotrigine post-marketing surveillance program.

3. PROSPECTIVE REGISTRY

3.1 New Data

Interim Reports were issued semiannually following the Advisory Committee's review of new data. Each issue contained historical information, as well as new data known to the Registry, and replaced all previous Reports. The new information in this Final Report includes data from all cases closed between 01 April 2009 and 31 March 2010 (see Table 1). Cases with birth defects are reported in Table 5.

Minor defects and those diagnosed on an out-patient basis weeks to months after delivery were not consistently ascertained. Conditions that do not meet the definition of a major malformation are listed in Appendix B as minor defects or other conditions reported at outcome of pregnancy. As with retrospective reports, these were all included in the review to detect any unusual patterns.

3.2 All Data

The Registry closed to new prospective enrollments on June 3, 2009, and continued to follow enrolled cases until March 31, 2010. Through March 31, 2010, there were 2444 prospectively registered pregnancies with 2492 outcomes (including 43 sets of twins, 1 set of triplets, and 1 set of quadruplets).

The status of all prospectively registered pregnancies with lamotrigine exposure is presented in Table 2.

The distribution by country (43 countries) of the 2444 prospectively registered pregnancies with outcomes is presented in Table 3.

Pregnancy outcomes are presented by trimester of exposure and exposure status (monotherapy and polytherapy) in Table 4.

A case history of each of the 76 prospectively reported major defects follows in

Table 5 (includes seven chromosomal anomalies which are not included in the analysis because they are genetic disorders). During this reporting period (01 April 2009 to 31 March 2010), six new major defect cases were prospectively reported, two of which were considered chromosomal abnormalities and were not included in the analysis of birth defect rates. One previously reported defect case of deafness was removed from the defect section of this Report when the health care provider revised the diagnosis to autism, which is not considered a defect.

Because prenatal testing is frequently performed after 16 weeks' gestation, Table 6 presents the prospective reports for lamotrigine monotherapy cases with first trimester of exposure, stratified by gestational age at enrollment.

Table 1. Prospective Registry – New Lamotrigine Data in Reporting Period

1 April 2009 – 31 March 2010

Status	Newly Registered Pregnancies	Previously Registered Pregnancies Closed This Period	Total
Pending	0	0	0
Lost to Follow-up	14	79	93
Closed	36	119	155
Number of Outcomes	37*	121**	158
No Birth Defects			
Live Birth	34	109	143
Fetal Death	0	0	0
Induced Abortion	1	0	1
Birth Defects			
Live Birth	0	4	4
Fetal Death	0	0	0
Induced Abortion	0	0	0
Spontaneous Loss	2	8	10

*Includes 1 set of twins
**Includes 2 sets of twins

Table 2. Prospective Registry – Status of All Lamotrigine Exposures in Pregnancy
1 September 1992 – 31 March 2010

Total Pregnancies Registered	**3416**
Closed with known outcomes	2444
Pending	0
Lost to follow-up	972 (28.5%)
• No response from registering health care provider	64.0%
• Patient did not remain under the registering health care provider's care	19.0%
• Patient could not be identified by the registering health care provider	7.0%
• Registering health care provider left the practice with no forwarding address	8.0%
• No response from patient	<1.0%
• Patient refused release of information	1.0%

Table 3. Prospective Registry – Lamotrigine Exposure in Pregnancy by Country of Origin

1 September 1992 - 31 March 2010

Country	Number of Reported Pregnancies[a]
Argentina	2
Australia	30
Austria	17
Belgium	46
Brazil	1
Canada	27
Costa Rica	1
Cyprus	3
Czech Republic	24
Denmark	53
Egypt	1
Estonia	1
Finland	41
France	26
Germany	75
Greece	2
Holland	11
India	1
Iran	3
Ireland	2
Israel	1
Italy	2
Japan	1
Jordan	3
Lebanon	22
Luxemburg	1
Malta	1
Namibia	1
New Zealand	6
Norway	17
Poland	214
Portugal	5
Puerto Rico	2
Russia	3
Singapore	1
South Africa	6
South Korea	2
Spain	27
Sweden	53
Switzerland	11
Turkey	13
United Kingdom	94
United States	1591
TOTAL	**2444**

[a] Includes only patients with known pregnancy outcomes

3.3 Excluded Birth Defects and Other Reported Conditions

The distinction between a major vs. minor malformation or dysmorphism vs. a normal variation, and the significance of each, is an area of ongoing discussion among experts in the fields of dysmorphology and clinical genetics. To provide consistency in definition of major defects in this Registry, CDC MACDP criteria were used for evaluation of defects (http://www.cdc.gov/ncbddd/bd/macdp_resources.htm and click on the 3rd bullet). Some of the conditions excluded from the MACDP criteria for major structural defects may actually have major clinical, functional or genetic significance, particularly when more than one condition is present in the same child. For example, the presence of multiple craniofacial dysmorphisms or variations may be associated with underlying developmental or neurologic deficits. However, not all patients with dysmorphisms exhibit such delays. Because the diagnosis of developmental or behavioral deficits may not be made until months to years after birth and may require subspecialty evaluation, monitoring the frequency of these abnormalities or assessing the impact of minor defects and dysmorphisms among children exposed prenatally to lamotrigine was beyond the scope of this Registry's methods. However, in the interest of complete disclosure, all reported birth defects which do not meet the criteria are listed in Appendix B. In addition, other reported outcomes which are not birth defects, e.g. biochemical abnormalities, transient conditions, are also listed in Appendix B.

Table 4. Prospective Registry – Lamotrigine Exposure in Pregnancy by Earliest Trimester of Exposure and Outcome

1 September 1992 - 31 March 2010

Lamotrigine Monotherapy

Earliest Trimester of Exposure	Major Birth Defects			No Major Birth Defects Reported[a]			Spontaneous Pregnancy Loss[b,e]	**Total Outcomes[d]**
	Live Birth[h]	Fetal Death[c]	Induced Abortion	Live Birth[g]	Fetal Death[c]	Induced Abortion		
First	31	1	3	1523	10	33	98	**1699**
Second	4	0	0	91	0	0	0	**95**
Third	1	0	0	17	0	0	0	**18**
Unspecified	0	0	0	5	0	0	0	**5**
Total	**36**	**1**	**3**	**1636**	**10**	**33**	**98**	**1817[f]**

Lamotrigine Polytherapy with Valproate

Earliest Trimester of Exposure	Major Birth Defects			No Major Birth Defects Reported[a]			Spontaneous Pregnancy Loss[b,e]	**Total Outcomes[d]**
	Live Birth	Fetal Death[c]	Induced Abortion	Live Birth	Fetal Death[c]	Induced Abortion		
First	14	0	2	134	1	4	6	**161**
Second	1	0	0	6	1	0	0	**8**
Third	0	0	0	3	0	0	0	**3**
Unspecified	0	0	0	1	0	0	0	**1**
Total	**15**	**0**	**2**	**144**	**2**	**4**	**6**	**173[f]**

Lamotrigine Polytherapy without Valproate

Earliest Trimester of Exposure	Major Birth Defects			No Major Birth Defects Reported[a]			Spontaneous Pregnancy Loss[b,e]	**Total Outcomes[d]**
	Live Birth	Fetal Death[c]	Induced Abortion	Live Birth	Fetal Death[c]	Induced Abortion		
First	11	0	1	418	3	19	22	**474**
Second	0	0	0	25	0	0	0	**25**
Third	1	0	0	2	0	0	0	**3**
Unspecified	0	0	0	0	0	0	0	**0**
Total	**12**	**0**	**1**	**445**	**3**	**19**	**22**	**502[f]**

[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] Totals include 43 sets of twins, 1 set of triplets, and 1 set of quadruplets.

[e] Includes defect and non-defect reports. Due to the likelihood of inconsistent identification of defects, spontaneous pregnancy losses <20 weeks' gestation are excluded from the calculation of the rate of birth defects.

[f] Fetal deaths and induced abortions without reported birth defects and all spontaneous pregnancy losses are excluded from defect rate calculations.

[g] Includes a set of quadruplets and a singleton birth that are new to this report although the pregnancies were registered and the outcomes were reported in a previous reporting period.

[h] A case of deafness was included in these defect cases in the previous reporting period. The case was removed once the reporter informed the Registry that the child was not deaf but had autism, which is not considered a defect.

Table 5. Prospective Registry – Lamotrigine Exposure in Pregnancy Summaries of Major Defects by Earliest Trimester of Exposure and Polytherapy Status

1 September 1992 - 31 March 2010

First Trimester Lamotrigine Exposures

Lamotrigine Monotherapy	
1.	**Live male infant. Cleft soft palate.** 40 weeks' gestation. Lamotrigine 200 mg/day preconception, 300 mg/day week 37 and throughout pregnancy.
2.	**Live female infant. Right club foot.** 40 weeks' gestation. Lamotrigine 500 mg/day preconception and throughout pregnancy.
3.	**Live male infant. Hydronephrosis with megaureter.** 41 weeks' gestation. Lamotrigine 100 mg/day preconception and throughout pregnancy.
4.	**Induced abortion. Anencephalic fetus.** 20 weeks' gestation. Lamotrigine 150 mg/day preconception.
5.	**Live male infant. Congenital atresia of anus with recto-cutaneous fistula reaching the perineum.** 33 weeks' gestation. Lamotrigine 25 mg/day from the first trimester, 50 mg/day week 20 and throughout pregnancy.
6.	**Live male infant. Ventricular septal defect.** 41 weeks' gestation. Lamotrigine 250 mg/day preconception to week 22.
7.	**Live female infant. Fetal hydronephrosis, oligohydramnios, intrauterine growth restriction.** 34 weeks' gestation. Lamotrigine 250 mg/day preconception and throughout pregnancy.
8.	**Live male infant. Minor subpulmonic muscular ventricular septal defect. Persistent foramen ovale-no surgery/intervention required.** 41 weeks' gestation. Lamotrigine 300 mg/day preconception to week 6, 250 mg/day week 6-7, 200 mg/day week 7-32, 250 mg/day week 32 and throughout pregnancy.
9.	**Live male infant. Bilateral club feet, requiring casting.** 40 weeks' gestation. Lamotrigine (dose unknown) preconception and throughout pregnancy.
10.	**Live infant. Absent right kidney.** 40 weeks' gestation. Lamotrigine 12.5 mg/day preconception to week 5, 25 mg/day week 16-24, 100 mg/day week 24 and throughout pregnancy.
11.	**Live male infant. Transposition of great vessels, ventricular septal defect requiring surgery/intervention.** 39 weeks' gestation. Lamotrigine 200 mg/day preconception to week 7.
12.	**Live male infant. Left polycystic kidney.** 39 weeks' gestation. Lamotrigine (dose unknown) preconception, 500 mg/day week 1, 400 mg/day week 1, 300 mg/day week 1-2, 200 mg/day week 2, 100 mg/day week 2 and throughout pregnancy.
13.**	**Live female infant. Down syndrome. No malformations noted (*because this is a chromosomal anomaly, it is not included in the analysis*)**. 37 weeks' gestation. Lamotrigine 225 mg/day preconception and throughout pregnancy.

*denotes cases that are new since the last Report

**chromosomal anomaly and/or spontaneous pregnancy loss not included in the analysis

Table 5. Prospective Registry – Lamotrigine Exposure in Pregnancy Summaries of Major Defects by Earliest Trimester of Exposure and Polytherapy Status (continued)
1 September 1992 - 31 March 2010

First Trimester Lamotrigine Exposures

Lamotrigine Monotherapy (continued)	
14.	**Live male infant. Hypospadias.** 34 weeks' gestation. Lamotrigine 200 mg/day preconception and throughout pregnancy.
15.	**Live female infant. Minor cleft of upper lip and soft palate.** 40 weeks' gestation. Lamotrigine 100 mg/day preconception and throughout pregnancy.
16.	**Live male infant. Hypoplastic left heart syndrome. The baby subsequently died.** 39 weeks' gestation. Lamotrigine 100 mg/day preconception and throughout pregnancy.
17.	**Live female infant. Hypoplasia of left ventricle of the heart. The baby subsequently died.** 37 weeks' gestation. Lamotrigine 400 mg/day preconception and throughout pregnancy.
18.	**Live male infant. "Fluid on left kidney".** 38 weeks' gestation. Lamotrigine 550 mg/day preconception and throughout pregnancy.
19.	**Live female infant. Cortical dysplasia.** 41 weeks' gestation. Lamotrigine 300 mg/day preconception and throughout pregnancy.
20.	**Stillbirth. Diaphragmatic hernia with dislocation of abdominal organs in the thorax.** 38 weeks' gestation. Lamotrigine 200 mg/day preconception and throughout pregnancy.
21.	**Induced abortion. Anencephaly diagnosed by prenatal ultrasound.** 15 weeks' gestation. Lamotrigine 400 mg/day preconception, 425 mg/day week 10 and throughout pregnancy.
22.	**Induced abortion. Anencephaly.** 19 weeks' gestation. Lamotrigine 200 mg/day preconception to week 6.
23.	**Live female infant. Bilateral hip dislocation, treated by an orthopedist with a Pavlik harness.** 39 weeks' gestation. Lamotrigine 200 mg/day preconception, 300 mg/day week 19, 400 mg/day week 26 and throughout pregnancy.
24.	**Live male infant. Club feet, treated with casting.** 39 weeks' gestation. Lamotrigine 300 mg/day preconception and throughout pregnancy.
25.	**Live female infant. Ventricular septal defect and patent foramen ovale.** 40 weeks' gestation. Lamotrigine 300 mg/day preconception to week 12, 400 mg/day week 12-21, 600 mg/day week 21 and throughout pregnancy.
26.	**Live female infant. Transposition of the great vessels and transposition of the ventricles, requiring surgery.** 40 weeks' gestation. Lamotrigine 100 mg/day preconception to week 6, 100 mg/day week 15 and throughout pregnancy.
27.	**Live infant. Pyloric stenosis, requiring pyloromyotomy.** 39 weeks' gestation. Lamotrigine (dose unknown) week 6 and throughout pregnancy.

*denotes cases that are new since the last Report
**chromosomal anomaly and/or spontaneous pregnancy loss not included in the analysis

Table 5. Prospective Registry – Lamotrigine Exposure in Pregnancy Summaries of Major Defects by Earliest Trimester of Exposure and Polytherapy Status (continued)
1 September 1992 - 31 March 2010

First Trimester Lamotrigine Exposures

Lamotrigine Monotherapy (continued)	
28.	**Live female infant. Congenital diaphragmatic hernia; pulmonary hypoplasia; complex congenital heart defect (transposition of the great arteries, tetralogy of Fallot). Infant died at 24 hours of age from refractory hypoxia.** 38 weeks' gestation. Lamotrigine 500 mg/day preconception and throughout pregnancy.
29.**	**Induced abortion. Prenatal ultrasound at approximately 19 weeks showed signs of Trisomy 21. Amniocentesis confirmed Trisomy 21 (*because this is a chromosomal anomaly, it is not included in the analysis*).** 20 weeks' gestation. Lamotrigine 250 mg/day preconception and throughout pregnancy.
30.	**Live female infant. 36 week twin infant with pulmonary stenosis. No immediate intervention; to be followed as an outpatient by the pediatric cardiologist. The co-twin has no defect.** 36 weeks' gestation. Lamotrigine 300 mg/day preconception and throughout pregnancy.
31.	**Live male infant. Eleven toes.** 37 weeks' gestation. Lamotrigine 200 mg/day preconception to week 12, 300 mg/day week 12-29, 400 mg/day week 29 and throughout pregnancy.
32.	**Live female infant. Six fingers on each hand, requiring surgery. There is a family history of polydactyly on the father's side.** 39 weeks' gestation. Lamotrigine 200 mg/day preconception and throughout pregnancy.
33.	**Live male infant. Minor heart defect, followed by pediatric cardiologist. No intervention required.** 38 weeks' gestation. Lamotrigine 250 mg/day preconception to week 36, 300 mg/day week 36 and throughout pregnancy.
34.	**Live infant. Pyloric stenosis.** 40 weeks' gestation. Lamotrigine 400 mg/day preconception to week 7, 25 mg/day week 7-9, 300 mg/day week 9 and throughout pregnancy.
35.	**Live infant. Epidermolysis bullosa.** 40 weeks' gestation. Lamotrigine 200 mg/day preconception and throughout pregnancy.
36.**	**Live infant. Down syndrome *(because this is a chromosomal anomaly, it is not included in the analysis)*.** 39 weeks' gestation. Lamotrigine 450 mg/day preconception to week 3, 550 mg/day week 3-8, 600 mg/day week 8-11, 700 mg/day week 11-16, 800 mg/day week 16-20, 900 mg/day week 20-31, 800 mg/day week 31 and throughout pregnancy.
37.	**Live female infant. Light spot across entire abdomen.** 38 weeks' gestation. Lamotrigine 250 mg/day preconception to week 6, 250 mg/day week 30 throughout pregnancy.

*denotes cases that are new since the last Report
**chromosomal anomaly and/or spontaneous pregnancy loss not included in the analysis

Table 5. Prospective Registry – Lamotrigine Exposure in Pregnancy Summaries of Major Defects by Earliest Trimester of Exposure and Polytherapy Status (continued)
1 September 1992 - 31 March 2010

First Trimester Lamotrigine Exposures

Lamotrigine Monotherapy (continued)	
38.*	**Live male infant. Coronal hypospadias.** 42 weeks' gestation. Lamotrigine 300 mg/day preconception to week 25.
39.* **	**Spontaneous abortion. Turner syndrome, karyotype 45, X, diagnosed by amniocentesis *(because this is a chromosomal anomaly it is not included in the analysis)*.** 16 weeks' gestation. Lamotrigine 500 mg/day week 9 throughout pregnancy.
40.* **	**Live infant. Trisomy 18 *(because this is a chromosomal anomaly, it is not included in the analysis)*.** 39 weeks' gestation. Lamotrigine 600 mg/day preconception to week 16, 750 mg/day week 16 throughout pregnancy.

Second Trimester Lamotrigine Exposures

Lamotrigine Monotherapy	
1.	**Live female infant. Left sided hip dysplasia.** 40 weeks' gestation. Lamotrigine 50 mg/day week 20-24, 100 mg/day week 24 and throughout pregnancy.
2.	**Live female infant. Sacrococcygeal teratoma; the infant also had pulmonary interstitial emphysema, cardiomyopathy, ascites and severe hydrops, and did not survive.** 29 weeks' gestation. Lamotrigine 100 mg/day week 18 and throughout pregnancy.
3.	**Live female infant. Torticollis.** 39 weeks' gestation. Lamotrigine 25 mg/day week 14-22, 50 mg/day week 22 and throughout pregnancy**.**
4.	**Live male infant. Hypospadias. Webbed toes 2nd and 3rd toes both feet.** 39 weeks' gestation. Lamotrigine 25 mg/day week 27-28, 50 mg/day week 28-30, 100 mg/day week 32-34, 200 mg/day week 34 and throughout pregnancy.

Third Trimester Lamotrigine Exposures

Lamotrigine Monotherapy	
1.	**Live female infant. Mild unilateral hydronephrosis.** 40 weeks' gestation. Lamotrigine 25 mg/day week 29, 50 mg/day week 29-30, 75 mg/day week 30, 100 mg/day week 30-31, 150 mg/day week 31, 200 mg/day week 31, 400 mg/day (unknown gestation week) and throughout pregnancy.

First Trimester Lamotrigine Exposures

Lamotrigine with Antiepileptic (AED) Polytherapy without Valproate	
1.	**Live male infant. One extra digit on one hand.** 40 weeks' gestation. Lamotrigine 2000 mg/day preconception to week 7. Carbamazepine preconception and throughout pregnancy.

*denotes cases that are new since the last Report
**chromosomal anomaly and/or spontaneous pregnancy loss not included in the analysis

Table 5. Prospective Registry – Lamotrigine Exposure in Pregnancy Summaries of Major Defects by Earliest Trimester of Exposure and Polytherapy Status (continued)
1 September 1992 - 31 March 2010

First Trimester Lamotrigine Exposures

Lamotrigine with Antiepileptic (AED) Polytherapy without Valproate (continued)	
2.	**Live male infant. Cardiac murmur and patent foramen ovale requiring banding around the pulmonary artery.** 37 weeks' gestation. Lamotrigine 600 mg/day preconception to week 37. Phenytoin and Primidone preconception and throughout pregnancy.
3.	**Live male infant. Skin tags on left ear; no opening to ear canal on right ear.** 37 weeks' gestation. Lamotrigine 400 mg/day preconception to week 13, 600 mg/day week 13-17, 800 mg/day week 17 and throughout pregnancy. Gabapentin preconception and throughout pregnancy.
4.	**Induced abortion. Lumbar neural tube defect with early evidence of ventriculomegaly and a derangement of the posterior fossa.** 17 weeks' gestation. Lamotrigine 700 mg/day preconception to week 17. Clobazam preconception and through first trimester.
5.	**Live female infant. Patent (persistent) ductus arteriosis. Atrium septum defect.** 38 weeks' gestation. Lamotrigine 250 mg/day week 7-11, 400 mg/day week 11-22, 600 mg/day week 22 and throughout pregnancy. Oxcarbamazepine preconception and throughout pregnancy.
6.**	**Live male infant. 2 x chromosomes and ambiguous genitalia (because this is a chromosomal anomaly, it is not included in the analysis).** 38 weeks' gestation. Lamotrigine 400 mg/day preconception and throughout pregnancy. Carbamazepine 600 mg/day preconception and throughout pregnancy.
7.	**Live male infant. Hypospadias.** 42 weeks' gestation. Lamotrigine 200 mg/day preconception, 100 mg/day (unknown gestation week). Clonazepam preconception and through first trimester.
8.	**Live male infant. Oesophageal malformation repaired by surgery.** 40 weeks' gestation. Lamotrigine 25 mg/day preconception, 450 mg/day week 6 and throughout pregnancy. Carbamazepine (dose unknown) preconception.
9.	**Live female infant. Esophageal atresia and anal atresia, both requiring surgery.** 41 weeks' gestation. Lamotrigine 300 mg/day preconception and throughout pregnancy. Carbamazepine 800 mg/day preconception and throughout pregnancy.
10.**	**Spontaneous pregnancy loss. Triploidy – karyotype 69, xxx (because this is a chromosomal defect, it is not included in the analysis).** 14 weeks' gestation. Lamotrigine 100 mg/day preconception to week 6. Tiagabine 800 mg/day preconception to first trimester.
11.	**Live male infant. Hydroencephalopathy (HPE), muscle spasticity, AV fistula.** 38 weeks' gestation. Lamotrigine 200 mg/day preconception to week 6, 25 mg/day week 31 and throughout pregnancy. Clonazepam 1 mg/day preconception and through first trimester.

*denotes cases that are new since the last Report
**chromosomal anomaly and/or spontaneous pregnancy loss not included in the analysis

Table 5. Prospective Registry – Lamotrigine Exposure in Pregnancy Summaries of Major Defects by Earliest Trimester of Exposure and Polytherapy Status (continued)
1 September 1992 - 31 March 2010

First Trimester Lamotrigine Exposures

Lamotrigine with Antiepileptic (AED) Polytherapy without Valproate (continued)	
12.*	**Live male infant. Omphalocele.** 40 weeks' gestation. Lamotrigine 100 mg/day prior to conception for unspecified duration, 400 mg for unspecified duration. Levetiracetam 4000 mg/day preconception and throughout pregnancy.
13.*	**Live female infant. Coarctation of the aorta repaired surgically after delivery.** 38 weeks' gestation. Lamotrigine 300 mg/day preconception to unspecified week, 200 mg/day to week 17, 250 mg/day week 17-35. Phenobarbital prior to conception and during 1st trimester. Topiramate prior to conception and during 1st trimester.
14.*	**Live male infant. Tetralogy of Fallot.** 39 weeks' gestation. Lamotrigine 300 mg/day week 5 through 7, 400 mg/day week 7 through unspecified time, 800 mg/day throughout pregnancy. Levetiracetam 1500 mg/day preconception and during 1st trimester. Oxcarbazepine 2700 mg/day preconception and during 1st trimester, 3000 mg/day during 2nd trimester and throughout pregnancy. Topiramate 800 mg/day preconception and during 1st trimester, 1000 mg/day during 2nd trimester and throughout pregnancy.

Third Trimester Lamotrigine Exposures

Lamotrigine with Antiepileptic (AED) Polytherapy without Valproate	
1.	**Live infant. Hypospadias and bilateral clubfoot.** 40 weeks' gestation. Lamotrigine 25 mg/day week 32-33, 50 mg/day week 33 and throughout pregnancy. Clonazepam 1 mg/day preconception and through first trimester.

First Trimester Lamotrigine Exposures

Lamotrigine with Antiepileptic (AED) Polytherapy with Valproate	
1.	**Live female infant. Bilateral talipes.** Unknown gestational age. Lamotrigine 50 mg/day preconception to week 40. Valproic acid throughout pregnancy.
2.	**Induced abortion. Ultrasound detection of hydrocephalus, sacral spina bifida (myelomeningocele), patent foramen ovale, ductus arteriosis. Antenatal ultrasound suggested Arnold-Chiari malformation.** 17 weeks' gestation. Lamotrigine 100 mg/day preconception to week 9. Valproate preconception and through second trimester.
3.	**Live female infant. Cleft palate, hypertelorism, broad nasal bridge, low set and posteriorly rotated ears, down-turned mouth, bilateral transverse palmar creases, short proximal thumbs, supra-umbilical hernia.** 39 weeks' gestation. Lamotrigine 100 mg/day preconception to week 8, 50 mg/day week 8-39, 100 mg/day week 39. Valproate preconception and throughout pregnancy.

*denotes cases that are new since the last Report
**chromosomal anomaly and/or spontaneous pregnancy loss not included in the analysis

Table 5. Prospective Registry – Lamotrigine Exposure in Pregnancy Summaries of Major Defects by Earliest Trimester of Exposure and Polytherapy Status (continued)
1 September 1992 - 31 March 2010

First Trimester Lamotrigine Exposures

Lamotrigine with Antiepileptic (AED) Polytherapy with Valproate	
4.	**Live male infant. Atrial septal defect.** 40 weeks' gestation. Lamotrigine 300 mg/day week 8-33. Valproate during first trimester.
5.	**Live male infant. Pulmonary stenosis after delivery, surgery performed. Baby subsequently died.** 38 weeks' gestation. Lamotrigine 200 mg/day preconception and throughout pregnancy. Valproate 1000 mg/day preconception and throughout pregnancy.
6.	**Live female infant. Pylorostenosis during the second week of life. Surgery took place during the third week of life.** 39 weeks' gestation. Lamotrigine 25 mg/day week 8 and throughout pregnancy. Valproate 300 mg/day preconception and through first trimester with down titration.
7.	**Live female infant. Cleft of the hard palate. Surgery was to be planned at the time of the report.** 41 weeks' gestation. Lamotrigine 300 mg/day preconception to week 18, 200 mg/day week 19-32, 300 mg/day week 32 and throughout pregnancy. Valproate preconception and throughout pregnancy.
8.	**Live male infant. Small ventricular septum defect noted at 3 months of age.** 41 weeks' gestation. Lamotrigine 300 mg/day preconception throughout pregnancy. Valproate preconception and throughout pregnancy.
9.	**Live male infant. Meningomyelocele; upper and lower limb deformities. Infant died.** 42 weeks' gestation. Lamotrigine 100 mg/day preconception to 5 weeks. Valproate preconception and throughout pregnancy.
10.	**Induced abortion. Microcephaly, abnormal posterior fossa, bony abnormality (location not specified), right occipital encephalocele, Chiari II malformation, Hind brain herniation, retrognathia.** 20 weeks' gestation. Lamotrigine 200 mg/day preconception. Valproate 500 mg/day preconception.
11.	**Live male infant. Transposition of great vessels.** 38 weeks' gestation. Lamotrigine 100 mg/day preconception, 150 mg/day week 11, 200 mg/day week 13 and throughout pregnancy. Valproate preconception and throughout the first trimester.
12.	**Live female infant. Right ventricular hypoplasia with tricuspid regurgitation and cardiac decompensation, diagnosed by prenatal ultrasound.** 28 weeks' gestation. Lamotrigine 200 mg/day preconception to week 17, 400 mg/day week 17 and throughout pregnancy. Valproate reported, but dose and timing are unknown.

*denotes cases that are new since the last Report
**chromosomal anomaly and/or spontaneous pregnancy loss not included in the analysis

Table 5. Prospective Registry – Lamotrigine Exposure in Pregnancy Summaries of Major Defects by Earliest Trimester of Exposure and Polytherapy Status (continued)
1 September 1992 - 31 March 2010

First Trimester Lamotrigine Exposures

Lamotrigine with Antiepileptic (AED) Polytherapy with Valproate (continued)	
13.	**Live female infant. Cleft palate, small head, ears and nose, hypoplastic small mouth, long fingers and toes, "overlip", typical middle face consistent with Valproate Syndrome per reporter.** 40 weeks' gestation. Lamotrigine 125 mg/day preconception and throughout pregnancy. Valproate 2100 mg/day preconception and through second trimester, 3000 mg/day in third trimester. Clonazepam 1 mg/day preconception and throughout pregnancy. Topiramate 50 mg/day preconception and throughout pregnancy.
14.	**Live male infant. Preaxial polydactyly with redundant left thumb.** 42 weeks' gestation. Lamotrigine 200 mg/day preconception, 650 mg/day week 20, 200 mg/day week 23 and throughout pregnancy. Valproate preconception and throughout pregnancy.
15.	**Live male infant. Gastroschisis; cleft lip and palate; left talipes equinovarus (clubfoot). The infant died.** 29 weeks' gestation. Lamotrigine 200 mg/day preconception and throughout pregnancy. Valproate 100 mg/day preconception and through second trimester.
16.	**Live male infant. Clubfeet.** 39 weeks' gestation. Lamotrigine 100 mg/day preconception to week 9. Valproate 1000 mg/day first, second, and third trimesters.

Third Trimester Lamotrigine Exposures

Lamotrigine with Antiepileptic (AED) Polytherapy with Valproate	
1.	**Live male infant. Single kidney with large ureter. Abnormal thoracic vertebrae, two fused vertebrae.** 38 weeks' gestation. Lamotrigine 125 mg/day week 25-31, 300 mg/day week 31 and throughout pregnancy. Topiramate 200 mg/day preconception and through first trimester. Valproate 2000 mg/day preconception and through first trimester.

*denotes cases that are new since the last Report
**chromosomal anomaly and/or spontaneous pregnancy loss not included in the analysis
A previously reported first trimester monotherapy exposure case of deafness was removed from this Table once the reporter revised the diagnosis to autism, which is not considered a defect.

Table 6. Prospective Registry – Gestational Age at Enrollment (weeks) – First Trimester Monotherapy Exposure

1 September 1992 - 31 March 2010

Number of Outcomes = 1558

	< 16 weeks	16 – 20 weeks	> 20 weeks	Unknown
Total	920 (59.1%)	183 (11.7%)	441 (28.3%)	14 (0.9%)
No Defect	898	181	430	14
Defect	22	2	11	0

Table 7. Prospective Registry Lamotrigine Monotherapy and Antiepileptic Drug Polytherapy Exposure in Pregnancy by Trimester of Exposure and Outcome

1 September 1992 - 31 March 2010

Concomitant Antiepileptic Drug Exposures	Outcomes Without Major Defects[1]					
	Outcomes w/ Birth Defects	Live Births	Fetal Deaths	Ind Abort	Spont Preg Loss	Overall
Exposure During First Trimester:						
Lamotrigine Monotherapy	35	1523	10	33	98	1699
Lamotrigine polytherapy with valproate						
valproate	15	103	1	4	5	128
carbamazepine & valproate	0	5	0	0	1	6
clonazepam & valproate	0	5	0	0	0	5
diazepam & valproate	0	2	0	0	0	2
ethosuximide & valproate	0	1	0	0	0	1
gabapentin & valproate	0	2	0	0	0	2
levetiracetam & valproate	0	2	0	0	0	2
phenytoin & valproate	0	7	0	0	0	7
topiramate & valproate	0	1	0	0	0	1
valproate & vigabatrin	0	2	0	0	0	2
carbamazepine & clonazepam & valproate	0	1	0	0	0	1
carbamazepine & phenytoin & valproate	0	1	0	0	0	1
clonazepam & topiramate & valproate	1	0	0	0	0	1
gabapentin & phenobarbital & valproate	0	1	0	0	0	1
barbexaclone & carbamazepine & phenytoin & valproate	0	1	0	0	0	1
Lamotrigine polytherapy without valproate						
barbexaclone	0	1	0	0	0	1
carbamazepine	3	113	1	5	3	125
clobazam	1	4	0	0	0	5
clonazepam	2	55	0	2	3	62
clorazepate	0	0	1	0	0	1
diazepam	0	4	0	0	1	5
ethosuximide	0	6	0	0	1	7
felbamate	0	1	0	0	0	1
gabapentin	1	15	0	0	1	17
levetiracetam	1	40	1	0	3	45
methylphenobarbitone	0	2	0	0	0	2
oxcarbazepine	1	22	0	0	1	24
phenobarbital	0	10	0	3	1	14
phenytoin	0	31	0	2	0	33
primidone	0	5	0	0	0	5
tiagabine	0	4	0	0	1	5
topiramate	0	28	0	2	0	30
vigabatrin	0	4	0	0	0	4
zonisamide	0	5	0	0	0	5
carbamazepine & clobazam	0	4	0	0	0	4
carbamazepine & clonazepam	0	11	0	0	1	12
carbamazepine & clorazepate	0	0	0	0	1	1
carbamazepine & gabapentin	0	1	0	0	0	1
carbamazepine & methylphenobarbitone	0	1	0	0	0	1
carbamazepine & oxcarbazepine	0	1	0	0	1	2
carbamazepine & phenobarbital	0	1	0	0	0	1
carbamazepine & phenytoin	0	7	0	1	1	9
carbamazepine & topiramate	0	2	0	0	2	4
carbamazepine & vigabatrin	0	3	0	1	0	4
carbamazepine & zonisamide	0	1	0	0	0	1

Table 7. Prospective Registry Lamotrigine Monotherapy and Antiepileptic Drug Polytherapy Exposure in Pregnancy by Trimester of Exposure and Outcome (continued)

1 September 1992 - 31 March 2010

Concomitant Antiepileptic Drug Exposures	Outcomes w/ Birth Defects	Outcomes Without Major Defects[1]				
		Live Births	Fetal Deaths	Ind Abort	Spont Preg Loss	Overall
Lamotrigine polytherapy without valproate (continued)						
clobazam & diazepam	0	1	0	0	0	1
clobazam & vigabatrin	0	1	0	0	0	1
clonazepam & diazepam	0	1	0	0	0	1
clonazepam & oxcarbazepine	0	2	0	0	0	2
clonazepam & phenytoin	0	2	0	0	0	2
clonazepam & primidone	0	1	0	0	0	1
clonazepam & topiramate	0	3	0	0	1	4
clonazepam & zonisamide	0	4	0	0	0	4
gabapentin & levetiracetam	0	1	0	0	0	1
gabapentin & phenobarbital	0	1	0	0	0	1
gabapentin & phenytoin	0	2	0	0	0	2
gabapentin & topiramate	0	3	0	0	0	3
levetiracetam & oxcarbazepine	0	1	0	0	0	1
levetiracetam & phenytoin	0	2	0	0	0	2
levetiracetam & zonisamide	0	1	0	0	0	1
oxcarbazepine & topiramate	0	1	0	0	0	1
phenobarbital & phenytoin	0	2	0	0	0	2
phenobarbital & topiramate	1	0	0	0	0	1
phenytoin & primidone	1	1	0	0	0	2
pregabalin & topiramate	0	0	0	1	0	1
carbamazepine & clobazam & clonazepam	0	2	0	0	0	2
carbamazepine & clonazepam & levetiracetam	0	1	0	0	0	1
carbamazepine & diazepam & gabapentin	0	1	0	0	0	1
carbamazepine & felbamate & phenytoin	0	0	0	1	0	1
carbamazepine & phenobarbital & primidone	0	0	0	1	0	1
clonazepam & clonazepam & diazepam	0	1	0	0	0	1
levetiracetam & oxcarbazepine & topiramate	1	0	0	0	0	1
clonazepam & levetiracetam & phenobarbital & topiramate & zonisamide	0	1	0	0	0	1
Exposure During Second Trimester:						
Lamotrigine Monotherapy	4	91	0	0	0	95
Lamotrigine polytherapy with valproate						
valproate	0	5	0	0	0	5
clonazepam & valproate	0	0	1	0	0	1
topiramate & valproate	1	1	0	0	0	2
Lamotrigine polytherapy without valproate						
carbamazepine	0	2	0	0	0	2
clonazepam	0	2	0	0	0	2
diazepam	0	1	0	0	0	1
gabapentin	0	3	0	0	0	3
levetiracetam	0	2	0	0	0	2
oxcarbazepine	0	2	0	0	0	2
phenobarbital	0	1	0	0	0	1
phenytoin	0	5	0	0	0	5
topiramate	0	1	0	0	0	1
trimethadione	0	1	0	0	0	1
carbamazepine & phenobarbital	0	1	0	0	0	1
clonazepam & oxcarbazepine	0	1	0	0	0	1
ethosuximide & topiramate	0	1	0	0	0	1
gabapentin & topiramate	0	1	0	0	0	1
levetiracetam & topiramate	0	1	0	0	0	1

Table 7. Prospective Registry Lamotrigine Monotherapy and Antiepileptic Drug Polytherapy Exposure in Pregnancy by Trimester of Exposure and Outcome (continued)

1 September 1992 - 31 March 2010

Concomitant Antiepileptic Drug Exposures	Outcomes Without Major Defects[1]					
	Outcomes w/ Birth Defects	Live Births	Fetal Deaths	Ind Abort	Spont Preg Loss	Overall
Exposure During Third Trimester:						
Lamotrigine Monotherapy	1	17	0	0	0	18
Lamotrigine polytherapy with valproate						
valproate	0	3	0	0	0	3
Lamotrigine polytherapy without valproate						
clonazepam	1	0	0	0	0	1
phenytoin	0	1	0	0	0	1
gabapentin & vigabatrin	0	1	0	0	0	1
Exposure During Unspecified Trimester:						
Lamotrigine Monotherapy	0	5	0	0	0	5
Lamotrigine polytherapy with valproate	0	1	0	0	0	1

[1] Birth defect not reported but cannot be ruled out.

4. DATA FROM OTHER SOURCES

Additional internal or external sources of data involving use of lamotrigine during pregnancy were identified. These are summarized in this section of the Interim Report.

4.1 Retrospective Reports

Through its spontaneous reporting system, GlaxoSmithKline received retrospective notification of lamotrigine-exposed pregnancies and their outcomes. Reports were considered retrospective when pregnancies involving lamotrigine exposure were 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 could be helpful in detecting a possible pattern of defects suggestive of common etiology. Such reports are presented below.

Retrospective Health Care Provider Reports

Through 31 March 2010, there were 164 pregnancy outcomes retrospectively reported involving birth defects. There were 142 that involved earliest lamotrigine exposure in the first trimester, 4 that involved earliest trimester of exposure in the second trimester, and 18 had an unspecified trimester of exposure. Ninety-four defects involved lamotrigine monotherapy while 70 involved antiepileptic drug polytherapy. A description of the reported defects is included in Table 8.

Table 8. Reports of Birth Defects Retrospectively Reported
1 September 1992 - 31 March 2010

Lamotrigine Monotherapy	
1.	Live infant. Polydactyly, talipes (ankle joints), dysmorphic features. Normal chromosome analysis.
2.	Live infant. Head circumference above the 97th percentile. Skull x-rays revealed sagittal synostosis. Surgery was performed, no other developmental sequelae.
3.	Live infant. Cardiac abnormality.
4.	Live infant. Hirschprung's disease.
5.	Live infant. Aortic valve stenosis.
6.	Induced abortion. Fetal diagnosis of anencephaly by prenatal ultrasound.
7.	Live infant. Infantile spasms at approximately 2 months of age. Treated with vigabatrin, spasms resolved. Chest mass on MRI. Head scan done. Surgical diagnosis was neuroblastoma. Surgery was curative.
8.	Live infant. Choanal atresia, to be surgically repaired in one year, hypothyroidism, treated with Synthroid.
9.	Live infant. Right-sided talipes (mild). No treatment required.
10.	Live infant. Congenital anomaly of ureter.
11.	Live infant. Short stature.
12.	Live infant. Hypoplastic left heart on prenatal ultrasound. Placental abruption, infant died.
13.	Live infant. Born without a thyroid gland.
14	Live infant. Coarctation of aorta, anomalous coronary arteries.
15.	Live infant. Intestinal duplication. Surgery performed, infant was recovering.
16.	Live infant. Tetralogy of Fallot.
17.	Live infant. Cleft lip, but no cleft palate was observed.
18.	Induced abortion. Absence of neural tissue above the base of the brain and above the orbits consistent with an anencephalic fetus, abnormal appearance to the cervical spine, dysraphism with a progressive widening of the caliber of the cervical spinal canal toward the foramen magnum.
19.	Live infant. Bowel blockage, also had seizures and was a premature birth. Surgery performed.
20.	Live infant. Ventricular septal hypertrophy.
21.	Live infant. Congenital structural cardiac defect - unspecified.
22.	Live infant. Symptomatic tetralogy of Fallot. Surgery was performed.
23.	Live infant. Down syndrome. Mosaicism.
24.	Live infant. Slightly dysmorphic, elbows fixed at 90 degrees, low set ears, broad base nose, dimple in the middle of nose, arthrogryposis, large hydrocephalus - barely any brain tissue visible. Infant showed no intrauterine growth restriction, but scoliosis of the lumbar spine, bilateral talipes with deformed angulated feet and severe congenital hydrocephalus of unknown cause. Infant died within minutes of birth from hydrocephalus and arthrogryposis diagnosed antenatally.
25.	Induced abortion. Severe heart defects.
26.	Live infant. Hydrocephalus, initially noted on a prenatal ultrasound. Amniocentesis was apparently normal. A ventriculo-peritoneal shunt was placed after delivery.
27.	Live infant. Karyotype: 47, XX, +18. Multiple defect congenital syndrome (Hypotrophia Intrauterina, undeveloped auricles, cleft palate). Infant lived for only 15 hours.
28.	Live infant. Colon atresia, requiring surgery.
29.	Live infant. Congenital cataract.
30.	Induced abortion. Trisomy 9.
31.	Live infant. Atrial fibrillation, requiring digoxin.
32.	Live infant. Cleft palate.
33.	Live infant. Pyloric stenosis (familial), congenital hypothyroidism, motor delays.
34.	Live infant. Valvular ejection murmur, persistent patent ductus arteriosus.

*denotes cases that are new since the last Report

Table 8. Reports of Birth Defects Retrospectively Reported (continued)
1 September 1992 - 31 March 2010

Lamotrigine Monotherapy (continued)	
35.	Live infant. Down syndrome and atrial ventricular septal defect with a relatively large ventricular septal defect requiring surgery.
36.	Live infant. Aortic isthmus hypoplasia not requiring surgery.
37.	Live infant. Hydronephrosis.
38.	Live infant. Cerebral malformation and developmental delay.
39.	Induced abortion. Gastroschisis in right umbilical area, evisceration of small intestine, liver, stomach, and pancreas.
40.	Induced abortion. Probable Dandy-Walker Syndrome diagnosed by prenatal ultrasound. Posterior fossa cyst confirmed after delivery.
41.	Live infant. Tracheal-esophageal fistula, retinal deficiency, optic nerve hypoplasia, narrow ear canals and ossicular abnormality.
42.	Induced abortion. Down syndrome.
43.	Live infant. Microcephaly and severe developmental delay.
44.	Live infant. Ambiguous genitalia.
45.	Live infant. Wolf-Hirschhorn syndrome, cardiac and stomach anomalies (not otherwise specified). Infant died.
46.	Spontaneous pregnancy loss. Lymphangioma in abdomen, chest, and neck.
47.	Live infant. Cleft lip and palate. Surgical repair is planned.
48.	Live infant. Second, third, and fourth digits on left hand missing. Thumb and fifth digit curve inward and nails meet.
49.	Live infant. Sacral spine defect, covered by skin.
50.	Induced abortion. Hypoplasia of the right ventricular of the heart, diagnosed by prenatal echocardiography.
51.	Live infant. Small ventricular septal defect.
52.	Live infant. Adenomatoid malformation of the lung.
53.	Live infant. Left-sided heart defect, requiring surgery.
54.	Live infant. Left-sided torticollis.
55.	Live infant. Left forearm missing.
56.	Live infant. Bilateral cleft lip and palate.
57.	Induced abortion. Lumbosacral myelomeningocele with Arnold Chiari malformation diagnosed by prenatal ultrasound.
58.	Live infant. Dysplastic brain, more in frontal lobes but parietal and temporal lobes are also abnormal. Microcephalic “from distance.”
59.	Live infant. Large diaphragmatic herniation containing spleen, stomach, entire small intestine, ascending colon and left half of liver. Compressed non-aerated left lung, small aerated right lung; right ventricular hypertrophy, patent foramen ovale and patent ductus. Overlap of cranial bones. Fracture of left humerus.
60.	Live infant. Isolated left congenital renal agenesis, requiring prolonged hospitalization.
61.	Live infant. Rib cage malformation; lymphangiectasia of the right lung with pulmonary hypoplasia.
62.	Live infant. Born with the liver outside.
63.	Live infant. Absence of the septum pellucidum.
64.	Live infant. Infant born with spina bifida and developed hydrocephalus. Infant also has club foot bilaterally. Surgery to close spina bifida.
65.	Live infant. Spinal and musculoskeletal abnormality. The diagnosis by prenatal ultrasound included club foot. The child was in neonatal intensive care after birth for unstated reasons.
66.	Live infant. Hypoplastic left ventricle.
67.	Live infant. Ductus arteriosus; cataract with persistent fetal vascularization in the left eye and retinal detachment; presumed cystic or polycystic kidneys.
68.	Live infant. Lissencephaly, presenting with a seizure at 3 months of age.
69.	Live infant. Hydrocephalus, due to aqueductal stenosis, first noted on prenatal ultrasound.

*denotes cases that are new since the last Report

Table 8. Reports of Birth Defects Retrospectively Reported (continued)
1 September 1992 - 31 March 2010

Lamotrigine Monotherapy (continued)	
70.	Live infant. Pulmonary atresia with intact ventricular septum.
71.	Induced abortion. Defects diagnosed by prenatal ultrasound: no radius, ulna or hand on the right; absent fibula in both legs; tibias short. The pregnancy was electively terminated at 20 weeks because of these defects.
72.	Live infant. Cleft lip and palate.
73.	Live infant. Term infant with gut malrotation, requiring surgery. Jitteriness, stiffness poor feeder, vomiting, irritability.
74.	Live infant. Infantile spasms.
75.	Live infant. Club foot, treated with casting.
76.	Live infant. Undescended right testicle. Surgical repair was performed shortly after the child was one year old. No further problems noted.
77.	Induced abortion. Anencephaly diagnosed by "echography" at 18 weeks' gestation. According to the report, the fetus also had spina bifida.
78.	Induced abortion. Dandy-Walker syndrome.
79.	Live infant. Microphthalmia,
80.	Live infant. Microphthalmia, cortical dysplasia, Chiari I malformation, exotropia, developmental delay.
81.	Induced abortion. Myelomeningocele with Chiari malformation diagnosed prenatally.
82.	Live infant. Tetralogy of Fallot.
83.	Live infant. Bilateral ovarian cysts, to be surgically ablated at a later date.
84.	Live infant. Cleft lip.
85.	Induced abortion. Left ventricular hypoplasia; ascending and transverse aorta hypoplasia diagnosed prenatally.
86	Live infant. Cleft lip first detected by prenatal ultrasound at 5 months post-LMP; also noted at delivery. It is reported there is a history of cleft lip and palate in the father's family.
87.	Live infant. Cleft palate.
88.	Live infant. Isolated cleft soft palate.
89.	Live infant. Face and neck malformation; reduced facial motor activity; bilateral club foot; heart in dextroposition, but normal anatomy; hand malformation; syndactyly left 2nd and 3rd fingers, and 5th finger (no nail); muscle malformation; pectoralis hyperplasia on left. The reporter states the child could have a combination of Poland syndrome (sequence) and Moebius syndrome (sequence).
90.	Induced abortion. Anencephaly.
91.*	Live infant. Microcephaly, ventriculomegaly, hypotelorism, mild hypotonia, and high-pitched cry.
92.*	Live infant. Macrosomia with macrocephaly; adductor muscle hypertonia.
93.*	Induced abortion. Anencephaly.
94.*	Induced abortion. Anencephaly.
Lamotrigine with Antiepileptic (AED) Polytherapy without Valproate	
1.	Live infant. Choanal atresia; stenosis later perforated. Mother also received carbamazepine preconception and throughout pregnancy.
2.	Live infant. "Congenital teratogenic face" with hypertelorism, downturned mouth, epicanthal folds, flattened nasal tip, micrognathia, slight bitemporal narrowing and marked hirsutes; has had "jittery hypotonicity." At time of follow-up, developmental delay (functioning at a 3-month-old level at 6 months of age). Mother also received carbamazepine preconception and throughout pregnancy.
3.	Live infant. Fetal hydrops and chylothorax. NICU care, mechanical ventilation, BP support, diuretics, problem with lung development and kidney failure. Mother also received felbamate throughout pregnancy.

*denotes cases that are new since the last Report

Table 8. Reports of Birth Defects Retrospectively Reported (continued)
1 September 1992 - 31 March 2010

Lamotrigine with Antiepileptic (AED) Polytherapy without Valproate (continued)	
4.	Live infant. Multiple congenital abnormalities: Congenital cataracts, double outlet right ventricle, pulmonary atresia, high membranous ventricular septal defect, right sided arch, anorectal agenesis without fistula, abnormal rotation of the large intestine, tracheal agenesis/laryngeal agenesis, bronchi arising from esophagus, abnormal lobar formation of the right lung, ambiguous genitalia, testes in high intraabdominal position, abnormal twisted left ribs, sacral dysgenesis with hypoplasia and abnormal segmentation, hypertelorism, down sloping palpebral fissures. Mother also received carbamazepine throughout pregnancy.
5.	Induced abortion. Diagnosis of anencephaly by ultrasound at 18 weeks' gestation. Mother also received carbamazepine preconception and during the first and second trimesters.
6.	Induced abortion. Diagnosis on a prenatal ultrasound: Derangement of the posterior fossa with no cerebellum seen, lumbosacral spina bifida, right talipes (clubfoot). Mother also received diazepam preconception and as needed.
7.	Live infant. Umbilical cord with one artery, one kidney (right). Mother also received carbamazepine during the first and second trimesters.
8.	Live infant. Hypospadias. Mother also received carbamazepine, clobazam, and topiramate preconception and throughout pregnancy.
9.	Live infant. Ambiguous external genitalia. Mother also received carbamazepine preconception and throughout pregnancy.
10.	Live infant. Hip dysplasia. Mother also received topamax preconception and throughout pregnancy.
11.	Live infant. Deafness. Mother also received phenytoin.
12.	Live infant. Congenital anomaly of the hip (dislocated). Infant weighed 11 lbs. 5 ozs at birth. Mother also received phenytoin.
13.	Live infant. Microcephaly, bilateral deafness and developmental delay. Mother also received carbamazepine.
14.	Live infant. Absent kidney. Mother also received carbamazepine preconception and throughout pregnancy.
15.	Live infant. Esophageal atresia, tracheo-esophageal fistula, intrauterine growth retardation. Two days after birth the fistula was closed. Mother also received primidone and topiramate.
16.	Live infant. Cleft lip and palate, congenital skull malformation (not otherwise specified), chromosomal abnormality (not otherwise specified), hypertelorism of orbit, pterygium colli, and finger deformity (not otherwise specified). Mother also received clobazam during the second and third trimesters of pregnancy.
17.	Live infant. Severe malformation type total diaphragm agenesia with pulmonary hypertension requiring surgery. Infant later died. Mother also received carbamazepine and phenobarbital.
18.	Live infant. Moderate subaortic perimembranous ventricular septal defect. Mother also received levetiracetam during the second and third trimesters of pregnancy.
19.	Induced abortion. Holoprosencephaly presumably diagnosed by prenatal ultrasound. Mother also received gabapentin.
20.	Live infant. Hip dysplasia. Mother also received carbamazepine, clobazam, and topiramate.
21.	Live infant. Microcephaly. Mother also received carbamazepine preconception and throughout pregnancy.
22.	Spontaneous pregnancy loss. Down syndrome. Mother also received clobazam preconception and throughout pregnancy.
23.	Live infant. Atrial septal defect and organ failure. Mother also received topiramate preconception and throughout pregnancy.
24.	Live infant. Cleft lip; infant also had left anisocoria and died from severe ischemic encephalopathy following prolonged maternal seizure prior to delivery. Mother also received topiramate.
25.	Live infant. Asymmetric skull. Mother also received levetiracetam.
26.	Live infant. Symbrachydactyly. Mother also received topiramate during the first, second, and third trimesters of pregnancy.

*denotes cases that are new since the last Report

Table 8. Reports of Birth Defects Retrospectively Reported (continued)
1 September 1992 - 31 March 2010

Lamotrigine with Antiepileptic (AED) Polytherapy without Valproate (continued)	
27.	Live infant. Agenesis of the corpus callosum diagnosed by MRI at 2 years of age. The child had pervasive developmental disorder with decreased social activity, speech deficit, and developmental language disorder. Mother also received topiramate.
28.	Live infant. Mild aortic coarctation first identified by prenatal ultrasound. Mother also received carbamazepine preconception and throughout pregnancy.
29.	Live infant. Agenesis of the corpus callosum and colpocephaly documented by MRI. The report states the metabolic work-up and chromosomes were normal. The child has mild developmental delay at one year of age. Mother also received clonazepam during the first and second trimester.
30.	Live infant. Cleft palate. Mother also received zonisamide preconception and throughout pregnancy.
31.	Live infant. Cleft palate requiring surgery. Mother also received carbamazepine preconception.
32.	Live infant. Partial cleft palate, which may require surgical correction at approximately one year of age. Mother also received oxcarbazepine prenatally at an unspecified time.
33.	Live infant. Pierre Robin syndrome (Robin sequence), butterfly vertebrae, hypoplastic iliac crest ("wing"). Karyotype normal. Mother also received clonazepam throughout pregnancy.
34.	Live infant. Small cleft soft palate. Mother also received gabapentin preconception and during the first trimester.
35.	Live infant. Facial dysmorphism, retrognathia, domed forehead, cauliflower ear. Short limbs were also noted on prenatal ultrasound at 22 weeks. It is unclear whether this was confirmed after delivery. Mother also received clobazam preconception and throughout pregnancy, oxcarbazepine preconception and during the first trimester, and topiramate preconception and throughout pregnancy.
36.	Live infant. Torticollis. Mother also received gabapentin during the third trimester.
37.*	Live infant. Cleft lip and palate. Mother also received oxcarbazepine and topiramate throughout pregnancy.
Lamotrigine with Antiepileptic (AED) Polytherapy with Valproate	
1.	Induced abortion. (Ultrasound detected neural tube defects). Spina bifida with meningocele, hydrocephalus, cerebellar deformity. Mother also received valproic acid preconception and throughout pregnancy.
2.	Live infant. Described as "abnormal," no details provided. Mother also received valproate preconception and throughout pregnancy.
3.	Stillbirth. Multiple abnormalities including hydrocephalus. Mother also received valproate preconception and throughout pregnancy and clobazam in the third trimester.
4.	Live infant. Stiff hands/wrists, mild contractures needing physiotherapy; reaction started when infant was 6 weeks old. Mother also received valproate preconception and throughout pregnancy.
5.	Live infant. Eyes slightly upturned with minor epicanthal folds. High and narrow forehead, premature fusion of metopic sutures. Small for gestational age. Mother also received valproate preconception and during the first trimester.
6.	Live infant. Left renal cysts; left kidney without function. Mother also received valproate preconception and throughout pregnancy.
7.	Live infant. Plane cutaneous angioma-hemifacies o/s (right). Mother also received diazepam during the second and third trimesters, phenobarbital preconception and throughout pregnancy and valproate preconception and during the first trimester.
8.	Live infant. Atrial septal defect, ventricular septal defect. Additional diagnoses from follow-up report: developmental delay, hypotonia, dysmorphic features – hypertelorism, slightly small chin, nose upturned, shallow philtrum, lips with thin vermillion border. Mother also received valproate preconception and throughout the pregnancy.
9.	Live infant. Congenital atrial septal defect, hypospadias/epispadias. Reporter suspects valproate syndrome. Mother also received valproate sodium throughout pregnancy.
10.	Live infant. Syndactyly, four webbed fingers on right hand. Mother also received folic acid, topiramate, and valproate preconception and throughout pregnancy.

*denotes cases that are new since the last Report

Table 8. Reports of Birth Defects Retrospectively Reported (continued)
1 September 1992 - 31 March 2010

Lamotrigine with Antiepileptic (AED) Polytherapy with Valproate	
11.	Live infant. Ventricular septal defect, breathing difficulties. Mother also received valproate preconception and throughout pregnancy.
12.	Induced abortion. Spina bifida, fetal growth delay in lower extremities, deformity of the skull, and dilatation of the right lateral ventricle identified at about 15 weeks' gestation. Mother also received valproate preconception and throughout the pregnancy and folic acid.
13.	Live Infant. Minor malformations such as hypertelorism, flattened nasal bridge, low-set malformed auriculas, micrognathia, very small and bow-shaped mouth with thin upper lip, cleft palate and arachnodactyly. Her karyotype was 47, XXX and she had a 3 mm secondary atrial septal defect. Mother also received valproate preconception and throughout pregnancy.
14.	Induced abortion. Congenital malformations of fetus, neural tube defect and malrotation (intestinal). Mother also received valproate.
15.	Live infant. Pulmonary stenosis, cleft lip, multiple malformations, auricular defect, defect left eyelid. Mother also received valproate.
16.	Live infant. Infant of a diabetic mother with ASD, PDA, thickened ventricular septum defect and LV wall, hypoplastic left kidney, median cleft palate, Dandy-Walker syndrome, prominent forehead, adrenal gland hyperplasia. Mother also received diazepam and valproate.
17.	Live infant. Congenital structural cardiac defect - unspecified. Mother also received valproate.
18.	Live infant. Bilateral microphthalmia. CT of the brain revealed the left eyeball to be smaller than expected and the lens appeared to be misplaced. Ultrasound showed small mitral valve insufficiency, but no sign of heart defect. Chromosome test was normal. Mother also received valproate.
19.	Induced abortion. Renal anomaly, not otherwise specified, detected on prenatal ultrasound and expected to be fatal. Mother also received valproate preconception and in first trimester.
20.	Induced abortion. Lethal osteochondrodystroplasia diagnosed by prenatal ultrasound. Mother also received valproate and carbamazepine preconception.
21.	Live infant. Congenital anomaly (not otherwise specified). Infant died. Mother also received valproate.
22.	Live infant. Microcalcifications in the lenticulstriate zones of the brain. Mother also received clobazam and valproate in the third trimester.
23.	Live infant. Glandular hypospadias and mild retrognathia. Mother also received valproate preconception and throughout pregnancy.
24.	Live infant. Cleft palate. Mother also received levetiracetam preconception and throughout pregnancy and valproate in the first, second, and third trimesters.
25.	Live infant. Subependymal cysts in the 3rd ventricle of the brain. Abnormal arm, leg, and head flexion movements. Mother also received clobazam in first, second, and third trimesters and valproate.
26.	Live infant. Spina bifida. Mother also received clobazam in first, second, and third trimesters, levetiracetam and valproate.
27.	Induced abortion. Hydrocephalus. Mother also received valproate preconception, first and second trimesters.
28.	Live infant. Congenital club foot, congenital nervous system anomaly, unspecified. Mother also received valproate preconception and first trimester.
29.	Induced abortion. Spina bifida, ventriculomegaly, Arnold-chiara malformation. Mother also received valproate.
30.	Induced abortion. Myelomenigocele and hydrocephalus. Mother also received valproate preconception, first and second trimesters.
31.	Live infant. Craniostenosis with trigonocephaly, first noted on prenatal ultrasound at approximately 31 weeks. The child reportedly had normal neurological development on pediatric exam at three months of age, and skull malformation and craniostenosis were resolved with sequelae. Mother also received valproate preconception and throughout pregnancy.

*denotes cases that are new since the last Report

Table 8. Reports of Birth Defects Retrospectively Reported (continued)
1 September 1992 - 31 March 2010

Lamotrigine with Antiepileptic (AED) Polytherapy (Concomitant AED Unspecified)	
1.	Live infant. Dysmorphic features including limb shortening, multiple joint contractures, camptodactyly, cryptorchidism, hooded prepuce, small mouth, high palate, simple ears and prominent eyes with a flat bridge of the nose. "Appearance of an arthrogryposis or a trisomy." Chromosomal analysis was normal. Other unknown antiepileptic medications were taken.
2.	Live infant. Macrocephalia, bilateral camptodactyly of the 4th finger with reduced extension in the MCI joint, shortening of 4th and 5th fingers, striking dermatoglyphics and hypoplastic toenails, large distance between the mamillae, a split uvula and a wide neck fold. Other unknown antiepileptic medications were taken.

*denotes cases that are new since the last Report

Other Reported Events

Some infants born without birth defects have been retrospectively reported to have other conditions or to be otherwise ill. A list of those retrospective reports is presented in Appendix B.

4.2 Other Studies

There is a growing body of literature on the potential association between lamotrigine exposure during pregnancy and birth defects. This section summarizes the results of some of these studies. It is important to note that these studies vary widely in methodology, ascertainment and classification of birth defects, geographic location, sample size, and other factors that could affect results.

The Swedish Medical Birth Registry

The Swedish Medical Birth Registry, affiliated with the Swedish Government Department for Health and Welfare, was established in 1973 and collects data on nearly all births (>95%) in Sweden (Olsen *et al*, 2002, Wide *et al*, 2004). Information on the women's pregnancy is collected prospectively by the attending midwife or physician starting with an interview at the first antenatal visit at 10-12 weeks. The information collected includes maternal socio-demographics, alcohol use and smoking during pregnancy, medical history, and medication taken during pregnancy. Data on medication exposure have been collected since 1992. The pregnancy outcome is assessed at birth by the attending physician and any malformations are described, coded according to the ICD-9 classification system, and entered into a central computer system. As malformations are recorded descriptively; there is no differentiation of major and minor malformations. These birth data are downloaded from several population based registers (congenital malformations, hospital discharge, and birth registers) and can be linked through unique health identifiers to the mother's history of medication exposure during pregnancy.

The following summary is based on delivery outcome among infants born to women who, at the first antenatal visit (usually week 10-12), reported the use of lamotrigine, irrespective of use of other drugs. The data represent all reported exposures between 1995 and 2008.

The total number of infants for whom outcome data were available following first trimester exposure to lamotrigine was 801. Among these, 629 reported the use of lamotrigine as monotherapy and 172 reported the use of lamotrigine in combination with other anticonvulsants.

The following malformations were recorded in infants exposed *in utero* to lamotrigine monotherapy during early pregnancy:

Malformation
Relatively major defects
Holoprosencephaly with hydrocephaly
Atrial septal defect (ASD) (twins both with same defect)
Atrial septal defect and endocardial cushion defect
Unspecified cardiac defect (2)
Ventricular septal defect (4)
Aortic valve stenosis
Median cleft palate (2), one with renal dyplasia
Cleft lip (2)*
Omphalocele with diaphragmatic malformation and ASD/ECD
Small gut stenosis
Hypospadias (3)
Syndactyly (fingers)
Down syndrome (2)
Turner Syndrome
Minor defects
Preauricular appendix
Unstable hip (2)
Hip (sub)luxation
Undescended testicle (2)
Nevus
Accessory nipple
Total 31 malformations

*One infant with cleft lip/palate previously included as exposed to lamotrigine monotherapy has been removed from the summary table as additional data indicated the infant was exposed *in utero* to lamotrigine polytherapy with carbamazepine

There were 31 reported malformations among 629 infants following first trimester exposure to lamotrigine monotherapy giving a rate of 4.9% (95% Confidence Interval: 3.4%-7.0%). This compares to a malformation rate of 3.5%-4.4% from the general population captured in the Swedish Birth Register. These included 23 relatively severe defects: one holoprosencephaly with hydrocephaly, four orofacial clefts (two cleft palate and two cleft lip), two atrial septal defects, four ventricular septal defects, two unspecified cardiac defect, one aortic valve stenosis, one omphalocele, one gut stenosis, three hypospadias, one syndactyly, two cases of Down syndrome and one case of Turner Syndrome, though the latter is unlikely to be associated with drug exposure.

There were 21 malformations among 172 infants with first trimester exposure to lamotrigine as part of a polytherapy combination giving a rate of 12.2% (95% CI 7.9% - 18.3%).

The odds ratio for having any malformation after exposure to lamotrigine monotherapy was 1.13 (95% CI 0.77 – 1.85) and for relatively severe malformations 1.19 (95% CI 0.77 – 1.85).

The Register reported 4 cases of orofacial clefts in 629 infant first trimester monotherapy exposures. The rate in lamotrigine monotherapy exposed pregnancies was 6.4 per 1000 versus a background general population rate of 2.0 per 1000 (data from 1995-2005). The Swedish Birth Register concluded “that even though this excess could be random, it supports some other observations in the literature”.

It should be noted that these data were shared directly by the Swedish Medical Birth Register, but have not been peer reviewed.

Danish Multicenter Study of Epilepsy and Pregnancy

Using linked data from the prospective Danish Medical Birth Pharmaco-epidemiological Prescription Registry Databases of North Jutland County, Sabers *et al.* reviewed data from pregnant women with epilepsy with or without AED therapy from 6 university hospitals in Denmark (Sabers *et al*, 2004). A total of 138 women were exposed to AEDs in the first trimester, including 51 exposed to lamotrigine (figures for monotherapy and polytherapy). One malformation, a VSD, was reported after first trimester exposure to lamotrigine (150 mg) and oxcarbazepine (2400 mg).

The Australian Registry of Antiepileptic Drugs in Pregnancy

The Australian Pregnancy Registry was established in 1999 to prospectively monitor adverse pregnancy outcomes in women exposed to AEDs (Vajda *et al*, 2003, Vajda *et al*, 2005). Women eligible for enrollment are asked by healthcare providers to call a toll free number where information on the Registry is provided and consent for enrollment is sought. Once consent is given, a structured interview is completed to obtain maternal demographic and socioeconomic details as well as information on AED treatment history, the mother's medical history, and details of the pregnancy itself. Further telephone interviews are completed at 7 months gestation, 4-8 weeks following the expected date of birth, and at 12 months after birth. The latter two interviews capture information concerning the infant's health including the presence of major congenital malformations. In addition, the woman's permission is sought to obtain information from healthcare providers to confirm details through medical records.

The most detailed lamotrigine specific information comes from data collected up until December 2003 when 630 women had been enrolled in the Registry and 555 pregnancies had reached completion with 565 infants (including 10 sets of twins) (Vajda *et al*, 2006). Sixty-five women were exposed to lamotrigine monotherapy during the first trimester of pregnancy. No outcomes with major malformations were recorded. An additional 70 women were exposed to lamotrigine polytherapy including valproate during the first trimester with 4 recorded major malformations (Vajda *et al*, 2006).

Table 9 describes the 4 major malformations (Vajda *et al*, 2003).

Table 9. Major Malformations Reported in the Australian Registry

Birth Defects	AED (dose – mg)	Folate
1. Spina bifida and hydrocephalus (aborted)	valproate (2500), lamotrigine (150)	Yes
2. CHD (VSD), plagiocephaly, bronchial narrowing and hypospadias	valproate (2000), lamotrigine (350)	No
3. Plagiocephaly	phenytoin (200),lamotrigine (600), diazepam (10)	Yes
4. Facial bone anomalies and hypospadias	valproate (2000), lamotrigine (150)	Yes

More recent data, reflecting 992 pregnancies with complete outcome data, captured information on 146 pregnancies exposed to lamotrigine monotherapy in the first trimester. The risk of malformations was 1.37% which produced an odds ratio of 0.37 (95% CI 0.06 – 2.26) versus women with epilepsy not exposed to AEDs captured by the registry (Vajda, 2007).

The Australian registry now forms part of EURAP, though country specific data continue to be analyzed.

The UK Epilepsy and Pregnancy Register

The UK AED Pregnancy Registry was established in 1996 to prospectively monitor adverse pregnancy outcomes in women exposed to AEDs and is headed by Dr. James I. Morrow, Department of Neurology, Royal Victoria Hospital, Belfast, Northern Ireland. Women are enrolled, with their consent, through healthcare providers, most commonly general practitioners, neurologists, and obstetricians. These providers collect information on exposure to AEDs during pregnancy (therapy type, timing, and dosage), maternal demographics, medical history, and details of the pregnancy. Close to the expected date of delivery, the healthcare providers are contacted for details of the infant's health. There is an additional follow-up at 3 months following birth. All malformation descriptions are reviewed by a geneticist affiliated with the Registry.

The UK Epilepsy and Pregnancy Register has collected full outcome data on 3607 pregnancies. The overall major congenital malformation rate for all AED exposed pregnancies was 4.2% (95% Confidence Interval: 3.6%-5.0%). The rate was significantly higher in polytherapy (6.0%) compared to monotherapy (3.7%) exposures. The rate was significantly higher in women exposed to valproate (6.2%, 95% CI 4.6%-8.2%) compared to carbamazepine (2.2%, 95% CI 1.4%-3.4%) in the first trimester of pregnancy. There were also fewer malformations in women exposed only to lamotrigine (3.2%, 95% Confidence Interval: 2.1%-4.9%) in the first trimester of pregnancy. The rate for women with epilepsy who had not taken AEDs during pregnancy was 3.5% (95% Confidence Interval: 1.8%-6.8%). A positive dose response for major congenital malformations was noted for lamotrigine. The mean daily dose of lamotrigine was significantly higher for those with a major congenital malformation compared with those without a major congenital malformation respectively (352.4 mg and 250.6 mg; p=0.005). (Morrow *et al*, 2006).

North American Antiepileptic Drug (AED) Pregnancy Registry

The North American Antiepileptic Drug (NAAED) Pregnancy Registry is an ongoing prospective, observational study. Women are recruited directly into the Registry when they call a toll free number that is advertised through healthcare providers, teratology counselors, epilepsy support foundations, and the lay and scientific press. Upon enrollment, women participate in a telephone interview to collect information on material demographic and socio-economic characteristics, AED exposure during pregnancy (therapy type, timing, and dosage), medical and prescription history, and details of the pregnancy. A further interview to confirm exposure information takes place at 7 months gestation and the health of the infant is established through an interview 4-8 weeks after the expected delivery date. Consent is also sought to access medical records to confirm details of the infant's health. All malformation descriptions are reviewed by two dysmorphologists blinded to maternal exposure. Patients enroll themselves into this Registry. Contact information is provided at the beginning of this Report.

The NAAED Pregnancy Registry has released findings on the frequency of major malformations in infants exposed to lamotrigine as monotherapy (Holmes *et al*, 2006, Holmes *et al*, 2008). As of March 2006, data were available for 684 infants exposed to lamotrigine monotherapy in the first trimester of pregnancy. Of these, 16 or 2.3%

(95% Confidence Interval 1.3%-3.8%) had a major malformation. It is noteworthy that no evidence of a dose-response relationship was found. Five infants (7.3/1000) had isolated oral clefts: cleft palate (3), cleft lip (1), and cleft lip and palate (1). The rate among the lamotrigine exposed infants showed a 10.4-fold increase (95% Confidence Interval: 4.3-24.9) in comparison to 206,224 unexposed infants surveyed at birth at Brigham and Women's Hospital in Boston, where the prevalence of oral clefts was 0.7/1000 (Holmes *et al*, 2008). The prevalence of isolated oral clefts reported by NAAED is also higher than the range reported in the published literature (0.5-2.2/1000) (Bille *et al*, 2005, Christensen 1999, Croen *et al*, 1998, Das *et al*, 1995, DeRoo *et al*, 2003, Hashmi *et al*, 2005, Kallen 2003, Menegotto *et al*, 1991, Tolarova *et al*, 1998, Vallino-Napoli *et al*, 2004) (Holmes *et al*, 2006).

European Registry of Anti-Epileptic Drug Use in Europe (EURAP)

EURAP is an ongoing multi-AED pregnancy registry that was established in 1999. Recruitment was initially in Europe, but the Registry has since expanded to recruit women from 42 countries in Asia, Oceania, and Latin America. Networks of reporting physicians within the participating countries record, with patient permission, details of AED exposure and maternal risk factors (maternal demographics, maternal health, timings of AED treatment during pregnancy, history of maternal epilepsy, frequency of seizures during pregnancy, family history of epilepsy and other congenital and inherited conditions). The Registry only includes pregnancies registered before the fetal outcome is known (prospective) and within the first 16 weeks of gestation for comparative risk assessments (against other AEDs). The infant outcome is monitored at regular intervals between enrollment and up to 14 months after birth (once a trimester, at birth, and at approximately one year of age). Each update form is reviewed by a national coordinator before transfer to the Central Registry in Milan for data input and analysis. In order to facilitate uniform and objective malformation assessments, malformation reports are regularly reviewed by an outcome assessment committee which remains blinded to the type of exposure.

Data concerning the risk of major malformations with respect to *in utero* exposure to specific AEDs were presented at the 9th European Congress on Epilepsy in June 2010. These data captured 5,707 pregnancies resulting in 5,537 live births, 88 still births, 43 perinatal deaths and 39 induced abortions in association with fetal abnormalities. There were 4,475 first trimester monotherapy exposures within the dataset.

The risk of major congenital malformations (MCMs), excluding chromosomal abnormalities, following first trimester lamotrigine exposure was 2.9% (95% CI 2.1% - 4.1%). The corresponding risks associated with exposure to other monotherapies were as follows: valproate 9.3% (95% CI 7.6% - 11.3%), carbamazepine 5.7% (95% CI 4.6% - 7.1%), phenobarbital 7.5% (95% CI 4.6% - 12.0%), and other monotherapies 3.4% (95% CI 2.2% - 5.3%).

In multivariable analyses factors significantly associated with an increased risk of MCMs included family history of a MCM, family history of epilepsy and folic acid usage. The adjusted relative risk of a MCM using lamotrigine monotherapy as the baseline was 3.4 (95% CI 2.1 – 5.7) for valproate, 2.1 (95% CI 1.3 – 3.5) for carbamazepine and 2.7 (95% CI 1.3 – 5.5) for Phenobarbital (Battino *et al,* 2010).

Neurodevelopmental Effects of Antiepileptic Drug (NEAD) Study

The NEAD study is a prospective, observational study enrolling mother-child pairs across 25 centers in the United States and United Kingdom. The main enrollment criterion is exposure to valproate, carbamazepine, lamotrigine or phenytoin during pregnancy. The children are then followed until six years of age to determine the cognitive and behavioral effects of *in utero* AED exposure. As the study collects information on all adverse events occurring in the mother and child, an analysis of the risk of major birth defects (potentially attributable to AED exposure) was completed. The prevalence of major birth defects by AED in the first 333 mother child pairs are described in the table below.

	Carbamazepine	Lamotrigine	Phenytoin	Valproate
Total n	110	98	56	69
Major birth defects	5 (4.5%)	1 (1.0%)	4 (7.1%)	12 (17.4%)

A comparison across AED exposure groups indicated a statistically significant difference in the risk of major birth defects (exact Mantel-Haenszel chi square, $p<0.001$) with the difference being driven by the poorer outcome following valproate exposure versus the lower risk associated with lamotrigine exposure. However, the authors concluded that larger data sets were needed to better quantify the risk associated with lamotrigine (Meador *et al*, 2006).

More recent publications from the NEAD group have concentrated on differences in IQ at three years of age. The mean IQ was 101 for children exposed *in utero* to lamotrigine versus 99 for phenytoin, 98 for carbamazepine and 92 for valproate. On average children exposed *in utero* to valproate had a 9 point lower IQ score than those exposed to lamotrigine (95% CI 3.1-14.6, p=0.009) (Meador *et al,* 2009).

Case control study of lamotrigine and oral clefts in the EUROCAT network

Pregnancy registries may generate hypotheses concerning the risk of specific birth defects associated with *in utero* drug exposure, but their design means the estimates of risk for rare defect types are very imprecise. The case control study design offers a better powered approach for assessing the potential association between drug exposure and specific defect types.

Following the signals for *in utero* lamotrigine exposure associated with an increased risk of isolated oral clefts, a case control study was completed in the European network of Congenital Anomalies and Twin registers, EUROCAT. This network of population-based registers covers more than a quarter of births across Europe maximizing the study's power to test an association between a rare outcome (clefts) and a rare exposure (lamotrigine). The central EUROCAT database holds standardized records of congenital birth defects since 1980 and covers live births, stillbirths, and terminations of pregnancy. Data on drug exposure during pregnancy have been collected over varying time periods for different participating regional/country registers. However, since 2005 drug exposure classification has been standardized and recorded according to the Anatomical Therapeutic

Classification (ATC) coding system. Data on drug exposure during the first trimester is obtained from obstetric records, through interviews after birth or through linkage with pharmacy databases.

In this study the odds of lamotrigine exposure among isolated oral cleft cases was compared with the odds of lamotrigine exposure among malformed non chromosomal, non oral cleft cases. Comparisons were restricted to oral cleft cases and other non chromosomal malformed controls as EUROCAT collects data on malformed infants alone. This comparison was deemed valid as there is no evidence to suggest that lamotrigine is associated with other defect types.

A total of 85,563 defect registrations were studied including 4,571 oral cleft cases and 80,052 non cleft defect controls. Thirty one of the 4,571 isolated oral cleft cases were exposed *in utero* to AEDs, including two lamotrigine monotherapy exposures compared with 451 AED exposures among the 80,052 malformed controls including 38 lamotrigine monotherapy exposures. The adjusted odds ratio for isolated oral clefts with AED v. no AED exposure was 1.21 (95% CI 0.82 – 1.72). The adjusted odds ratio for isolated oral clefts with lamotrigine monotherapy versus no AED was 0.80 (95% CI 0.11 – 2.85).

The authors concluded that they found no evidence of an increased risk of isolated oral clefts relative to other non chromosomal defects for lamotrigine monotherapy, However, given the rarity of both exposure and outcome, the confidence intervals around the odds ratio estimate were relatively wide, though the data set made a greater than threefold increased risk very unlikely. The control group of other non chromosomal defects complicates interpretation: either the risk of oral clefts with lamotrigine is not raised or is raised to the same extent as for all other malformations. Exploratory analyses within the EUROCAT dataset did not indicate increased risks of other defects types, which is consistent with data from ongoing pregnancy registries and makes the latter explanation unlikely (Dolk *et al,* 2008).

The EUROCAT study has been extended with the intention of capturing births until 2011. A control group of chromosomal defects, unlikely to be associated with drug exposure, also is being added to further and more powerfully study the potential association between oral clefts, as well as other specific defects, and *in utero* lamotrigine exposure.

Prescription-Event Monitoring (PEM) Study

A study was performed through prescription-event monitoring by the Drug Safety Research Unit, Southampton, United Kingdom (Mackay *et al*, 1997). The study population consists of all lamotrigine users obtaining drug prescriptions through a general practitioner in Britain from December 1991 through February 1995.

During 6-month follow-up of 11,316 subjects exposed to lamotrigine, 66 pregnancies were identified. Of these 66, 60 involved earliest exposure during the first trimester and the remaining 6 involved either second or third trimester exposure only. Outcomes are shown in the following table.

Table 10. Outcomes of Pregnancies Reported to the PEM with 6 Month Follow-up – By Earliest Trimester of Lamotrigine Exposure

December 1991 - February 1995

Earliest Trimester of Exposure	Live Birth	Spontaneous Pregnancy Loss	Missed Abortion	Induced Abortion	**Total Outcomes**
First	40	10	1	9	**60**
Second or Third Only	6	0	0	0	**6**
Total	**46***	**10**	**1**	**9**	**66**

* Includes:

- 1 infant born prematurely at 29 weeks.
- 1 infant diagnosed with IUGR and subsequent radiologic evidence of pyloric stenosis.
- 3 infants with congenital anomalies (3/46= 6.5%) described as:
  a. 1 infant with large ventricular septal defect; mother took concomitant phenobarbital and valproic acid throughout pregnancy.
  b. 1 infant with cleft palate and hypospadias; mother took concomitant carbamazepine and valproic acid during pregnancy.
  c. 1 infant born prematurely with hemiplegia and epilepsy after a preeclamptic pregnancy; mother took labetolol in last 4 months of pregnancy, but no other anticonvulsants.

During 18-month follow-up of 3,994 subjects exposed to lamotrigine, there were 12 pregnancies, all involving earliest exposure in the first trimester. Outcomes are shown in the following table.

Table 11. Outcomes of Pregnancies Reported to the PEM with 18 Month Follow-up – By Earliest Trimester of Lamotrigine Exposure

December 1991 - February 1995

Earliest Trimester of Exposure	Live Birth	Spontaneous Pregnancy Loss	Induced Abortion	**Total Outcomes**
First	9	1	2*	**12**
Total	9	1	2*	**12**

*Both induced abortions involved spina bifida and both mothers had taken concomitant valproic acid in the first trimester.

5. LITERATURE REVIEW

Throughout the life of this Registry, the published medical literature was reviewed for case reports with outcomes of pregnancies exposed to lamotrigine. As of 31 March 2010, seven articles had been found and are listed in the following literature table (Table 12).

Table 12. Reported Cases From the Medical Literature of Lamotrigine Exposure in Pregnancy

1 September 1992 - 31 March 2010

PUBLICATION		TREATMENT			OUTCOME	
FIRST AUTHOR	YEAR	LAMOTRIGINE DOSE	GESTATION WEEK TX BEGAN	AED POLYTHERAPY	GESTATION WEEK AT OUTCOME	OUTCOME
Quattrini, A	1996	200 mg/day	0	Carbamazepine 1000 mg/day Barbexaclone 200 mg/day	39	Live infant – no defects
Rambeck, B	1997	300 mg/day	0	Valproic Acid in weeks 0-3 (dose unknown)	39	Live infant – no defects
Tomson, T	1997	200 mg/day week 0-20, 300 mg/day week 21-41	0	none	41	Live infant – no defects
Ohman, I	2000					A case series reported no birth defects in the pregnancies exposed to lamotrigine; however, these cases were collected for other purposes and may not be representative of all exposed pregnancies.
Popescu, L	2005	200 mg/day	unknown	Phenobarbital 200 mg/day (timing unknown) –dose progressively switched with lamotrigine	unknown	Live infant – clinodactyly, partial syndactyly, withdrawal symptoms including lack of appetite, neuromotor hyperexcitability, and irritability.
Voermans, N	2005	unknown	unknown	None	unknown	Live infant – no defects
Gentile, S	2005	300 mg/day	0	None	39	Live infant – no defects

In addition, there are two case series reported in the literature. A study monitoring the pharmacokinetics of lamotrigine during pregnancy, observed 12 infants born to women exposed to lamotrigine monotherapy and no malformations (de Haan *et al*, 2004). A second case series of 12 AED exposed pregnancies included two exposures to lamotrigine monotherapy. Neither of the infants had malformations (Cissoko *et al*, 2002).

Literature Case References

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6. DATA SUMMARY

The Committee reviewed the accumulated data for 2492 prospectively reported pregnancy outcomes in the Registry according to the criteria described under "Methods".

Review of the composite data:

Prospective Reports of First Trimester Exposure:

Monotherapy Exposures:

In the prospective reports with first trimester lamotrigine exposure as monotherapy, there were 35 major birth defects reported in 1558 outcomes (excluding fetal deaths and induced abortions not involving major defects and all spontaneous pregnancy losses). The observed proportion of births with major defects was 2.2% (95% Confidence Interval for observed proportion: 1.6%-3.1%) (Fleiss 1981). Table 6 presents gestational age at enrollment for this exposure group.

Polytherapy including Valproate:

In the prospective reports with first trimester exposure to polytherapy including valproate, there were 16 major birth defects reported in 150 outcomes (excluding fetal deaths and induced abortions not involving major defects and all spontaneous pregnancy losses). The observed proportion of births with major defects was 10.7% (95% Confidence Interval: 6.4%-17.0%) (Fleiss 1981). This exposure group exhibited the highest proportion with major defects following first trimester exposures.

Polytherapy not including Valproate:

In the prospective reports with first trimester exposure to polytherapy not including valproate, there were 12 major birth defects reported in 430 outcomes (excluding fetal deaths and induced abortions not involving major defects and all spontaneous pregnancy losses). The observed proportion of births with major defects was 2.8% (95% Confidence Interval: 1.5%-5.0%) (Fleiss 1981).

Prospective Reports of Second Trimester Exposure:

Monotherapy Exposures:

In the prospective reports with second trimester lamotrigine exposure as monotherapy, there were 4 major birth defects reported in 95 outcomes (excluding fetal deaths and induced abortions not involving major defects and all spontaneous pregnancy losses).

Polytherapy including Valproate:

In the prospective reports with second trimester exposure to polytherapy including valproate, there was 1 major birth defect reported in 7 outcomes (excluding fetal deaths and induced abortions not involving major defects and all spontaneous pregnancy losses).

Prospective Reports of Third Trimester Exposure:

Monotherapy Exposures:

In the prospective reports with third trimester lamotrigine exposure as monotherapy, there was 1 major birth defect reported in 18 outcomes (excluding fetal deaths and induced abortions not involving major defects and all spontaneous pregnancy losses).

Polytherapy not including Valproate:

In the prospective reports with third trimester exposure to polytherapy not including valproate, there was 1 major birth defect reported in 3 outcomes (excluding fetal deaths and induced abortions not involving major defects and all spontaneous pregnancy losses).

Review of Prospective and Retrospective Birth Defects:

A review of all reported birth defects revealed no unique or consistent pattern to suggest a common cause.

7. COMMITTEE CONSENSUS

The Lamotrigine Pregnancy Registry was a prospective, observational study which aimed to detect a signal of any large risk of major malformations following exposure to lamotrigine during pregnancy.

The percentage of pregnancies resulting in offspring with major malformations may vary across studies as the methodologies vary widely. Between-study variation in the reported rates of major birth defects can be related to such factors as the inclusion and exclusion criteria for major birth defects, the geographic regions included, how early in pregnancy women are enrolled, the source of pregnancy outcome information, the length and timing of follow-up, whether or not elective abortions are included, and the population of women included. Despite the methodological differences, consistency is emerging across several large AED pregnancy registries with the International Lamotrigine Pregnancy Registry reporting a rate of major congenital malformations following first trimester exposure monotherapy exposures of 2.2% (95% Confidence Interval: 1.6%-3.1%), NAAED reporting a rate of 2.3% (95% Confidence Interval: 1.3%-3.8%) (Holmes *et al*, 2008), and the UK Epilepsy and Pregnancy Register reporting a rate of 3.2% (95% Confidence Interval: 2.1%-4.9%) (Morrow *et al*, 2006).

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

Given the difficulty in identifying appropriate comparison groups for the Lamotrigine Pregnancy Registry, estimates of the frequency of birth defects in the offspring of women with epilepsy from the current literature are also presented. These range between 3.3% and 4.5% in cohorts of women using AED monotherapy (Holmes *et al,* 2001, Morrow *et al,* 2001, Morrow *et al,* 2003, Morrow *et al*, 2006, Samren *et al,* 1999). Therefore, comparing the rate of major birth defects in pregnancies exposed to lamotrigine monotherapy with that of pregnancies in the general population without epilepsy may overestimate the risk of lamotrigine use because of the hypothesized elevated risk among women with epilepsy. However, some published data have shown that women with epilepsy do not have an increased risk of birth defects (Holmes *et al*, 2001).

The Registry has not detected evidence of an appreciable increase in the overall risk of major birth defects and this should provide some assurance when counseling patients. In particular, if the baseline frequency of total birth defects is 2-3 in 100 live births, a sample size of 1558 first trimester lamotrigine monotherapy exposures has an 80 percent chance (80% power) of correctly detecting at least a 1.39-1.48-fold increase over baseline in the overall rate of birth defects. Upon closure of the Registry, the rate of major birth defects for first trimester monotherapy exposures was 2.2% (95% Confidence Interval for observed proportion: 1.6%-3.1%) (Fleiss 1981). While this frequency is reassuring, the lamotrigine monotherapy sample size at Registry closure was too small for formal comparisons of the rates of specific birth defects (e.g. cleft lip). For these relatively rare outcomes, a Registry may generate signals, defined as a report or reports of an event with an unknown causal relationship to treatment, around specific defects that are worthy of further exploration and continued surveillance.

The Lamotrigine Pregnancy Registry Advisory Committee noted the two prospectively reported cases of hypoplasia of the left ventricle and hypoplastic left heart syndrome, as well as three cases of anencephaly among first trimester monotherapy exposures. Attempts to obtain more information for purposes of classification of the cardiac defect cases were unsuccessful. For anencephaly other data sources were examined to look for consistency. No additional cases of anencephaly have been reported to five other ongoing AED registries with first trimester lamotrigine monotherapy with denominators ranging from 51 to over 1000. The one case of anencephaly reported to the NAAED is a duplicate of a case in this Registry. Two cases of spina bifida have been reported, one from the NAAED and one from the UK Epilepsy and Pregnancy Register. In consideration of these data, the Committee considered there to be no consistent evidence to suggest an increased risk of neural tube defects associated with first trimester lamotrigine monotherapy.

The Committee noted the signal of an increased risk of isolated oral clefts reported from the North American Anti-Epileptic Drug Registry and the Swedish Medical Birth Register (see Other Studies section 4.2). No apparent increase in the risk of oral clefts has been observed within the prospective cases included in the Lamotrigine Pregnancy Registry. The Committee noted that a case control study was specifically mounted in the EUROCAT system to test the hypothesis of an association between first trimester lamotrigine exposure and isolated oral clefts, and the analysis did not support an increase. The odds ratio for all isolated oral clefts compared to other non cleft malformations following first trimester lamotrigine monotherapy exposure was 0.8 (95% Confidence Interval: 0.11- 2.85) (Dolk *et al*, 2008).

The Lamotrigine Pregnancy Registry Advisory Committee noted the higher frequency of major malformations within the group exposed to AED combinations that include both lamotrigine and valproate. Published studies report that women using valproate have experienced elevated rates of specific birth defects (Arpino *et al*, 2000, Artama *et al*, 2005, Omtzigt *et al*, 1992; Thisted *et al*, 1993, Wyszynski *et al*, 2005, Morrow *et al*, 2006, Vajda *et al*, 2004). However, because the number of AEDs used may be inextricably tied to the frequency and severity of seizures and a valproate monotherapy exposure group internal to the Registry is not available, it is difficult within this Registry to assess the contribution of each of these factors to the risk of major malformations.

Because Morrow *et al*, 2006 noted a positive dose-response effect for major congenital malformations with lamotrigine use; data related to dose from the Lamotrigine Pregnancy Registry were examined and published (Cunnington *et al*, 2007). That analysis found no increase in major defects with daily doses up to 600 mg; data for doses of 600 mg or more were insufficient to confirm or refute a dose effect. The Committee continued to monitor dose data through 31 March 2010. There are 197 exposures at doses of 400 mg or more included in this Report, including 44 exposures in the range of 601 – 1200 mg (Table 13). The Committee considered the data as reassuring, providing no evidence of a dose effect. The available data are insufficient to make a definitive conclusion, but they do suggest that any dose effect that might exist is likely to be small.

Table 13. Lamotrigine Dosing – Maximum Recorded Dose[1] for First Trimester Lamotrigine Exposed Patients
1 September 1992 - 31 March 2010

Lamotrigine Dose (mg)*	Defect / Exposure / Percentage	
Overall	35/1558	(2.2%)
Patients with missing dose	1/35	(2.9%)
>0 – 100	7/276	(2.5%)
101 – 200	9/556	(1.6%)
201 – 300	10/274	(3.6%)
301 – 400	3/220	(1.4%)
401 – 600	5/153	(3.3%)
601 – 1200	0/44	
Logistic Regression[2]		
Odds Ratio per 100 mg increase (90% CI)	1.000 (0.998 – 1.001)	
P-value	0.338	
Goodness of Fit p-value	0.358	

* No patients have a recorded dose >1200 mg/day

[1] Maximum non-missing lamotrigine dose recorded on the CRF prior to conception or during first trimester.

[2] Based on a logistic regression model with dose level as the independent variable and defect status as the dependent variable. The confidence interval and p-value (one-sided test for odds ratio > 1) are based on Wald statistics. P-value < 0.05 is considered statistically significant. The Goodness of Fit p-value is based on Hosmer-Lemeshow, and a p-value < 0.10 is evidence of a poor model fit.

Several factors may have introduced some bias into the calculation of the rate of major defects in the Registry data. As reporting of exposed pregnancies was totally voluntary, it is possible that high-risk pregnancies or low-risk pregnancies may have been more frequently reported. It is also possible that outcomes among pregnancies lost to follow-up could have differed from those with documented outcomes. Voluntary terminations and fetal deaths (pregnancy losses $\geq$20 weeks' gestation) for which no defects have been detected and all spontaneous abortions (pregnancy losses <20 weeks' gestation) were excluded from the rate calculations, but in reality, it is unknown what percentage of these pregnancies may have actually had defects. While the data collection form attempted to obtain information on birth defects detected at the time of the outcome, the reporting physician may not have always known the condition of the aborted fetus.

The rate of spontaneous abortion in the general population is 14%-22% (Kline *et al*, 1989). Comparisons across studies are problematic since the rate of spontaneous abortion declines throughout pregnancy and the observed rate will vary depending on the gestational week at which study follow-up begins. Because women were enrolled in the Lamotrigine Pregnancy Registry at different times in gestation, calculation of the rate of spontaneous abortion with lamotrigine exposure was beyond the scope of the Registry activities.

While the analyses of Registry data were limited to prospective reports, some pregnancy exposures were reported after the pregnancy outcome had occurred (retrospective reports). The Lamotrigine Pregnancy Registry Advisory Committee reviewed each retrospective report. In general, retrospective notification of outcomes following exposure to drugs could be biased towards reporting severe and unusual cases, and may not reflect the general experience with the drug. Moreover, information about the total number of exposed persons is unknown. Therefore, rates of outcomes could not be calculated from the retrospective reports. However, a

series of reported birth defects could be analyzed to detect specific patterns of defects and identify early signals of new drug risks. Table 8 describes all birth defects in retrospectively reported cases and all other events are described in Appendix B. The Committee did not note a specific pattern of defects among these cases.

Despite these limitations, the Registry provides a useful tool for supplementing animal toxicology studies, other epidemiologic studies and clinical trials to assist clinicians in weighing the risks and benefits of treatment for individual patients.

The Committee notes that the Registry has considerably passed the milestone of 1000 outcomes for prospective first trimester exposures to lamotrigine monotherapy and thus has met its primary objective, which was to determine whether the overall rate of major malformations was increased among the offspring of exposed women. The Registry has not detected an appreciable increase in the singular outcome of major birth defects overall; however, the population monitored was only large enough to detect a signal of major teratogenicity and was not powered to exclude increases in the rates of specific defects. It was further noted by the Committee that when the sample size exceeds 1000 exposed subjects without an excess of major birth defects as a singular outcome (background rate of 2%-3%), the confidence interval is sufficiently narrow to indicate that there is not an appreciable effect of the exposure on the risk of major birth defects overall. At the same time, the Committee recognizes that as the Registry exceeds 1000 subjects, the likelihood of chance findings for specific defects (which may occur at baseline rates of 1/1000 or less) increases, and the Committee agreed that other methods (e.g., various case-control approaches) are more appropriate and powerful to identify increases in the rates of specific defects. For these reasons, the Committee recommended termination of this Registry. Monitoring of the risk of specific birth defects following *in utero* lamotrigine exposure will continue through the EUROCAT network (analyses extended to capture births up to 2011). The case control approach will offer a more powerful approach to the study of these rare defect types.

8. REGISTRY CLOSURE AND ACKNOWLEDGEMENTS

The Registry began in September 1992, closed to new prospective on June 3, 2009, with continued follow up on existing enrollments through March 31, 2010,

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.

The case registration approach used in this Registry could have been successful only with the continued participation of health professionals who registered patients and assisted in providing follow-up information postpartum. The assistance of health professionals who have provided information to the Registry is greatly appreciated.

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Appendix A: Methods

Registration and Follow-up

Reporting of exposed pregnancies was voluntary. Health care professionals with patients exposed to lamotrigine during pregnancy were encouraged to enroll each patient in the Registry as early in the pregnancy as possible. When a patient initiated contact with the Registry they were asked to provide permission, and sufficient contact information, for the Registry to follow-up with their health care professional for the purpose of disseminating Registry data and completing the pregnancy registration process.

The Registry required prospective registration of pregnancies exposed to lamotrigine. To further increase the validity of the data, the Registry strongly urged providers to enroll their patients as early in pregnancy as possible, if possible before any prenatal testing for defects was done. Prospectively reported pregnancies were those reported during pregnancy before the pregnancy outcome was known. Because the outcome of the pregnancy was unknown when the exposure was reported, follow-up to determine the outcome was required.

Retrospective reports of outcomes with defects were also carefully reviewed by the Registry, although they may have been biased toward the reporting of more abnormal outcomes and were much less likely to be representative of the general population experience. When a pregnancy was prospectively reported, registration was accomplished by calling the Registry and verbally furnishing requested data or completed via a mailed questionnaire (Appendix D). To assure patient confidentiality the Registry assigned a Patient ID number, which was used as the reference ID for follow-up communication with the reporting health professional.

Near the estimated date of delivery, follow-up was obtained through a short follow-up form sent to the health 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 lamotrigine exposure and pregnancy outcome determination was obtained. A report could also be closed as “lost to follow-up” when the Registry did not receive the above minimum requirements. Reports of exposures were closed as “lost to follow-up” only after the reporting health professional had been repeatedly contacted for follow-up information well beyond the expected delivery date, or if the reporting health professional could no longer locate the patient. Only data from “closed” reports of exposed pregnancies with known outcomes were summarized in this Report.

The Registry continually made efforts to assure patient confidentiality within the Registry. Earlier in the Registry’s history, the Registry collected maternal date of birth, (but later began collecting the mother’s age at conception) and requested an unspecified identifier of the reporter’s choice (other than name), rather than patient initials and/or chart number. Later it was felt that the Registry should make a further effort to assure patient anonymity in the Registry, and therefore, no patient identifier which could compromise patient confidentiality was collected. The patient identifier was a Registry assigned patient identification number provided to the reporter at the time the patient was registered.

Independent review by specialists in epidemiology, neurology, and teratology provided

interpretation of the data and provided 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 sought IRB approval from Western IRB (WIRB®) in December 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 with the provision of additional required quarterly interim status reports.

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 May 7, 2003, WIRB® approved a request for a waiver of authorization for use and disclosure of PHI. WIRB® determined that documentation received from this Registry satisfied 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 lamotrigine exposures in pregnancy for major defects that may 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, or 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 from birth defects surveillance programs, which define a child with a birth defect as follows: any live or stillborn infant, or electively terminated fetus, of any gestational age with a major structural or chromosomal abnormality diagnosed before 6 years of age, however outcomes were generally reported during the first year of life. Because access to pediatric evaluations and records to obtain follow-up information about the presence of defects was beyond the scope of its methods, the Registry primarily monitored the frequency of major defects that were external, recognizable in the delivery room and/or symptomatic shortly after birth. Minor defects and those diagnosed on an out-patient basis, weeks to months after delivery, were not consistently ascertained and were therefore not included in the Registry. To provide consistency in the definition of major defects in this Registry, the CDC MACDP criteria were used as a guide for evaluation of defects (Correa-Villasenor *et al,* 2003, Correa *et al*, 2007). However, all reported defects are described in this Report and were reviewed by the Advisory Committee for inclusion as major defects for analysis. Birth defects not meeting the inclusion criteria and conditions not classified as birth defects appear in Appendix B.

The Registry disqualified as defects those findings that were present in infants, ≤36 weeks’ gestation (or weighing ≤2500 gm, if gestation age is not available) and were attributable to prematurity itself, such as patent ductus arteriosus or inguinal hernias.

Genetic disorders, such as Trisomy 21, were also excluded from the defects classification as they are not likely to be related to drug exposure. In addition, anatomic findings from prenatal sonography, such as "mild hydronephrosis" and choroid plexus cysts, which were not detected by the examining physician at birth, were excluded from the defects classification for this Registry. Likewise, 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.

Exclusions of Reported Exposures

For this Registry, emphasis was placed on prospective registration of pregnancies involving use of lamotrigine during pregnancy. However, the Registry encouraged reporting of all known prenatal exposures to lamotrigine, though not all reports were appropriate for inclusion in the analysis of data. Pregnancies included in the data analysis were those prospectively registered by health care providers. 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 were summarized in Appendix C. Retrospective reports from health care providers were also received in the Registry. These outcomes were reviewed and were helpful for detecting a possible pattern of defects. Retrospective reports were excluded from the Registry data, but retrospectively reported birth defects are summarized in Section 4 as data from other sources.

Analysis

An important aspect of the Registry was the Advisory Committee formed to oversee the process and results. The Committee was composed of representatives from GlaxoSmithKline and external specialists in epidemiology, neurology, obstetrics, and teratology, who reviewed all the Registry data on an ongoing basis and 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 each Report contained historical information as well as new data, the most recent report completely replaced all previous Reports. These Reports were available to health care providers treating this specialized population and reported exposed pregnancies to the Registry or who requested this information.

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 beginning at week 14, and the third trimester beginning at week 28. It should be noted that no birth defect rates were calculated in the various subgroups until a sufficient number of cases were obtained.

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 remaining outcomes involving birth defects. Fetal deaths and induced abortions without reported birth defects were excluded from this calculation. Due to the likelihood of inconsistent identification of defects in spontaneous pregnancy losses < 20 weeks' gestation and that the earlier in pregnancy the spontaneous loss occurs the more likely it is due to a fetal abnormality

incompatible with life, 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 5.

To determine if the risk of birth defects in pregnancies exposed to lamotrigine was elevated, the proportion of birth defects in all prospectively reported pregnancies was compared with those reported in the literature for the general population and for completed pregnancies in cohorts of women with epilepsy. Data from the Collaborative Perinatal Project which used a broader case definition, longer follow-up after birth, and prospective case ascertainment, have indicated birth defect rates as high as 5%-7% (Chung *et al*, 1975). Other sources using the CDC case definition and prospective ascertainment show lower rates of all birth defects, approximately 2-3% depending on time of ascertainment after birth (Correa *et al*, 2007). Comparison of rates of birth defects in the Lamotrigine Pregnancy Registry to rates observed in the general population could overestimate risk related to lamotrigine use because of 1) elevated risk associated with other antiepileptic drugs also used by women in this Registry and 2) elevated risk associated with maternal epilepsy. Because the increased risk of birth defects in the literature is associated with AED polytherapy, the Registry monitored the frequency of polytherapy in the prospectively reported pregnancies.

To determine whether there was a specific type of defect that could be associated with lamotrigine use, all prospectively and retrospectively reported defects were reviewed for patterns of birth defects that could suggest a specific etiology.

Individual birth defects were evaluated for timing of exposure to lamotrigine relative to the origins of the defect, presence of other causes (e.g., recognized genetic or chromosomal defect or exposure to a known teratogen), whether the defect was totally unknown or a previously unseen event, and whether there was a unique combination of defects. The Data Summary section of this Report describes the independent reviewers' assessments of the data according to these criteria.

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

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

Infants with only transient or infectious conditions, biochemical abnormalities, or minor defects 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 infants with minor defects are noted in the following tables of reports of infants with conditions other than birth defects.

Prospective Registry – 1st Trimester Exposure

1. First postnatal visit "slight jitteriness of legs", not seen at second visit.
2. A primary anastomosis performed for localized volvulus of ileum with dilated loops filled with meconium of normal consistency. Colon contained meconium, but not Meckel's diverticulum. The gall bladder, liver, spleen, and stomach were normal. Bowel rotation normal.
3. Suspected infection.
4. Mild jaundice.
5. Mild colic and gestational reflux.
6. Umbilical cord around infant's neck at delivery.
7. Slight tapering of the distal metacarpals.
8. Respiratory rate = 60 at birth. Required oxygen at 1 hour. At 3 hours post delivery, good breath sounds but slightly indrawing.
9. Slight growth retardation.
10. Non-development of fetus.
11. Jaundice for 10 days.
12. Umbilical cord around the neck - slipped over.
13. Massive pulmonary hemorrhage immediately following birth; full resuscitation given along with blood, fresh frozen plasma and vitamin K. Infant was pronounced dead 3 hours after delivery. Postmortem showed no anatomical abnormalities.
14. Web toe (right foot middle digits) and jaundice.
15. Slight bruising.
16. Jaundice.
17. Cyanosis of the face observed for the first three days after birth, attributed to delivery.
18. Slight respiratory problem after birth observed for some hours.
19. Ultrasound showed several periventricular cysts (pseudo cysts) thought to be secondary to intrauterine cytomegalovirus infection. Respiratory distress and a patent ductus arteriosus dilatation of side ventricle. A year later, no developmental defect noted.
20. Amniotic fluid discolored.
21. Respiratory distress and severe bradycardia immediately after birth. Apgar scores were 10/1, 1/5, 7/10. Treated for streptococcus pneumonia.
22. The mother experienced placental abruption at week 32. The neonate was not able to be saved, the autopsy was normal.
23. Umbilical cord around the neck.

Prospective Registry – 1st Trimester Exposure (continued)

24. After the birth, the baby experienced apneic conditions 3 times. The reporter did not think the condition was related to lamotrigine.

25.** Facial asymmetry, especially of the mandible.

26.** Wide set eyes, no epicanthic folds, infraorbital creases, broad nose, large mouth, bilateral undescended testes, sinus-bridge of nose, right facial palsy, persistent patent ductus arteriosus (PDA) (M-ECHO, MRI normal).

27.** Light facial dysmorphy: no philtrum, syndactyly 2nd and 3rd toes bilateral.

28. Perinatal asphyxia; meconium trachea intake. The newborn baby was moved to ICU and intubated.

29. Heart murmur was noted and later had disappeared. The pediatrician clarified that the child was healthy.

30. 4 nevi with growth tendency on head, ears, chest and feet. No other pathologic findings.

31. Mild retrognathia and glandular hypospadias.

32. Incidental 2.0 x .7 cm extra – axial hemorrhage in right fronto-parietal temporal region (questionable epidural vs subdural) uncovered on CAT Scan when baby had confined apnea/bradycardia episode without sequel. Probably secondary to vacuum assists to non-spontaneous vaginal delivery in combination with moderately severe shoulder dystocia and variable decelerations.

33. Intrauterine growth retardation. Premature delivery.

34. Jaundice just after the birth, but did not need phototherapy.

35. Two-vessel cord, but no problem noted.

36. Heart murmur was heard at birth and taken for a defect, although it disappeared before any investigation was done.

37. Acid reflux.

38. Possible tracheomalacia, but baby was feeding well at time of the report.

39. Patient had to undergo a caesarean section because of transient fetal low heart rate; at time of report the infant's condition was fair.

40. Respiratory problems – atelectasis right lung. Child has slight asthmatic bronchitis.

41. Slight bruising of little toe. Strawberry nevi.

42. Dehydration.

43. Index fingers on both hands are longer than middle fingers.

44. Mild left brachial plexus traction injury probably related to large size of fetus. Very mild weakness of left upper limb, completed resolved at one month.

45. Intrauterine fetal demise at approximately 36 weeks. Per autopsy: 1) Segmental umbilical cord dilatation with marked dilatation of umbilical vein; no evidence of thrombosis; 2) Transverse skin/soft tissue depression at superior/medial aspect of both legs, probably due to umbilical cord entrapment; 3) Pedunculated rudimentary 6th digits at lateral proximal aspect of both 5th fingers; 4) Overlapped cranial plates; 5) Flattened nose; 6) Extensive skin sloughing; 7) Marked softening of internal organs; 8) No internal developmental abnormalities.

46. Hypospadias and hydrocele. The child was examined at 7 weeks of age by a pediatrician who was not sure that the hypospadias was real. Ultrasound of kidney and urethra were normal.

47. Second to last toe on each foot potentially slightly longer than others. Possible need for surgery in the future.

48. Two vessel umbilical cord.

49. Severe hypoglycemia at delivery.

50. "Innocent heart murmur". Cardiology consult was "ok".

Prospective Registry – 1st Trimester Exposure (continued)

51. Suspected amnion infection. Therapy with antibiotics for 7 days. Infection resolved.
52. Infant lived about 30 minutes after birth. Placenta torn away from uterine wall.
53. Infant transferred to NICU and subsequently died.
54. Ultrasound examination of the infant's head revealed asymmetry of lateral chambers of the brain (left greater than right), bilateral hyperechogenicity of choroid plexuses accompanied by distension of region "C"; rounded occipital horn on the left side; third and fourth brain chambers with no changes. Umbilical cord was wrapped around the infant's neck two times and one time around the trunk.
55. Cord wrapped around neck and infant was initially slow to respond.
56. Infant hospitalized due to staphyloccomia.
57. Infant hospitalized due to prematurity.
58. Intrauterine growth restriction, borderline small.
59. Ring finger on both hands bends very far back.
60. Infant small due to patient's smoking.
61. Possible blindness (genetic) and anemia of unknown etiology.
62. Placental abruption. Prematurity requiring ventilation and tracheostomy.
63. Meconium present in amniotic fluid.
64. Anxiety and seizures secondary to absence Phenobarbital Syndrome.
65. Infant delivered face up and requiring suctioning due to cord around neck.
66. Vertical nystagmus/opsoclonus.
67. Scar after a cleft lip – surgery not required.
68. "Intense physiologic icterus of the newborn" and an umbilical hernia.
69. Meconium aspiration and breathing problems attributed to high altitude.
70. Small hemangioma on arm.
71. Cord wrapped around neck; infant died from strangulation.
72. Heart murmur and cord wrapped around neck.
73. Mitral incompetence.
74. Bilateral congenital dislocation of hips.
75. Undeveloped lungs.
76. Prematurity and jaundice.
77. Nuchal cord wrapped twice.
78. Home delivery, no fetal movement-infant did not survive.
79. Fetal distress.
80. Poor sucking reflex at birth.
81. Jaundice.
82. Lethargic at birth.
83. Death due to aspiration of amniotic fluid, maceration, and pulmonary atelectasis.
84. Benign heart murmur.
85. Mild colic.
86. Infant died 1 hour after birth. The placenta was tested and said to be abnormal.

Prospective Registry – 1st Trimester Exposure (continued)

87. Abnormal placenta and meconium stained amniotic fluid.
88. Port wine stain on forehead.
89. Palpable metopic suture.
90. Prolonged hypoglycemia.
91. Spinal meningitis.
92. Bilateral hydroceles, macropenis, grade 2/6 systolic heart murmur.
93. Inguinal hernia, requiring surgical repair at less than two months of age.
94. Tremors after delivery.
95. NICU for one week for "undiagnosed etiology."
96. Shoulder fracture occurred secondary to the extraction.
97. Jaundice and failed hearing test in left ear.
98. Macrosomia.
99. Infant hospitalized for 9 days, needed intubator.
100. Infant swallowed meconium during delivery, was intubated and admitted to the NICU.
101. Trouble nursing.
102. Delivery complications. Infant had decreased heart rate during labor and meconium staining.
103. Apnea and polycythemia.
104. Baby premature, on ventilator after delivery and had acid reflux. Infant hospitalized for double pneumonia.
105. Infant remains in hospital requiring feeding, no longer needs artificial respiration.
106. Baby remained in NICU for 48 hours due to low blood glucose.
107. Transient tachypnea.
108. Jaundice, blood glucose decreased.
109. "Neonatal adaptation disorder", "Dystrophic habitus." The mother had idiopathic thrombocytopenic purpura during pregnancy.
110. Severe intrauterine growth retardation.
111. Prematurity.
112. The infant was in the NICU prophylactically; fetal demise of a twin occurred at approximately 19 weeks' gestation.
113. Neonatal abstinence syndrome related to mother's use of methadone.
114. Neonatal abstinence syndrome related to mother's use of methadone.
115. Reflux.
116. Attached frenulum of mouth requiring surgical detachment.
117. Turned in foot.
118. Umbilical cord wrapped around neck twice.
119. Abnormal placenta at delivery – half of placenta was "dead."
120. Small feeding difficulty, hypoglycemia, non-structural disorder (not specified). Small for gestational age.
121. Nuchal cord complications – cord was tight around baby's head (near ear level).
122. Baby went to the Neonatal Intensive Care Unit (presumably due to preterm delivery and maternal oligohydramnios).

Prospective Registry – 1st Trimester Exposure (continued)

123. Pulmonary hypertension.

124. Heart murmur reported by pediatrician. Fetal echo was normal during pregnancy.

125. Mild tracheomalacia, no surgical intervention required.

126. Ankyloglossia (tongue tie) expected to require surgical intervention.

127. Pulmonary issues related to pre-term delivery.

128. Cord was wrapped around baby's neck.

129. Dilated fetal 3rd ventricle noted on sonogram at 33 weeks' gestation and 39 weeks' gestation with no growth noted.

130.*** Autism reported at approximately 1 year of age; previously misdiagnosed as deafness.

131.* Premature delivery.

132.* Infant born with meconium in mouth, meconium not swallowed, no lung issues; difficulty maintaining body temperature for 4-5 days, resolved with skin-to-skin contact.

133.* Forceps used during delivery because inefficient expulsive effort led to fetal cardiac rhythm disorder.

134.* Chromosomal non-viable fetus.

135.* Fetal heart valves open per echocardiogram. Health care provider reports this condition to be genetic – infant's mother and maternal grandmother had the same condition. Infant lethargic and not feeding well due to suction delivery.

136.* Infant born with fluid on lungs, incubated for 2 days, issue resolved.

137.* Questionable simian crease, which is awaiting pediatric evaluation.

138.* Infant born with Anti-E.

139.* Meconial amniotic fluid.

140.* Undescended right testis and right hip click.

141.* Tacchyarrhythmia.

142.* Fetal cardiac arrhythmia.

Prospective Registry – 2nd Trimester Exposure

1. Permeable ductus arteriosus and hip click at delivery. Both disappeared on repeat examination one hour later.

2. Mother reported infant disliked breastfeeding. Milk was grayish and watery. After breastfeeding, infant was awake and did not sleep. This improved when breastfeeding stopped.

3. Barbiturate found in newborn's blood.

4. Reflux requiring hospitalization.

5. Jaundice and weight loss.

6. Missed labor, macerated fetus.

7. Fetal arrhythmia.

8. Right ear failed initial hearing screen.

9. Bilateral preauricular skin tags.

10. Infant on continuous positive airway pressure after delivery.

11.* Infant developed jaundice on day 3, resolved with "conservative management" including fluids and ultraviolet lights. Infant was Coombs positive.

Prospective Registry – 3rd Trimester Exposure

1. Intrauterine growth retardation.

Retrospective Reports

1. Infant with squint (strong family history of squint).
2. Shivers.
3. Jitteriness.
4. Respiratory distress and acidosis requiring ventilation for 3 days.
5. Jaundice, Respiratory Distress Syndrome due to prematurity.
6. Respiratory insufficiency.
7. Abnormal on an oto-acoustic emission test; no emission on right side (small canal); normal emission on the left side, sepsis.
8. Hyaline membrane disease, sepsis.
9. Infant irritable.
10. Mild postnatal jaundice.
11. Two reports of jaundice requiring readmission.
12. Poor head control at birth, mild tachypnea, mildly elevated temperature, both resolved. Muscle tone improved over the hospital stay. No dysmorphic features. Event attributed to the mother's use of magnesium during labor.
13. Infant was pale, had broad forehead, had very distinctive ears with pointed helix on left - ear measured 3.3 cm, prominent anti-helix on right - ear measured 3.0 cm, eyes were normal, broad nasal bridge, questionable trismus - palate normal, small chin, neck short with redundant skin, heart had slight gallop, right testes was retractile, left testes was not fully descended, extra hair on lower back, long fingers and toes with digitalized thumb.
14. Spontaneous abortion at week 12. The patient was told that the fetus was not normally developed.
15. Fetal valproate syndrome.
16. Autism/Asperger's syndrome.
17. Breathing problems immediately after birth, growing and drinking poorly at time of report.
18. Spontaneous abortion. Histology showed fetal tissue with chronic villi.
19. Two reports of infants with finely tapered fingers.
20. Cerebral bleeding. Infant died within a week of birth.
21. Webbed feet (2nd and 3rd toes on both feet).
22. Erb's palsy, brachial plexus palsy, congenital disorder.
23. Patent ductus arteriosus.
24. Slight joining of the 2nd and 3rd toes on both feet.
25. Laryngomalacia. Respiratory problems requiring hospital treatment. Infant died at five months of age due to respiratory problems and infections.
26. Right anterior leg nevus.
27. Apnea, gastro-esophageal reflux.
28. Meconium staining in amniotic fluid.
29. Peripheral facial paralysis; minor left inferior lip hypotonia – resolved.
30. Empty amniotic sac without embryo.
31. Blind sacrococcygeal fistula.

Retrospective Reports (continued)

32. Dermoid cysts on left brow and mouth.

33. Sacral dimple.

34. Postnatal development of juvenile rheumatoid arthritis at ~1 year of age.

35. "Dysmorphic face" including extrusion of the tongue and slight epicanthus. The infant also had hypotonia and gastroesophageal reflux.

36. Baby died due to SIDS.

37. Deafness.

38. Two reports of infants with facial palsy.

39.** Partial syndactyly of the skin (no bone involved) between the second and third digits (toes) bilaterally.

40. Maternal cardiac arrhythmia. Dilatation of the cerebral ventricles, but not hydrocephalus, by postnatal ultrasound. At birth, the child was a bit growth inhibited.

41. Apnea, irregular pulse, tachypnea, somnolence, cyanosis, listlessness, increased respiration rate, tachycardia, and tiredness. Echocardiogram showed benign peripheral pulmonary stenosis. Symptoms resolved.

42. Port wine stain on trunk and limbs, predominantly on the left side.

43. Labia minora epidermal fusion due to transient estrogenic impregnation disorder.

Note: One case of an undescended right testicle has been reclassified upon receipt of further information and is now listed on Table 8.

Prospective Patient Reports

1. Lungs were not fully developed and infant had heart disease.

Retrospective Patient Reports

1. Pyloric stenosis.

2. Pierre Robin Sequence, cleft palate – complete, heart murmur.

3. Down syndrome; septal heart defect, type not specified. The mother has Type 1, insulin-dependent diabetes, diagnosed prior to pregnancy.

*denotes cases that are new since the last Report

**denotes cases that were previously listed as birth defects and have now been classified as minor defects by the Lamotrigine Advisory Committee definition of birth defects

***denotes case that was previously classified as a birth defect and upon receipt of additional information, was reclassified as no defect

Appendix C: Patient Reported Prenatal Lamotrigine Exposures

Criteria for inclusion in the prospective Registry required registration and follow-up by a health care professional. Prospectively registered pregnancies that were reported to the Registry by the patient and confirmed by a health care professional were included in the prospective registry. Patient reported pregnancies which had no health care professional confirmation of the pregnancy information were not included in the prospective registry.