The Sumatriptan/Naratriptan/ Treximet Pregnancy Registry

Final Report

1 January 1996 through 19 September 2012

Issued: April 2013

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

A Project Conducted by GlaxoSmithKline

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POLICY FOR ORAL PRESENTATION OF DATA

The sponsor encourages the responsible sharing of the information contained in this Report with health 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 Report without written permission of GlaxoSmithKline.**

1. The data in Table 2 (Prospective Registry - Exposure in Pregnancy by Earliest Trimester of Exposure and Outcome) are the most appropriate for presentation. Presentation of results stratified by earliest trimester of exposure is imperative.
2. A statement regarding the Committee Consensus (page 26) must be referenced in any presentation of these data, including emphasis on the limitations of a voluntary prenatal drug exposure Registry such as this.

REGISTRY CLOSURE INFORMATION

The Registry began enrollment in January 1996 and ended enrollment in January 2012.

Follow-up of existing enrollments continued through September 2012.

This Final Report reflects all data collected over the life of the Registry.

SUMATRIPTAN/NARATRIPTAN/TREXIMET

PREGNANCY REGISTRY

FINAL REPORT

1 January 1996 – 19 September 2012

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TABLE OF CONTENTS

FOREWORD

This Final Report describes the experience of the ongoing study of prospectively reported pregnancy outcomes in the Sumatriptan/Naratriptan/Treximet Pregnancy Registry for all reporting countries and covers the period 1 January 1996 through 19 September 2012, and replaces the previous Interim Report covering the period 1 January 1996 through 31 October 2011. This Report also includes data collected prior to the initiation of the Registry.

Sumatriptan, naratriptan, and Treximet are medications used to treat migraines. Because of the potential for unintentional exposure during the first trimester of pregnancy and potential risks of any new chemical entity, the Registry was established as part of an ongoing program in post-marketing epidemiologic surveillance. Through this Registry patients exposed to sumatriptan, naratriptan, and Treximet during pregnancy were identified, their pregnancies were followed, and the outcomes were ascertained by voluntary reports from health care providers.

The Registry was intended 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.

The data in this Report represent the experience of a relatively small number of pregnancies; recommendations for use in pregnancy based on this small sample size are, therefore, inappropriate.

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

Jan Brandes, MD Nashville Neuroscience Group	Sara Ephross, PhD Worldwide Epidemiology GlaxoSmithKline
Roger Cady, MD Headache Care Center	Arseniy Lavrov, MD Director, Neurosciences MDC GlaxoSmithKline
Janet Cragan, MD, MPH National Center on Birth Defects and Developmental Disabilities Centers for Disease Control and Prevention US Public Health Service	Marion Verp, MD The University of Chicago Department of OB/GYN The Chicago Lying-in Hospital
Merle Diamond, MD Diamond Headache Clinic	

GlaxoSmithKline sponsored the Sumatriptan/Naratriptan/Treximet Pregnancy Registry. For questions regarding these medications, please contact GlaxoSmithKline's Customer Response Center at (888) 825-5249.

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SUMATRIPTAN/NARATRIPTAN/TREXIMET PREGNANCY REGISTRY INTERNATIONAL FINAL REPORT 1 JANUARY 1996 THROUGH 19 SEPTEMBER 2012

EXECUTIVE SUMMARY

There is no evidence of teratogenicity from preclinical studies of sumatriptan and naratriptan. Treximet is a sumatriptan and naproxen combination treatment for acute migraine. Preclinical studies of naproxen alone, and in combination with sumatriptan, have reported increased rates of fetal abnormalities. Clinical studies have confirmed an increased risk of premature closure of the ductus arteriosus following third trimester exposure to naproxen and other NSAIDs. However, clinical and epidemiological data concerning risks following first and second trimester exposure to naproxen are less clear. Therefore, the medical division of GlaxoSmithKline sponsored the Sumatriptan/Naratriptan/Treximet Pregnancy Registry as part of an ongoing program in epidemiologic safety monitoring. Women with migraines may require or be unintentionally exposed to sumatriptan, naratriptan, or Treximet during pregnancy. The Registry was considered important because of the potential for exposure in the first trimester of pregnancy and the unknown risks in pregnancy for any new chemical entity.

The purpose of the Registry was to detect an early signal of teratogenicity associated with prenatal use of sumatriptan, naratriptan, or the sumatriptan/naproxen combination therapy also known as Treximet, if it existed, by collecting voluntary prospective reports of sumatriptan, naratriptan, and Treximet prenatal exposures. Sumatriptan (Imitrex®/Imigran®), Naratriptan (Amerge®/Naramig®) and sumatriptan with naproxen sodium (Treximet™) are assigned FDA Pregnancy Category C status, meaning that safety in human pregnancies has not been determined. 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, but proportions of birth defects in sumatriptan-, naratriptan-, and Treximet-exposed pregnancies were compared to proportions of birth defects reported in the medical literature. One limitation of an exposure-registration study is that the pregnancies reported may not be representative of the target population. Because reports of exposure are voluntary, they are subject to numerous selection biases.

Throughout this Report, references to sumatriptan include exposures to Imitrex® and/or Imigran®, references to naratriptan include exposures to Amerge® and/or Naramig®, and references to Treximet™ include exposures to sumatriptan in combination with naproxen sodium.

Prior to April 2001, the reports of exposures to sumatriptan and naratriptan were represented in two separate registries – the Sumatriptan Pregnancy Registry and the Naratriptan Pregnancy Registry. Since April 2001, the Registries have been combined. In June 2008, Treximet was added to the Sumatriptan and Naratriptan Pregnancy Registry. There were 9 reports of exposure to both sumatriptan and naratriptan (two of which were lost to follow-up without pregnancy outcome available). A conservative position has been taken, which was to report (and cross-reference) the dual exposure as

both a sumatriptan and a naratriptan exposure. There were no reports of dual exposures to sumatriptan and Treximet or naratriptan and Treximet.

This Report contains a description of all prenatal exposures to sumatriptan, naratriptan, or Treximet voluntarily and prospectively reported to the Registry. Prospectively reported exposures are those reported during the pregnancy before the pregnancy outcome is known. Because the outcome of the pregnancy was unknown when the prenatal exposure was reported, follow-up to determine the pregnancy outcome was required. Prospective reporting of ongoing pregnancies prior to knowledge of the pregnancy outcome reduces bias and permits estimation of the proportion of birth defects following exposure.

Retrospective reports where the pregnancy outcome was known at the time of reporting were also reviewed. Retrospective reports can be biased toward the reporting of more unusual and severe outcomes and are less likely to be representative of the general population experience. Therefore, the inclusion of such reports for calculation of the proportion of birth defects is inappropriate. The purpose of summarizing the retrospective reports is to assist in the detection of any unusual patterns that may have existed among the reported birth defects.

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

As of 19 September 2012, the Sumatriptan/Naratriptan/Treximet Pregnancy Registry had a total of 673 pregnancy exposures to sumatriptan, naratriptan, and/or Treximet with outcome information reported, 610 with pregnancy exposures to sumatriptan (7 sets of twins and 1 set of triplets), 50 with pregnancy exposures to naratriptan, 7 exposures to both sumatriptan and naratriptan, and 6 exposures to Treximet. Six of the exposures to both sumatriptan and naratriptan occurred in the first trimester. One was an exposure to naratriptan in the second trimester and sumatriptan in the third trimester (see Table 1b).

Sumatriptan – As of 19 September 2012, 626 pregnancy outcomes have been obtained from 617 pregnancies (includes 7 sets of twins and 1 set of triplets) involving exposure to sumatriptan. Of the 528 outcomes reported involving earliest prenatal exposure in the first trimester, there were 474 live-born infants, 34 spontaneous pregnancy losses, 15 induced abortions, and 5 stillbirths. Of these outcomes reported involving earliest prenatal exposure in the first trimester, there were 20 reports of birth defects, 16 live-born infants (1 also with a first trimester exposure to naratriptan), 1 stillbirth, and 3 induced abortions with reported birth defects. Of the 78 pregnancy outcomes following earliest prenatal exposure in the second trimester, all were live-born infants. Of these, there were 3 infants with birth defects. There have been 16 pregnancy outcomes reported following

earliest exposure in the third trimester; all outcomes were live-born infants without reported birth defects. There have been 4 pregnancy outcomes obtained where earliest trimester of exposure was unspecified. These include 3 live-born infants without reported birth defects and 1 induced abortion with a reported birth defect. The 24 birth defect reports are summarized in Table 3.

The observed proportion with birth defects (n=20) for outcomes following earliest exposure in the first trimester (n=478, excluding fetal deaths and induced abortions without reported defects and all spontaneous pregnancy losses) is 4.2% (95% Confidence Interval (CI): 2.6% - 6.5%). The observed proportion with birth defects (n=24) for outcomes with any trimester of exposure (n=576, excluding fetal deaths and induced abortions without reported defects and all spontaneous pregnancy losses) is 4.2% (95% CI: 2.7% - 6.2%)(Fleiss, 1981).

Naratriptan – As of 19 September 2012, 57 pregnancies with known outcomes have been reported. Of the 52 with first trimester exposures, there were 46 live infants, 5 spontaneous pregnancy losses, and 1 induced abortion. Of these, there was 1 live infant with a birth defect reported (also with a first trimester exposure to sumatriptan). There were 5 live births following earliest prenatal exposure in the second trimester exposure with no defects reported.

Treximet – As of 19 September 2012, 6 pregnancy exposures to Treximet with known outcomes have been prospectively reported, 5 pregnancies with earliest Treximet exposure in the first trimester and 1 in the second trimester. Of these 5 first trimester exposures, there were 4 live births and 1 spontaneous pregnancy loss. The 1 outcome following earliest prenatal exposure in the second trimester was a live-born infant. No defects were reported in any of these Treximet exposure outcomes. Although only limited data are available regarding Treximet exposure during pregnancy, an increased risk of premature closure of the ductus arteriosus is recognized following third trimester exposure to naproxen containing products.

Although the number of pregnancies accumulated to date in the Registry represents a sample of insufficient size for reaching reliable and definitive conclusions regarding the risk of sumatriptan or naratriptan to pregnant women and their developing fetuses, the Registry findings do not suggest evidence of a large increase in the proportion of birth defects among the prospectively reported pregnancies. Because of the international scope of the Registry, the voluntary nature of enrollment, and other methods used, no comparable group of unexposed pregnant women exists with whom to directly compare the observed prevalence of defects.

The Sumatriptan/Naratriptan/Treximet Pregnancy Registry used the inclusion and exclusion criteria of the Metropolitan Atlanta Congenital Defects Program (MACDP) list of major birth defects. 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, Correa *et al*, 2008). For reference, the Advisory Committee adopted the list of birth defects recognized by the MACDP. This 6-digit code list is available from the CDC web site at: http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf. The

prevalence of birth defects among deliveries to women with migraine has been estimated at 3.4% (95% CI: 2.1% - 4.6%) (Wainscott *et al*, 1978) and 2.9% for major malformations (Nezvalová-Henriksen *et al*, 2010, Nezvalová-Henriksen *et al,* 2012). No consistent pattern of defects has been observed among the birth defects reported to the Registry.

Poor enrollment and high rates of loss to follow-up within the Registry over an extended period of time led the Committee to review whether continuation of the Registry would add substantial new information concerning the risk of major birth defects following *in utero* exposure to the anti-migraine medications of interest. The low enrollment rates suggested continuation of the Registry would offer little additional power to rule out more moderate increases in the risk of birth defects. Indeed the Committee noted the stability of the sumatriptan defect risk estimate over many years indicating that continuation of the registry was unlikely to affect the width of the confidence intervals around the risk estimate and hence the level of risk the registry was able to exclude.

The Committee reviewed data on over 500 prospectively enrolled first trimester sumatriptan exposures during pregnancy. Despite this limited sample size, lack of an appropriate comparison group and the high lost to follow-up rate, these data do not indicate a signal for major teratogenicity. This is supported by larger datasets (such as the Swedish Medical Birth Register), which have failed to observe an increased risk of birth defects versus the general population. This gives a level of reassurance concerning the risk of all major birth defects following *in utero* sumatriptan exposure. The Committee recommended planned termination of this Registry around the current level of reassurance for overall birth defects for sumatriptan, a level of reassurance which was unlikely to change significantly at the level of enrollment.

The Committee notes the small number of prospectively enrolled naratriptan and Treximet pregnancy exposures. Poor enrollment and high rates of loss to follow-up have continued despite several awareness and reporting incentive initiatives. This may reflect limited use of these medications in women of childbearing age or the failings of the study design to adequately capture intermittently used anti-migraine medications. The Committee considers there is sufficient evidence that, despite corrective initiatives, this Registry was unable to meet its primary objective, in being adequately powered, to detect a signal of major teratogenicity for naratriptan and Treximet.

The Committee therefore recommended planned termination of this Registry for naratriptan and Treximet in light of the lack of feasibility of collecting information of further scientific value. Following this recommendation, GlaxoSmithKline submitted to the FDA documentation regarding discontinuation of the Registry. GlaxoSmithKline was informed on 10 January 2012, that the FDA had formally agreed to GlaxoSmithKline's proposal to end the Sumatriptan/Naratriptan/Treximet Pregnancy Registry. To complete data collection on all active patients, Registry closure was planned for mid-September of 2012 and the Registry actually was closed on 19 September 2012.

1 INTRODUCTION

The purpose of the Registry was to detect any major teratogenic effect in pregnancies inadvertently or intentionally exposed to IMITREX®/IMIGRAN® (sumatriptan), AMERGE®/NARAMIG® (naratriptan), or Treximet™ (sumatriptan with naproxen sodium). The combination of the large number of women with migraines who are of reproductive capacity and the lack of data concerning sumatriptan, naratriptan, or Treximet use during pregnancy made such a Registry an essential component of the ongoing program of epidemiologic studies of the safety of sumatriptan, naratriptan, and Treximet. This Registry was an observational, exposure-registration follow-up study. The study has undergone Institutional Review Board (IRB) review and approval (see 6.2.1 Institutional Review Board (IRB) Review, page 31). The IRB approval included a waiver from requiring patient informed consent for participation based on the Registry's process for protecting patient confidentiality. Additionally, the Registry submitted and received a HIPAA (Health Insurance Portability and Accountability Act) full waiver through the IRB. Patient confidentiality was strictly upheld. The intent of the Registry was to prospectively collect data concerning exposure to sumatriptan, naratriptan, or Treximet during pregnancy, potential confounding factors (such as exposure to other antimigraine medications, the number and severity of headaches/migraines occurring during pregnancy), and information related to the outcome of the pregnancy.

The Sumatriptan/Naratriptan/Treximet Pregnancy Registry was maintained by GlaxoSmithKline in consultation with specialists in obstetrics, neurology, internal medicine, epidemiology, pediatrics, clinical research, genetics, family practice, and teratology from academic centers and the Centers for Disease Control and Prevention (CDC), a US-based institution. These individuals constituted an Advisory Committee for the Registry and provided independent review of the data. The Sumatriptan Pregnancy Registry began in January 1996 and the Naratriptan Pregnancy Registry began in October 1997. They were managed as separate Registries up until April 2001, when they were combined to better address pregnancy exposures to both sumatriptan and naratriptan. There were 7 reports of exposures with outcomes with known exposure to both sumatriptan and naratriptan in the analysis. In June 2008, Treximet was added to the Sumatriptan and Naratriptan Pregnancy Registry. There were no reports of dual exposures to sumatriptan and Treximet or to naratriptan and Treximet.

2 PROSPECTIVE REGISTRY

An Interim Report was issued semiannually following the Registry Advisory Committee's review of new and previously received data. Each issue contained historical information, as well as new data received by the Registry, and therefore superseded all previous Reports. The new information in this Final Report includes data from all cases closed between 1 November 2011 and 19 September 2012.

This Registry was an international registry. At the end of the Registry, there were 673 sumatriptan, naratriptan, and/or Treximet exposures in pregnancy with outcomes which were registered from 18 different countries (Table 1a).

Reports of Infants with Conditions Other Than Birth Defects – As described in the Introduction, the purpose of the Registry was to detect any major teratogenic effect following a pregnancy exposure to sumatriptan, naratriptan, or Treximet. As described in the Methods section, live-born 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(s) reported may have indicated an unrecognized birth defect. These conditions, though sometimes reported, were not systematically collected and therefore not within the scope of this Registry to be evaluated. However, so as to provide all the information reported, this information, as well as birth defects which are excluded from the CDC Metropolitan Atlanta Congenital Defects Program (MACDP), are listed in Appendix A.

Table 1.a. Prospective Registry – Exposure in Pregnancy by Country of Origin[c]
1 January 1996 – 19 September 2012

Country	Sumatriptan[a]	Naratriptan[a]	Treximet[a]
Australia	6	0	0
Belgium	5	0	0
Brazil	0	1	0
Canada	16	6	0
Denmark	13	2	0
France	6	7	0
Germany	25	3	0
Ireland	1	0	0
Italy	7	2	0
Norway	5	0	0
Peru	0	1	0
Slovenia	1	0	0
Spain	3	1	0
Sweden	24	0	0
Switzerland	1	0	0
The Netherlands	10	0	0
United Kingdom	34	3	0
United States	460[b]	31[b]	6
Total	617	57	6

[a] Includes only patients with known pregnancy outcomes.
[b] Dual exposures to sumatriptan and naratriptan are included in both summaries (n=7).

Table 1.b. Populations for Analysis – Prospective Registry Cases Enrolled
1 January 1996 – 19 September 2012

	Overall
Sumatriptan	
Pregnancies Enrolled	810
Pending cases [1],[4]	0 (0%)
Cases lost to follow-up [2],[5]	193 (23.8%)
Reports included in analysis [3],[4]	617 (76.2%)
Naratriptan	
Pregnancies Enrolled	92
Pending cases [1],[4]	0 (0%)
Cases lost to follow-up [2],[5]	35 (38.0%)
Reports included in analysis [3],[4]	57 (62.0%)
Treximet	
Pregnancies Enrolled	9
Pending cases [1],[4]	0 (0%)
Cases lost to follow-up [2],[5]	3 (33.3%)
Reports included in analysis [4]	6 (67.7%)

[1] Cases where the outcome of pregnancy is not yet known
[2] Cases where the outcome of pregnancy has never been received despite requests
[3] Includes 7 reports with exposure to both sumatriptan and naratriptan
[4] Percentage based on total pregnancies enrolled
[5] Percentage excludes pending cases

2.1 SUMATRIPTAN

2.1.1 New Data Since the Last Report (1 November 2011 through 19 September 2012)

During this period, 2 additional pregnancies involving exposure to sumatriptan were prospectively registered. One of these pregnancies was closed with known outcome, and the other was lost to follow-up (the reporter could not identify the patient at the time of follow-up). Nine previously registered pregnancies were closed. Of these 9, 4 were closed with known outcomes and 5 were lost to follow-up (for 3 of these 5 cases, there was no response from the reporting health care provider; for 1 of these 5 cases, the patient did not remain under the reporter's care; and for the 1 other case, the HCP could not identify the patient at the time of follow-up). In total, 5 outcomes from 5 pregnancies were reported this period and added to Table 2.

Outcomes from pregnancies with earliest exposure in the first trimester:

Of the 5 outcomes obtained, 4 involved earliest exposure in the first trimester. All 4 of these outcomes were live-born infants without reported defects.

Outcomes from pregnancies with earliest exposure in the second trimester:

One live birth outcome was obtained involving earliest exposure in the second trimester, with no reported birth defects.

Outcomes from pregnancies with earliest exposure in the third trimester:

No new outcomes were obtained involving earliest exposure in the third trimester. All prospectively reported birth defects are described in Table 3.

2.1.2 Summary of Data

Through 19 September 2012, 810 reports of women exposed to sumatriptan during pregnancy have been registered prospectively. Of the 810 reports, none are pending outcome information. One hundred ninety three (193/810, 23.8%) were lost to follow-up. The 193 reports were lost to follow-up for the following reasons:

111 no response from the reporting health care provider
39 the patient did not remain under the reporting health care provider's care
21 the reporter could not identify the patient at time of follow-up from the information provided at time of enrollment
13 the reporting health care provider left the practice from which the report was made and left no forwarding address
5 no response to the reporter from the patient
4 patient refused to provide release of information

Of the 617 pregnancies with outcomes reported (Table 1.b), 626 outcomes (includes 7 sets of twins and 1 set of triplets) have been obtained (Table 2). Table 4 presents the distribution of reasons for treatment by outcome of pregnancy and earliest trimester of exposure. At this time, no pattern or relationship between outcomes and reason for treatment is evident.

Outcomes from pregnancies with earliest exposure in the first trimester:

Of the 528 outcomes reported involving earliest prenatal exposure in the first trimester, there were 458 live-born infants without reported birth defects (includes 4 sets of twins and 1 member of a fifth set of twins). There were 20 reports of birth defects. Of these 20 reports, 16 were live-born infants (1 of which also had a first trimester exposure to naratriptan and 1 includes 1 member of a set of twins), 1 was a stillbirth, and 3 were induced abortions. There were also 12 induced abortions and 4 stillbirths (includes 1 member of a set of twins) without birth defects reported. In addition, there were 34 spontaneous pregnancy losses (includes 1 member of 1 set of twins, and both members of another set of twins).

Outcomes from pregnancies with earliest exposure in the second trimester:

Of the 78 outcomes reported involving earliest exposure in the second trimester, there were 75 live-born infants without reported birth defects (includes 1 set of triplets) and 3 live-born infants with birth defects.

Outcomes from pregnancies with earliest exposure in the third trimester:

There have been 16 outcomes obtained from pregnancies involving earliest exposure in the third trimester. All 16 outcomes were live-born infants without reported birth defects.

Outcomes from pregnancies with earliest trimester of exposure unspecified:

There were 4 outcomes reported where earliest trimester of exposure was unspecified. Outcomes include 3 live infants born without reported birth defects and 1 induced abortion involving a birth defect.

Overall, among the prospective reports of sumatriptan exposure in pregnancy, there were a total of 24 reports of birth defects (Table 2). Of these 24, there were 16 live-born infants, 3 induced abortions, and 1 stillbirth with reported earliest pregnancy exposure in the first trimester, 3 live births with reported earliest exposure in the second trimester, and 1 induced abortion with earliest trimester of exposure unspecified.

There are a total of 7 reports with outcomes of exposure to both sumatriptan and naratriptan during pregnancy. Six reports were of exposures to sumatriptan and naratriptan in the first trimester (1 infant with a birth defect) and 1 with a sumatriptan exposure in the third trimester and to naratriptan in the second trimester. All of these pregnancy outcomes were live infants.

2.2 NARATRIPTAN

2.2.1 New Data since the Last Report (1 November 2011 through 19 September 2012)

During this period, there were no additional pregnancies involving exposure to naratriptan prospectively registered. Two previously registered pregnancies were deemed lost to follow-up in this reporting period. There were no new outcomes reported this period.

2.2.2 Summary of Data

Through 19 September 2012, 92 reports of women exposed to naratriptan during pregnancy have been registered prospectively. Of the 92 reports, none are pending outcome information. Thirty-five pregnancies (35/92, 38.0%) were lost to follow-up. The 35 reports were lost to follow-up for the following reasons:

22 no response from the reporting health care provider
8 the patient did not remain under the reporting health care provider's care
4 the reporter could not identify the patient at time of follow-up from the information provided at time of enrollment
1 the reporting health care provider left the practice from which the report was made and left no forwarding address

There are 57 pregnancies with outcomes reported (Table 2). Table 4 presents the distribution of reasons for treatment by outcome of pregnancy and earliest trimester of exposure. At this time, no pattern or relationship between outcomes and reason for treatment is evident.

Outcomes from pregnancies with earliest exposure in the first trimester:

Of the 52 pregnancies with outcomes reported involving earliest exposure in the first trimester, there were 45 live-born infants without reported birth defects, and 1 live-born

infant with a birth defect (also an exposure in the first trimester to sumatriptan). There was also 1 induced abortion without a reported defect and 5 spontaneous pregnancy losses. The outcome with a birth defect is described in Table 3.

Outcomes from pregnancies with earliest exposure in the second trimester:

There were 5 outcomes with earliest exposure in the second trimester. All were live-born infants without reported birth defects.

2.3 TREXIMET

2.3.1 New Data since the Last Report (1 November 2011 through 19 September 2012)

During this period, no additional pregnancies involving exposure to Treximet were prospectively registered. Three previously registered pregnancies were closed during this reporting period. Of the 3 previously registered pregnancies closed during this reporting period, 1 was deemed lost to follow-up in this reporting period, and outcomes were reported for the other 2 pregnancies.

2.3.2 Summary of Data

Through 19 September 2012, 9 reports of women exposed to Treximet during pregnancy have been registered prospectively. Of the 9 reports, none are pending outcome information, and 3 were lost to follow-up. Two reports were lost to follow-up because there was no response from the reporting health care provider, and the other case was lost to follow-up because the reporter could not identify the patient at time of follow-up from the information provided at time of enrollment.

There are 6 pregnancies with outcomes reported (Table 2).

Outcomes from pregnancies with earliest exposure in the first trimester:

Of the 5 pregnancies with outcomes reported involving earliest exposure in the first trimester, there were 4 live-born infants without reported birth defects and 1 spontaneous pregnancy loss.

Outcomes from pregnancies with earliest exposure in the second trimester:

There was 1 outcome with earliest exposure in the second trimester. This outcome was a live-born infant without reported birth defects.

Table 2. Prospective Registry – Exposure in Pregnancy by Earliest Trimester of Exposure and Outcome
1 January 1996 – 19 September 2012

All Sumatriptan Exposures

Earliest Trimester of Exposure	Birth Defects			No Birth Defects Reported[a]				
	Live Birth	Fetal Death[c]	Induced Abortion	Live Birth	Fetal Death[c,d]	Induced Abortion[d]	Spontaneous Pregnancy Loss[b,d,f]	Total Outcomes[g]
First	16[e]	1	3	458[e]	4	12	34	528
Second	3	0	0	75	0	0	0	78
Third	0	0	0	16[e]	0	0	0	16
Unspecified	0	0	1	3	0	0	0	4
Total	19	1	4	552	4	12	34	626

All Naratriptan Exposures

Earliest Trimester of Exposure	Birth Defects			No Birth Defects Reported[a]				
	Live Birth	Fetal Death[c]	Induced Abortion	Live Birth	Fetal Death[c,d]	Induced Abortion[d]	Spontaneous Pregnancy Loss[b,d,f]	Total Outcomes[g]
First	1[e]	0	0	45[e]	0	1	5	52
Second	0	0	0	5[e]	0	0	0	5
Third	0	0	0	0	0	0	0	0
Unspecified	0	0	0	0	0	0	0	0
Total	1	0	0	50	0	1	5	57

All Treximet Exposures

Earliest Trimester of Exposure	Birth Defects			No Birth Defects Reported[a]				
	Live Birth	Fetal Death[c]	Induced Abortion	Live Birth	Fetal Death[c,d]	Induced Abortion[d]	Spontaneous Pregnancy Loss[b,d,e]	Total Outcomes[f]
First	0	0	0	4	0	0	1	5
Second	0	0	0	1	0	0	0	1
Third	0	0	0	0	0	0	0	0
Unspecified	0	0	0	0	0	0	0	0
Total	0	0	0	5	0	0	1	6

[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] Not included in the risk calculation
[e] Includes reports of exposure to both sumatriptan and naratriptan
[f] 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 risk of birth defects.
[g] Fetal deaths and induced abortions without reported birth defects and all spontaneous pregnancy losses are excluded from defect rate calculations.

Table 3. Prospective Registry – Sumatriptan, Naratriptan, and/or Treximet Exposure in Pregnancy Summaries of Defects by Earliest Trimester of Exposure

1 January 1996 – 19 September 2012

First Trimester Sumatriptan Exposure:

#	Maternal Age	Route	Dose	Indication	Country	Infant Sex	Gestational Weeks at Outcome	Outcome
1.	25	Oral	200 mg/day from week ?-?	Migraine	Italy	M	38	Live infant. Hypertrophic pyloric stenosis.
2.	36	Oral	100 mg/day from week 0-0	Migraine	UK	M	?	Live infant. Odd cry, low ears, abnormal head circumference, single palmar crease, soft systolic murmur.
3.	34	Oral	100 mg/day from week 5-5	Migraine	UK	F	?	Live infant. Cerebral abnormality with developmental delay.
4.	20	Subcu-taneous	6 mg/day from week 0-0	Migraine	Germany	?	23	Stillbirth. Malformation of left hand (one digit missing, concretion and shortening of two others).
5.	35	Subcu-taneous	6 mg/day in week 0 12 mg/day in week 2 12 mg/day in week 4 24 mg/day in week 9 12 mg/day in week 13 12 mg/day in week 18 12 mg/day in week 19 12 mg/day in week 22	Migraine	USA	?	37	Live infant. Diaphragmatic hernia at 18 months.
6.	40	Oral	Unknown mg/day from week 0-4	Migraine	Norway	M	40	Live infant. Ventricular septal defect, initially assumed to close by itself and considered to be without clinical importance. Approximately 9 months later, the VSD closed, according to cardiologist's assessment.
7.	37	Oral	25 mg/day from week 5-6	Migraine	USA	F	42	Live infant. Anterior displacement of the anus.
8.	37	Oral	100 mg/day from week 0-?	Migraine	Sweden	M	36	Live infant. Polydactyly.
9.	38	Oral Oral Oral Oral Oral Oral Intra-nasal	50 mg/day in week 0 100 mg/day in week 2 100 mg/day in week 6 100 mg/day in week 10 100 mg/day in week 12 100 mg/day in week 14 100 mg/day in week 14	Migraine	UK	F	21	Induced abortion. Down Syndrome.

*Denotes cases that are new since the last Report

**Note: This report of a birth defect has an exposure to both sumatriptan and naratriptan

Note: No defect data are available following Treximet exposure in pregnancy

Table 3. Prospective Registry – Sumatriptan, Naratriptan, and/or Treximet Exposure in Pregnancy Summaries of Defects by Earliest Trimester of Exposure (continued)

1 January 1996 – 19 September 2012

First Trimester Sumatriptan Exposure (continued):

#	Maternal Age	Route	Dose	Indication	Country	Infant Sex	Gestational Weeks at Outcome	Outcome
10.	32	Oral	25 mg/day in week 3	Migraine	Australia	M	40	Live infant. Partial small cleft lip.
		Oral	50 mg/day in week 4					
		Oral	25 mg/day in week 17					
		Oral	25 mg/day in week 21					
		Oral	25 mg/day in week 28					
		Oral	25 mg/day in week 31					
		Oral	25 mg/day in week 36					
11.**	36	Oral	Sumatriptan	Migraine	USA	M	39	Live infant. 2.5 mm ventricular septal defect. Expected to close spontaneously.
			? mg/day in week 4					
			? mg/day in week 6					
			Naratriptan					
			? mg/day in week 4					
12.	36	Oral	50 mg/day (8-10 Imitrex tablets per month until week 15)	Migraine	USA	?	?	Live infant. Ventricular septal defect.
13.	36	Oral	50 mg/day in week 1	Migraine	Sweden	?	21	Induced abortion. Abortion was based on a prenatal test result indicating Down Syndrome.
		Oral	50 mg/day in week 2-3					
		Oral	50 mg/day in week 5-10					
		Oral	50 mg/day in week 12					
14.	23	Oral	100 mg/day from week 0-4	Migraine	USA	F	37	Live infant. Ventricular septal defect.
15.	31	Oral	50 mg for 1 week	Migraine	USA	?	20	Induced abortion. Abortion was based on a prenatal test result indicating Trisomy 18.
16.	28	Oral & Subcu-taneous	6 mg/day in week 5	Migraine	USA	M	34	Live infant. Pyloric stenosis requiring surgery.
			100 mg/day in week 6					
			6 mg/day in week 6-7					
			100 mg/day in week 7					

*Denotes cases that are new since the last Report

**Note: This report of a birth defect has an exposure to both sumatriptan and naratriptan

Note: No defect data are available following Treximet exposure in pregnancy

Table 3. Prospective Registry – Sumatriptan, Naratriptan, and/or Treximet Exposure in Pregnancy Summaries of Defects by Earliest Trimester of Exposure (continued)

1 January 1996 – 19 September 2012

First Trimester Sumatriptan Exposure (continued):

#	Maternal Age	Route	Dose	Indication	Country	Infant Sex	Gestational Weeks at Outcome	Outcome
17.	29	Oral	100 mg/day in week 0 100 mg/day in week 21	Migraine	USA	F	40	Live infant. Biliary atresia, requiring liver transplant at 5 months of age.
18.	34	Oral	100 mg/day in week 0	Migraine	USA	F	39	Live infant. Pyloric stenosis, diagnosed at 4 weeks of age and repaired surgically.
19.	31	Oral	100 mg/day from weeks 1-37	Migraine	USA	F	38	Live infant. Hip dysplasia, treated with surgery at 7 weeks and a harness until age 5 months.
20.	42	Intra-nasal	20 mg/day in week 4 20 mg/day in week 5-7	Migraine	USA	M	38	Live infant. Moderate craniostenosis in a twin infant, thought to be due to *in utero* compression.

Second Trimester Sumatriptan Exposure:

#	Maternal Age	Route	Dose	Indication	Country	Infant Sex	Gestational Weeks at Outcome	Outcome
1.	29	Unknown	? mg/day in week 16	Migraine	UK	F	?	Live infant. Congenital hypothyroidism.
2.	27	Oral	50 mg/day in week 14	Migraine	USA	F	37	Live infant. Trisomy 21.
3.	41	Oral	200 mg/day from week 23-?	Migraine	USA	M	40	Live infant. Slight webbing below the first joint of the last three toes of the left foot.

Unspecified Trimester of Sumatriptan Exposure:

#	Maternal Age	Route	Dose	Indication	Country	Infant Sex	Gestational Weeks at Outcome	Outcome
1.	36	Oral	? mg/day from week ?-?	Migraine	Denmark	F	?	Induced abortion. Down Syndrome.

First Trimester Naratriptan Exposure:

#	Maternal Age	Route	Dose	Indication	Country	Infant Sex	Gestational Weeks at Outcome	Outcome
1. **	36	Oral	Sumatriptan ? mg/day in week 4 ? mg/day in week 6 Naratriptan ? mg/day in week 4	Migraine	USA	M	39	Live infant. 2.5 mm ventricular septal defect. Expected to close spontaneously. (This is the same case as #11 above.)

* Denotes cases that are new since the last Report

**Note: This report of a birth defect has an exposure to both sumatriptan and naratriptan

Note: No defect data are available following Treximet exposure in pregnancy

Table 4. Prospective Registry – Exposure in Pregnancy by Reason for Treatment and Outcome
1 January 1996 – 19 September 2012

Reason for Treatment by Earliest Trimester of Exposure	Outcomes With Birth Defects	Outcomes without Reported Birth Defects[a]			
		Live Births	Fetal Deaths	Induced Abortions	Spontaneous Pregnancy Losses
First Trimester:					
Migraine					
Sumatriptan	20[b,c]	415[b,c]	4[b]	10	30
Naratriptan	1[c]	44[c]	0	1	5
Treximet	0	4	0	0	1
Non-Migraine Headache					
Sumatriptan	0	16	0	0	2
Unspecified					
Sumatriptan	0	27	0	2	2
Naratriptan	0	1	0	0	0
Second Trimester:					
Migraine					
Sumatriptan	3	69[b]	0	0	0
Naratriptan	0	4[c]	0	0	0
Treximet	0	1	0	0	0
Non-Migraine Headache					
Sumatriptan	0	3	0	0	0
Other					
Sumatriptan	0	1	0	0	0
Naratriptan	0	1	0	0	0
Unspecified					
Sumatriptan	0	2	0	0	0
Third Trimester:					
Migraine					
Sumatriptan	0	14[c]	0	0	0
Non-Migraine Headache					
Sumatriptan	0	1	0	0	0
Other					
Sumatriptan	0	1	0	0	0
Unspecified Trimester:					
Migraine					
Sumatriptan	1	2	0	0	0
Unspecified					
Sumatriptan	0	1	0	0	0

[a] Birth defect not reported but cannot be ruled out.
[b] Includes multiple birth outcomes.
[c] Includes dual reporting of a case with an exposure to both sumatriptan and naratriptan.

3 DATA FROM OTHER SOURCES

Summarized in this section are data on use of sumatriptan and/or naratriptan and/or naproxen, alone or within the Treximet combination, during pregnancy as identified from other internal and external sources.

3.1 The Swedish Medical Birth Register

The Swedish Medical Birth Register, affiliated with the Swedish Government Department for Health and Welfare, was established in 1973 and collects data on nearly all births (>95%) in Sweden. Information on the women's pregnancies is collected prospectively by the attending midwife or physician starting with an interview at the first antenatal visit, most commonly at 10 to 12 weeks. The information collected includes maternal socio-demographics, 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 (up until 1997) or ICD-10 (1997 onwards) classification system, and entered into a central computer system. There is no subdivision into major and minor malformations. Data on birth outcomes are supplemented from several population-based registers (Congenital Malformations Register and Hospital Discharge Register) and can be linked through unique health identifiers to the mother's history of medication exposure during pregnancy.

Källén and Lygner (2001) evaluated delivery outcomes in 658 women who had used sumatriptan in pregnancy and 254 infants whose mothers had used other acute migraine drugs, but not sumatriptan, using the Swedish Medical Birth Register.

Women who used drugs for migraine were older and more likely to be giving birth for the first time. There appeared to be no difference in the rate of congenital malformations seen in infants exposed to sumatriptan and those exposed to other drugs for migraine. Among the 905 infants in the study, 28 [3.1% (95% CI: 2.1 - 4.4)] had a congenital malformation; among the 658 infants exposed to sumatriptan only, 18 [2.7% (95% CI: 1.6 - 4.3)] had a malformation. Of infants exposed to sumatriptan and infants exposed to other drugs for migraine, 1.3% and 2.8%, respectively, had major malformations (p=0.14) and there was no pattern observed in the malformations. The authors state that the prevalence of congenital malformations in the general population is 3.6%.

The authors concluded, "the data indicate that use of sumatriptan in early pregnancy does not result in a large increase in teratogenic risk, but does not rule out the possibility of a moderate increase in risk for a specific birth defect."

Regular updates from the Swedish Medical Birth Register were made available to GlaxoSmithKline and data up until October 2009 are described below. Drug exposure data are collected at the first antenatal visit (usually week 10 to 12) and therefore relate to exposure during the first trimester of pregnancy. For purpose of comparison, expected numbers of the various outcomes are given, based on infants of women from the general population giving birth since July 1, 1995 up to 2009 (n=1,342,479). Malformation data are drawn from the National Birth Register, Hospital Discharge Register and Congenital Malformations Register up until the end of 2007 and malformation data can be considered complete. Data from the National Birth Register alone were available for 2008 and 2009. These data should therefore be viewed as preliminary and have not been peer reviewed.

The Swedish Medical Birth Register				
	Observed number	%	Expected number	%
	Total number of infants: 2339			
Known sex:				
Male	1195	(51.2)	1199	(51.5)
Female	1137	(48.8)	1133	(48.5)
Multiple births	57	(2.4)	69.5	(3.0)
Singleton births	2282	(97.6)	2214.2	(97.0)
Among them:				
Birth weight				
<1500 grams	7	(0.3)	13.7	(0.6)
<2500 grams	70	(3.1)	73.9	(3.1)
>4999 grams	82	(3.6)	90.7	(3.9)
Gestational Age				
<32 weeks	7	(0.3)	16.1	(0.7)
<37 weeks	117	(5.1)	114.6	(4.9)
Among all infants:				
Stillborn	9	(0.4)	8.2	(0.3)
Liveborn, dead	3	(0.1)	6.1	(0.3)
With any malformation	81	(3.5)	82.9	(3.5)

Data on malformation outcomes are available to October 2009. The following 81 malformations were recorded among 2339 sumatriptan first trimester exposures, a risk of 3.5%:

The Swedish Medical Birth Register – Malformations

ICD code	Malformation	number
Q040+Q320	Corpus callosum malf.+tracheomalacia	1
741X,Q05	Spina bifida	2
Q170	Preauricular appendix	5
Q180	Branchial fistula or cyst	1
Q21	Unspecified cardiac septum defect	1
Q201+Q210+Q897	Double outlet right ventricle and ventricular septum defect and situs inversus	1
Q210+Q251	Ventricular septum defect and coarctation of aorta	1
745E,Q210	Ventricular septum defect	8
Q211	Atrium septum defect	1
Q211+Q234	Atrium septum defect+mitral insufficiency	1
Q211+Q257	Atrium septum defect+pulmonary artery anomaly	1
Q210+Q211	Ventricular and atrium septum defect	2
Q213	Tetralogy of Fallot	1
Q249	Unspecified cardiac defect	1
Q250	Open ductus arteriosus	1
Q309	Unspecified nose malformation	1
Q314	Laryngocele	1
Q374	Cleft lip and palate	2
Q391	Esophageal atresia	2
Q391+Q600+Q627	Esophageal atresia+unilat.renal agenesis+vesico-uretro-renal reflux	1
Q411	Jejunal stenosis or atresia	1
Q513	Bicornuate uterus*	1
Q53x	Undescended testicle	8
Q540	Hypospadias	1
Q540+Q210+Q250 +Q531	Hypospadias+ventricular septum defect+open ductus Ateriosus+undescended testicle	1

The Swedish Medical Birth Register – Malformations (continued)		
ICD code	**Malformation**	**number**
Q619	Unspecified cystic kidney	1
Q619+Q627	Unspecified cystic kidney+reflux	1
Q620	Hydronephrosis	2
Q65x	Unstable hip	13
Q660	Pes equino-varus	1
Q680	Deformity of sternocleidomastoid muscle	1
Q688	Unspecified musculoskeletal deformity	1
Q690	Accessory finger	3
Q699	Unspecified polydactyly	1
Q713	Absence of hand and fingers	1
754C	Malformation of spine	1
756A	Unspecified malformation of skull and face	1
Q825	Nevus	2
Q870	Syndrome mainly affecting face	1
Q909	Down syndrome	2
Q992	Fragile X syndrome	1

Note that in the Swedish version of ICD-9, the decimal is replaced with a letter (0=A, 1=B, etc.)
*This malformation probably referred to the mother and was miscoded as an infant malformation.

The authors concluded, “The delivery outcome after sumatriptan, as evaluated from the Medical Birth Registry, seems normal. Observed and expected numbers of all outcomes agree well. There is only one divergent observation that was previously reported: the presence of three infants with esophageal atresia among sumatriptan exposed pregnancies. This malformation occurs at a rate of 0.21 per 1000 so one would only expect 0.5 cases and three occurred. They were born in 2000, 2001, and 2002, respectively and during the following 7 years no further case occurred. The three cases could have been a random cluster but it could also represent a true increase in risk which may show up at continued follow-up. Among the three cases of esophageal atresia exposed to sumatriptan, two reported no other exposure, one the use of orphenadrine+paracetamol.”

An analysis of women exposed to medications for migraine in the Swedish Medical Birth Register from 1995 through 2008 was more recently published (Källén *et al*, 2011). This analysis included 2229 pregnant women with first trimester sumatriptan exposures and 22 pregnant women with first trimester naratriptan. Among 2257 births with first trimester exposure to sumatriptan were 107 infants with malformations [RR 0.99 (95% CI: 0.91 - 1.21)]. Among 22 births with first trimester exposure to naratriptan was one infant with a malformation (rate not presented). This study is summarized in section 3.3 Literature Review.

Treximet is not marketed in Europe, therefore no exposure and outcome data for Treximet are available from the Swedish Medical Birth Register.

3.2 Retrospective Reports

In addition to reports received directly by the Registry, GlaxoSmithKline's spontaneous reporting system provided the Registry with retrospective notification of sumatriptan-, naratriptan-, and Treximet-exposed pregnancies when outcomes with birth defects were reported. Reports were considered retrospective when pregnancies involving sumatriptan, naratriptan, and/or Treximet exposure were reported after the pregnancy outcome was already known. Retrospective reports may have been biased toward the reporting of more abnormal outcomes, and were much less likely to be representative of the general population experience (Honein *et al,* 1999). These outcomes were reviewed because they may have been helpful in detecting a possible pattern of birth defects suggestive of common etiology. Retrospective reports of birth defects from health care providers are presented in the following table.

Sumatriptan

Through 19 September 2012, there have been 26 birth defects reported from among the retrospective reports of prenatal sumatriptan exposures. All involved earliest sumatriptan exposure in the first trimester except "u" where the earliest trimester of exposure is the second and "l" and "o" where the trimester of exposure is unspecified. A description of the reported defects follows:

(a) Live infant: Bilateral club feet, deformed ulna; absence of both hands, wrist on right arm and one toe on left foot, sixth toe on right foot, retrognathia, bilateral talipes, bilateral acheiria.

(b) Live infant: Delayed myelination on MRI, delayed development, slow movement and motor development, delayed speech, muscle flaccidity. At 17 months, child unable to walk or talk.

(c) Live infant: Shortened legs, decreased chest circumference. MSAFP and karyotyping normal.

(d) Live infant: Holoprosencephaly.

(e) Induced abortion: Splenomegaly, small adrenal glands, hypoplastic lungs. Fetus triploid, karyotype of 69 XXY, single umbilical artery present.

(f) Live infant: Central cleft palate, fused flexion deformity of left thumb, single palmar crease on left hand, no left kidney; tight anus with dilated fibrous ring. Normal chromosomal analysis.

(g) Live infant: Head circumference above the 97th percentile, sagittal synostosis.

(h) Live infant: Glycogenosis.

(i) Live infant: Born with frontal nasal encephalocele, agenesis absent (corpus callosum).

(j) Live infant: Tracheoesophageal fistula and esophageal atresia (esophagus connected to lungs by trachea not to stomach).

(k) Live infant: Malformed heart with defect in the partition and valve between the atria and ventricles, possibly an AV canal; ventricular inversion; no functional outlet from ventricle on the right side; abnormal pulmonary venous return to the liver. Two equal lobes in liver; no spleen.

(l) Live infant: Pulmonary stenosis.

(m) Induced abortion: Cardiac axis-lungs, diaphragm, stomach, bowel, right kidney, right hand and foot, clubbing of right leg, left and right arms.

(n) Live infant: Spina bifida, hydrocephalus, absence of bladder, absence of rectal function, paresis in legs.

(o) Live infant: Hypoplastic left ventricle, the infant died.

(p) Live infant: Left external auditory canal is narrow.

(q) Live infant: D transposition of great vessels, perimembranous ventricular septal defect.

(r) Live infant: Mild cerebral palsy, right parietal close lip schizencephaly, absence of septum pellucidum.

(s) Live infant: Coarctation of aorta, valve problems, wall between the ventricles did not form, ventricular septal defect.

(t) Spontaneous loss: Multiple malformations.

(u) Live infant: Tetralogy of Fallot, hole in heart, enlarged right ventricle, and narrowing of coronary artery.

(v) Live infant: Six toes on right foot and hypospadias.

(w) Live infant: Congenital tricuspid valve atresia, to be corrected surgically.

(x) Live infant: Small corpus callosum, optic nerve slightly small, patent foramen ovale, ventricular septal defect (resolved), patent ductus arteriosus, undescended testicle, cleft palate (repaired by surgery).

(y) Induced abortion: "Half a brain", skeletal dysplasia, abnormalities of internal organs (bladder U-shaped). Karyotype was normal.

(z) Live infant: Gastroschisis.

Naratriptan

Through 19 September 2012, there have been 4 birth defects reported retrospectively. They all involved an earliest naratriptan exposure in the first trimester. A description of the reported defects follows:

(a) Induced abortion: Pentalogy of Cantrell-abdominal wall defect, pericardial defect, agenesis of the diaphragm, absence of sternum, congenital heart disease.

(b) Live infant: Club foot, treated with surgery in the second month of life.

(c) Live infant: Unspecified congenital abnormality. The child was age 5 at the time of the report. Attempts to obtain further information were unsuccessful.

(d) Induced abortion: Congenital hydrocephalus.

*New reports in this period

Treximet

As of 19 September 2012, there were no retrospective reports of birth defects following exposure to Treximet in pregnancy.

3.3 Literature Review

3.3.1 Migraine and Pregnancy Outcomes

A comprehensive review of the peer-reviewed literature revealed only 2 published studies addressing the prevalence of birth defects among migraineurs (Wainscott *et al*, 1978), Bánhidy *et al*, 2006). In addition, a published literature review was identified (Czeizel and Bánhidy, 2008).

Wainscott *et al* (1978) conducted a study of 450 ever-pregnant female migraine patients compared to 136 ever-pregnant wives of male migraine patients at the Princess Margaret Migraine Clinic in London between 1973 and 1974. Infants of the migraineurs had no increased risk of either major or minor abnormalities compared to infants in the comparison group. The prevalence of birth defects reported for both migraineurs (3.35%)

and the comparison group (3.97%) were similar to overall birth defects reported in the London area.

Bánhidy *et al* (2006) used population-based data from the Hungarian Case-Control Surveillance of Congenital Abnormalities for births from 1980 -1996. Cases were diagnosed with congenital abnormalities in the second trimester of pregnancy through three months after delivery, with chromosomal and Mendelian abnormalities excluded. Two non-malformed controls were matched to each case by gender, birth week, and district of parents' residence. Exposure and outcome were ascertained by review of medical records and maternal questionnaire or interview. Confounders assessed were maternal age, birth order, maternal marital and employment status, maternal diseases other than migraine, medication use including pregnancy supplements. There were 22,843 case mothers (565 with migraine) and 38,151 controls (713 with migraine). Case mothers had a higher prevalence of migraine than control mothers [crude prevalence odds ratio (OR) 1.3 (95% CI: 1.2 - 1.5)]. Anti-migraine drugs included ergotamine with or without other drugs; triptans were not in use in Hungary during this period. The frequency of any type of limb deficiency, neural tube defects, and poly/syndactyly were higher in mothers who had migraine any time during pregnancy; only limb deficiencies were associated with migraine occurrence in the second and third months of gestation [prevalence OR 2.5 (95% CI: 1.1 - 5.8)]. The association of limb deficiencies with migraine did not vary with medication use.

In a review article, Czeizel *et al* (2008) summarize the findings from the study using the Hungarian Case-Control Surveillance of Congenital Abnormalities discussed above (Bánhidy *et al*, 2006). No additional information on malformations is presented.

3.3.2 Sumatriptan / Naratriptan and Pregnancy Outcomes

1) A multi-national study conducted between December 1991 and March 1996 (Shuhaiber *et al,* 1998) prospectively collected and followed reports to a teratogen information service of pregnancies involving use of either oral or subcutaneous sumatriptan. Prevalence rates of birth defects in this group were compared with rates in two other groups. There were 95 pregnant women with earliest exposure to sumatriptan during the first trimester, 12 of which were also exposed during the second trimester, and 6 of which were also exposed during the third trimester. One patient was exposed during the second and third trimesters only. The prevalence rates of major birth defects were 1.2%, 1.1%, and 1.1% in the study group, a disease-matched comparison group (pregnant women suffering from migraine who used other drugs during pregnancy, including acetaminophen, nonsteroidal anti-inflammatory drugs, and narcotic analgesics) and a non-teratogen comparison group (pregnant women who took drugs during pregnancy that are known to be non-teratogenic), respectively. There were no differences reported for maternal history, numbers of live births, birth weight, gestational age, preterm deliveries, spontaneous abortions, or therapeutic abortions among the three groups.

2) O'Quinn *et al* (1999) compared pregnancy outcomes between 76 women who had taken at least one injection of 6 mg of sumatriptan in the first trimester of pregnancy with 92 women who had taken at least one injection of the drug prior to, but not during

pregnancy, in an open label prospective study. There were no differences in pregnancy outcomes between the two groups. There were no birth defects noted in the sumatriptan-exposed group, and 4 minor birth defects in the comparison group.

3) Using linked data from the Danish Medical Birth Registry and the Pharmaco-epidemiological Prescription Database of North Jutland County, Olesen *et al* (2000) compared pregnancy outcomes among: 1) 34 women who redeemed a prescription for sumatriptan during pregnancy; 2) 89 migraine patients who did not redeem prescriptions for migraine treatment during pregnancy; and 3) 15,955 healthy women. Among the 34 newborns exposed to sumatriptan during pregnancy, there were no birth defects or stillbirths reported to the birth Registry. The risk of preterm delivery (before 37 weeks) was elevated in the group exposed to sumatriptan compared with both the migraine comparison group [OR 6.3 (95% CI: 1.2 - 32.0)] and healthy women [OR 3.3 (95% CI: 1.3 - 8.50)]. The risk of having a low birth weight baby (less than 2500 grams) was elevated in both migraine groups (sumatriptan-exposed and not-exposed), compared to the healthy women, but the increases were statistically significant only in the migraine comparison group not exposed to sumatriptan.

4) Fox *et al* (2002) conducted an evidenced-based evaluation of pregnancy outcome after exposure to sumatriptan based on three of the four studies above, plus the registry data, and two case reports. However, the two case reports cited did not report pregnancy outcomes. The authors concluded that there is no evidence to suggest that sumatriptan adversely affects pregnancy outcome based on the studies reviewed.

5) Nezvalová-Henriksen *et al* (2010, erratum 2012) used linked data from the Norwegian Mother and Child Cohort Study (1999-2007) and records from the Medical Birth Registry of Norway (since 1967) which included live births, stillbirths after 16 weeks, and elective terminations after 12 weeks. Participants completed a questionnaire before the first ultrasound at 17-18 weeks and again at 30 weeks gestation. Registry data was obtained from standardized forms completed by the midwife, obstetrician, and/or pediatrician; 69,929 pregnant women and newborn infants participated. Triptan exposure was classified as any use during pregnancy, use during the first trimester, or use during the second or third trimesters. Those who reported use only during the six months before pregnancy, but not while pregnant, made up the migraine control group. Women who did not have migraine and did not report any use of triptans comprised the non-migraine control group. Use of a triptan during pregnancy was reported for1535 women, and 373 used a triptan only during the six months preceding pregnancy. First trimester use was distributed as follows: 47% sumatriptan, 23.6% rizatriptan, 17.5% zolmitriptan, 12.9% eletriptan. There was little naratriptan or almotriptan use. Women who used triptans were significantly more likely to use NSAIDs and paracetamol with or without codeine, take a potentially teratogenic or detrimental drug, have an elevated BMI, take folic acid, be on sick leave more than two weeks, be exposed to caffeine, have other medical conditions (emesis, fever, high blood pressure in the first trimester, folate-deficiency anemia), and have obstetric complications (pre-eclampsia or eclampsia, hospitalization, vaginal bleeding) than women who did not have migraine. Compared with the migraine control group, women who used a triptan were more likely to have an elevated body

mass index, use folic acid, be exposed to caffeine, and to have folate-deficiency anemia, vaginal bleeding during pregnancy, and proteinuria. The overall frequency of congenital malformations did not differ significantly among groups: 4.9% in the triptan exposed; 5.9% in migraine control group; 5.0% in non-migraine control group. The frequency of major malformations also did not differ: 3.0% in the triptan exposed; 2.9% in both control groups.

6) In a study using the Swedish Medical Birth Register, women using triptans or ergots during pregnancy were identified and compared with women who did not use drugs for migraine (Källén *et al*, 2011). Main outcome measures included pregnancy complications, pregnancy duration and birth weight, neonatal morbidity and mortality, and congenital malformations. First trimester exposure to ergots or triptans occurred in 3286 women with 3327 infants, and second and third trimester exposures occurred in 1394 women with 1419 infants. Compared to women who did not use ergots and triptans, exposed women were more likely to be older, first parity (no previous infant), with higher body mass index. The authors reported an increased risk for pre-eclampsia among first trimester exposed-women [OR: 1.40 (95% CI: 1.22 – 1.61)] and second/third trimester-exposed women [OR: 1.44 (95% CI: 1.17 - 1.76)]. The risk of pre-term birth was increased after use of drugs for migraine later in pregnancy [OR 1.50 (95% CI: 1.22 -1.84)]. The risk for birth defects (any malformation) following exposure to any migraine drug was not elevated [OR 0.95 (95% CI: 0.80 - 1.12)] relative to pregnancies with no migraine drug exposure. This analysis included 2229 pregnant women with first trimester sumatriptan exposures and 22 pregnant women with first trimester naratriptan. Among 2257 births with first trimester exposure to sumatriptan were 107 infants with malformations [RR: 0.99 (95% CI: 0.91 -1.21)]. Among 22 births with first trimester exposure to naratriptan was one infant with a malformation (rate not presented).

No other published literature on naratriptan and pregnancy outcomes has been identified to date.

3.3.3 Treximet / Naproxen and Pregnancy Outcomes

There are currently no observational studies in the literature investigating the risk of congenital birth defects following *in utero* exposure to Treximet. There are, however, data concerning naproxen either alone or considered within the NSAID class. Naproxen and other NSAIDs are prostaglandin synthesis inhibitors which can cause constriction of the ductus arteriosus *in utero*. This has been confirmed through case reports (Wilkinson *et al,* 1979, Talati *et al,* 2000) and case control studies (Van Marter *et al,* 1996, Alano *et al,* 2001, Hernandez-Diaz *et al,* 2006) observing an increased risk of premature closure of the ductus arteriosus and pulmonary hypertension of the newborn following third trimester exposure.

Data on the risk of congenital birth defects following first trimester exposure to naproxen are less consistent:

1) A single study, by Rosa *et al* (1993), investigated the risk of all congenital birth defects following first trimester exposure to naproxen. The study involved 229,101 completed pregnancies among Michigan Medicaid recipients, of which 1448 newborns were

exposed to naproxen in the first trimester. A total of 70 (4.8%) major birth defects were observed compared with the 62 expected from the general study population data. These findings failed to support the hypothesis of an association between first trimester naproxen exposure and birth defects.

2) Additional studies considering the risk of all congenital birth defects combined all NSAIDs to be considered as a drug class. Nielsen *et al* (2001) completed a cohort study of 1106 women who had filled prescriptions for NSAIDs during the 30 days prior to conception up until the end of the first trimester and 17,259 women who had not been prescribed any drugs during pregnancy. The study reported an adjusted OR of 1.27 (95% CI 0.93 – 1.75) for any congenital birth defect associated with NSAID prescription uptake.

3) In contrast the case control study by Ofori *et al* (2006), using a data from three administrative healthcare databases from Quebec, identified 93 births with birth defects in 1056 (8.8%) women who had filled prescriptions for NSAIDs in the first trimester compared with 2479 birth defect cases among 35,331 (7.0%) women who were unexposed to NSAIDs during the first trimester. This equated to an adjusted OR of 2.21 (95% CI: 1.72 – 2.85).

4) Two studies within the Swedish Medical Birth Register investigated the association of first trimester naproxen exposure and specific birth defects. The study by Ericson *et al* (2001) used data from 279,734 infants born in Sweden between July 1995 and December 1998 (98% coverage of all births in Sweden during that time period). There was no significant increase in the risk of all birth defects following *in utero* exposure to NSAIDs [OR 1.04 (95% CI: 0.84 – 1.29)], though an excess of relatively mild ventricular and atrial septal defects was observed [OR 1.86 (95% CI: 1.32 – 2.62)]. The risk of cardiac defects was similar across different NSAIDs with an absolute risk of 1.4% reported following *in utero* naproxen exposure. A relative risk of 3.6 (95% CI: 1.2 – 8.3) for orofacial clefts was associated with first trimester naproxen exposure.

5) A case control study, collecting data from the Swedish Medical Birth Register between 1995 and 2001, investigated the potential association between naproxen and cardiac defects further (Källén *et al,* 2003). Twenty-four cardiac defects were reported among 1679 first trimester naproxen exposures (absolute risk of 1.4%). Comparing naproxen exposure among the 5015 cardiac defects and 577,730 non cardiac defect controls gave an OR of 1.70 (95% CI: 1.14 – 2.54). As the authors made multiple comparisons across many drugs and drug classes, they acknowledge that this association may represent a true drug association, but could be due to underlying confounding or multiple testing (Källén *et al,* 2003).

6) The risk of ventricular septal defects (VSD) was also investigated in relation to NSAID exposure during pregnancy by Cleves *et al* (2004) within the National Birth Defects Prevention Study. This analysis included 168 VSD cases identified from seven participating states and 692 controls without birth defects were randomly selected from birth certificate and hospital discharge listings from the same states. NSAIDs were not associated with muscular VSDs: adjusted OR of 1.00 (95% CI: 0.64 – 1.59).

3.3.4 Case Reports in the Literature

On an ongoing basis, the published medical literature was reviewed for case reports with outcomes of pregnancies exposed to sumatriptan, naratriptan, or Treximet. As relevant articles were found, they were listed separately and added to the list of References.

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4 DATA SUMMARY

Beginning with the April 2001 Interim Report, the Sumatriptan and Naratriptan individual registries were combined into the Sumatriptan and Naratriptan Pregnancy Registry. This change simplified the Report and provided a means to describe pregnancy exposures to both sumatriptan and naratriptan. In June 2008, Treximet was added to the Sumatriptan and Naratriptan Pregnancy Registry.

The Advisory Committee reviewed the accumulated outcome data for the 673 pregnancy exposures (610 sumatriptan, 50 naratriptan, 7 to both sumatriptan and naratriptan, and 6 to Treximet). This represents 682 prospectively reported pregnancy outcomes in the Sumatriptan/Naratriptan/Treximet Pregnancy Registry (619 sumatriptan, 50 naratriptan, 7 outcomes with exposures to both sumatriptan and naratriptan, and 6 outcomes with exposure to Treximet). See Section 6, METHODS, page 30 for classification criteria.

4.1 Sumatriptan

Review of the composite data:

Reports of <u>First Trimester Exposure</u>:

In reviewing the prospective pregnancy outcomes (excluding fetal deaths and induced abortions without reported birth defects and all spontaneous pregnancy losses) involving earliest sumatriptan exposure in the first trimester, the observed proportion of births with defects (n=20/478) was 4.2% (95% CI: 2.6% - 6.5%) (Fleiss, 1981). Note: In the Registry, 1 of the 20 birth defect reports and 5 live infants without reported defects also included a first trimester exposure to naratriptan. These reports are included in the analysis of risk for both products.

As previously reported, in reviewing all birth defect reports, the Advisory Committee noted the occurrence of VSD in 4 of the 478 (0.84%) prospective first trimester exposures to sumatriptan. Two of the four VSDs were expected to resolve spontaneously. The interpretation of this cluster of VSDs is discussed further within the Committee Consensus Statement.

Reports from <u>All Trimesters of Exposure</u>:

In reviewing the prospective pregnancy outcomes (excluding fetal deaths and induced abortions without reported birth defects and all spontaneous pregnancy losses) involving sumatriptan exposure in any trimester, the observed proportion of births with defects (n=24/576) was 4.2% (95% CI: 2.7% - 6.2%) (Fleiss, 1981).

Note: One of the 24 birth defect reports also included a first trimester exposure to naratriptan. In the denominator, there are 6 live infants without reported defects

who had exposures to naratriptan as well. These reports are included in the analysis of risk for both products.

Review of Prospective and Retrospective Birth Defects:

In reviewing all birth defects from prospective and retrospective reports, the defects show no uniqueness or consistent pattern to suggest a common etiology.

4.2 Naratriptan

Review of the composite data:

There were 57 outcomes involving naratriptan exposure during pregnancy, and 46 were live born infants with earliest exposure in the first trimester. Of the 46, there was 1 birth defect report. The 1 report of a birth defect also included a first trimester exposure to sumatriptan and is included in the analysis of risk for sumatriptan, as well. There was also 1 induced abortion with a first trimester exposure and 5 live-born infants with second trimester exposure, all without reported defects. In addition there were 5 spontaneous pregnancy losses with a first trimester exposure. Given the limited number of outcomes following a pregnancy exposure to naratriptan in the Registry to date, calculation of the risk of birth defects in this population is not advised as it is unlikely to provide a reliable risk estimate.

4.3 Treximet

Review of the composite data:

Six outcomes involving Treximet exposure during pregnancy were reported to the Registry. None of these outcomes had defects. One spontaneous pregnancy loss reported to the Registry involved a first trimester exposure. The 5 live births included 4 first trimester exposures and 1 second trimester exposure.

5 COMMITTEE CONSENSUS

The Sumatriptan/Naratriptan/Treximet Pregnancy Registry was a prospective, observational study which aimed to detect a signal of any large risk of major malformations following exposure to sumatriptan, naratriptan, or Treximet during pregnancy. The estimated percentage of pregnancies resulting in offspring with major malformations varies widely across studies as the methodologies vary widely. Between-study variation in the estimated risk of major birth defects can be related to such factors as the criteria used to include or exclude specific defects, the geographic regions included, how early in pregnancy women are enrolled, the source of the pregnancy outcome information, the length and timing of follow-up, whether or not elective abortions are included, and the population of women monitored. Because of the international scope of the Sumatriptan/Naratriptan/Treximet Pregnancy Registry, the voluntary nature of the recruitment, and other methods used, there was no directly comparable group of unexposed pregnant women against which to compare the observed prevalence of birth defects in the Registry.

The Sumatriptan/Naratriptan/Treximet Pregnancy Registry used the inclusion and exclusion criteria of the Metropolitan Atlanta Congenital Defects Program (MACDP) for major birth defects, which includes some defects diagnosed solely by prenatal ultrasound (http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf). The overall frequency of major malformations recognized in the first year of life in metropolitan Atlanta reported by the MACDP from 1968 through 2003 was 2.67 per 100 births; the prevalence of defects diagnosed before the seventh day of life was 2.09 per 100 births (Correa *et al*, 2007, Correa *et al*, 2008). The prevalence of such "early diagnoses" were important for Registry comparisons since the majority of outcome reports received were from clinicians, such as obstetricians or adult subspecialists, who may have had limited access to pediatric diagnoses made after the newborn hospitalization. Another study in a northeastern US hospital from a different time period reported a frequency of 1.6% - 2.2% at birth, depending on whether chromosomal anomalies and other genetic disorders were included (Nelson and Holmes, 1989).

Several factors may have introduced bias into the calculation of the risk of major defects in data from the Sumatriptan/Naratriptan/Treximet Pregnancy Registry. As reporting of exposed pregnancies was totally voluntary, it is possible that even among prospectively reported pregnancies there could have been differential reporting of high-risk or low-risk pregnancies. In addition, reporting of defects from maternal, rather than pediatric, health care providers may have limited detection of defects not immediately apparent at birth. 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 for which no defects were detected and all spontaneous abortions were excluded from the risk calculations. However, in reality, it is unknown what proportion of these pregnancies actually has 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 always have known the condition of the aborted fetus.

The rate of spontaneous abortion in the general population is estimated at 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 Sumatriptan/Naratriptan/Treximet Pregnancy Registry at different times in gestation, calculation of the risk of spontaneous abortion with exposure was beyond the scope of the activities of the Registry. However, despite these factors, the Registry provided 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.

Sumatriptan: If the baseline frequency of total birth defects is 2-3 in 100 live births, a sample size of 478 for first trimester sumatriptan exposures has an 80 percent chance (80% power) of correctly detecting at least a 1.73 to 1.91-fold increase from baseline in the frequency of total birth defects. If the baseline frequency for a specific birth defect is 1 in 1000 live births, a sample size of 478 for first trimester exposure has an 80 percent chance (80% power) of correctly detecting at least a 6.48-fold increase from baseline in the frequency of a specific birth defect. At the end of the Registry, the frequency of major birth defects for first trimester sumatriptan exposures in the Registry was 4.2% (95% CI:

for observed proportion: 2.6% - 6.5%). While this frequency is encouraging, the number of exposed pregnancy outcomes accumulated during the life of the Registry represents a sample of insufficient size for making comparisons of the frequency of specific birth defects or for reaching definitive conclusions regarding the possible teratogenic risk of sumatriptan. It is expected that a teratogenic exposure in the first trimester would result in an increased frequency of one or a combination of individual defects or types of defects, but not necessarily in all defects.

The Advisory Committee noted the occurrence of ventricular septal defect (VSD) in 4 of the 478 (0.84%) prospective first trimester sumatriptan exposures. However, two of the VSDs were expected to resolve spontaneously and one of these was described as "without clinical importance." The Swedish Medical Birth Register (Källén *et al*, 2001) reported a similar occurrence of VSDs in 7 of 658 (1.1%) mostly first trimester sumatriptan exposures. Interpretation of this cluster of VSDs in comparison to other studies was complicated by changes in diagnostic technology over time, differences in the frequency of use of newborn echocardiography, and the inclusion or exclusion of clinically insignificant defects. For example, the prevalence of VSDs reported by the population-based Metropolitan Atlanta Congenital Defects Program increased from 0.11% in 1982 to 0.45% in 2003, most probably due to technical improvements in diagnosis. While the occurrence of VSDs in the Registry was higher than these estimates, the Registry finding was lower than the 5.3% reported in a clinical study using echocardiography to screen for VSDs in 1053 consecutive neonates (Roguin *et al*, 1995). Given the range of prevalence estimates in the literature, the committee did not find the occurrence of four VSDs within the Registry to be of specific concern.

Naratriptan: If the baseline frequency of total birth defects is 2-3 in 100 live births, a sample size of 46 for first trimester naratriptan exposures has an 80 percent chance (80% power) of correctly detecting at least a 3.80 to 4.60-fold increase from baseline in the frequency of total birth defects. If the baseline frequency for a specific birth defect is 1 in 1000 live births, a sample size of 46 for first trimester exposure has an 80 percent chance (80% power) of correctly detecting at least a 30.25-fold increase from baseline in the frequency of a specific birth defect. Currently, the Registry reports 1 birth outcome with a birth defect among 46 first trimester naratriptan exposures. While this frequency is encouraging, the number of exposed pregnancy outcomes accumulated to date represents a sample of insufficient size for making comparisons of the frequency of specific birth defects or for reaching definitive conclusions regarding the possible teratogenic risk of naratriptan. It is expected that a teratogenic exposure in the first trimester would result in an increased frequency of one or a combination of individual defects or types of defects, but not necessarily in all defects.

Treximet: Outcome data are available for only 5 first-trimester Treximet exposed pregnancies enrolled in the registry. Four were live births without reported defects and there was 1 spontaneous pregnancy loss. However, the Advisory Committee notes previous published data indicating an increased risk of premature closure of the ductus arteriosus following third trimester exposure to naproxen/NSAID containing products.

Registry Continuation

Poor enrollment and high rates of loss to follow-up within the Registry over an extended

period of time led the Committee to review whether continuation of the Registry would have added substantial new information concerning the risk of major birth defects following *in utero* exposure to the anti-migraine medications of interest. Since 2006, enrollment of pregnancies in this international registry has decreased to an average of 24 enrollments per year for sumatriptan, and substantially fewer for naratriptan (55 total since 2001). Since its approval in April of 2008, only 9 pregnancies have been enrolled for Treximet. Such low enrollment suggested continuation of the Registry would have offered little additional power to rule out more moderate increases in the risk of birth defects. Indeed the Committee noted the stability of the sumatriptan defect risk estimate over many years indicating that continuation of the Registry was unlikely to affect the width of the confidence intervals around the risk estimate and hence the level of risk the registry was able to exclude.

The Committee reviewed data on over 500 prospectively enrolled first trimester sumatriptan exposures during pregnancy. Despite this limited sample size, lack of an appropriate comparison group, and the high lost to follow-up rate, these data did not indicate a signal for major teratogenicity. This coupled with the failure of larger datasets with internal comparator groups (Swedish Medical Birth Register) to observe an increased risk of birth defects, gives a level of reassurance concerning the risk of all major birth defects following *in utero* sumatriptan exposure. Thus, the Committee recommended planned termination of this Registry around the current level of reassurance for overall birth defects for sumatriptan, a level of reassurance which was unlikely to change significantly at the current level of enrollment.

While the population exposed and monitored through the Registry was sufficient to detect major teratogenicity associated with sumatriptan, the Registry did not have adequate power to detect increases in specific types of defects. Ongoing data sources, such as the Swedish Medical Birth Register, with larger sample sizes and general population comparators, provide further reassurance and offer the opportunity for continued monitoring.

The Committee noted the small number of prospectively enrolled naratriptan and Treximet pregnancy exposures. Poor enrollment and high rates of loss to follow-up continued despite several awareness and reporting incentive initiatives. This may have reflected limited use of these medications in women of childbearing age or the failings of the study design to have adequately captured intermittently used anti-migraine medications. The Committee concluded that, despite corrective initiatives, this Registry was unable to meet its primary objective, to detect a signal of major teratogenicity for naratriptan and Treximet, with adequate statistical power.

The Committee therefore recommended planned termination of this Registry for naratriptan and Treximet in light of the lack of feasibility of collecting information of further scientific value. Following this recommendation, GlaxoSmithKline submitted to the FDA documentation regarding discontinuation of the Registry. GlaxoSmithKline was informed on 10 January 2012, that the FDA had formally agreed to GlaxoSmithKline's proposal to end the Sumatriptan/Naratriptan/Treximet Pregnancy Registry. To complete data collection on all active patients, Registry closure was planned for mid-September of 2012 and the Registry was actually closed on 19 September 2012.

NOTE: This Final Report is issued following the independent review of new data. Each Report has included the historical information as well as new data known to the Registry and, therefore, supersedes all previous Reports.

6 METHODS

6.1 Registration and Follow-up

Reporting of exposed pregnancies was voluntary. Pregnancies were registered following prenatal exposure to sumatriptan, naratriptan, or Treximet and prior to knowledge of the pregnancy outcome. The Registry considered any report of an exposure received, whether written or verbal, to be entered even if the initial report provided insufficient baseline data to allow for adequate follow-up. At the patient's estimated date of delivery, follow-up was initiated to obtain and assess the pregnancy outcome. Registration of pregnancies exposed to sumatriptan, naratriptan, or Treximet were required to be prospective – that is, reported during pregnancy before the pregnancy outcome was known. Retrospective reports, those where the outcome was already known, were also 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, and therefore could not be used for risk assessment or analysis. Health care providers with patients exposed to sumatriptan, naratriptan, or Treximet during pregnancy who were willing to provide follow-up information at outcome were encouraged to enroll their patients in the Registry as early in the pregnancy as possible to maximize the validity of the study.

When the pregnancy was reported prospectively, the Registry collected registration data from the treating health care provider through telephone interview or a short registration form. In this study, there were minimum requirements for how much and what kind of data must be collected before a pregnancy could be considered eligible for registration. The minimum data points required included: 1) country of origin of report, 2) documentation that the Registry drug was taken during pregnancy, 3) enough information to confirm that the pregnancy was being prospectively reported, 4) the date the pregnancy was registered, 5) whether the report was made by a patient or medical professional, 6) whether the pregnancy outcome was already known or was still pending delivery, 7) the timing of the prenatal exposure to the Registry medication (no broader than during which trimester – note: there were 4 historical cases with unspecified trimester of exposure enrolled prior to this requirement), 8) whether the patient was involved in a study at the time of the prenatal exposure, and 9) full provider contact information to allow for follow-up.

In the month of the estimated date of delivery, a short follow-up form was sent to the health care provider requesting information on maternal risk factors throughout the pregnancy, pregnancy outcome, and neonatal health. Additional follow-up was not sought from subsequent health care providers.

A report of an exposure was closed when the following information had been obtained: clear information on the sumatriptan, naratriptan, or Treximet exposure and pregnancy outcome determination. A report was closed as "lost to follow-up" when the Registry did not receive the above minimum information following 4 written and 2 verbal attempts at follow-up or 3 months after expected outcome. Reports of exposures were closed as "lost to follow-up" only after the reporting health care provider had been repeatedly contacted for follow-up information well beyond the expected delivery date, or if the reporting health care provider could no longer locate the patient. Only data from "closed" reports of exposed pregnancies with known outcomes were summarized in this Report.

6.2 Patient Confidentiality

The Registry on a regular basis made efforts to assure patient confidentiality, including review of data privacy issues. For this reason, an additional patient confidentiality measure was established. Each registered patient received a Registry-assigned patient identification number provided to the reporter at the time of patient registration. This number was used in all subsequent communication with the health care provider.

6.2.1 Institutional Review Board (IRB) Review

To assure the Registry's overall procedures and its efforts at assuring patient confidentiality were adequate, the Registry protocol was submitted for IRB review. The Registry protocol received IRB approval from Western IRB (WIRB®) in July 2002. With the IRB approval, the Registry was granted a waiver from having to obtain patient informed consent. The IRB conducted an annual review with requests for interim status updates.

6.2.2 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 has documentation that an IRB has waived the requirement for authorization.

On 8 July 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/privacy/hipaa/administrative/index.html, *Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule,* http://privacyruleandresearch.nih.gov/).

6.3 Classification of Outcomes

The Registry adopted the term "birth defect" for abnormalities usually referred to as "congenital abnormalities." For purposes of data reporting, pregnancy outcomes were categorized as one of the following: 1) outcomes with birth defects, 2) outcomes without reported birth defects, or 3) spontaneous pregnancy losses. The second category was further classified as, a) live births, b) fetal deaths, and c) induced abortions. The Registry adopted the following definition for birth defects surveillance programs, which define a

child with a birth defect as any live or stillborn infant with a structural or chromosomal abnormality diagnosed before the child is 6 years of age. For reference, the Advisory Committee adopted the list of birth defects recognized by the CDC MACDP (http://www.cdc.gov/ncbddd/birthdefects/documents/MACDPcode0807.pdf). All defects were classified in consultation with the CDC Division of Birth Defects and Developmental Disabilities. All defects were included in the "outcomes with birth defects" category, whether or not the infant was born alive (including any structural defect in an infant born prior to 20 gestation weeks or weighing <500 gm). The Registry, however, did conform to the CDC MACDP guidelines in disqualifying as defects those findings that were present in infants born at less than 36 weeks of gestation and were attributable to prematurity itself, such as patent ductus arteriosus or inguinal hernias. The CDC MACDP classification does include chromosomal defects. Though these defects were not likely to contribute to a risk for a drug exposure, the Registry included these defects to maintain this consistency with the CDC MACDP.

Live-born infants with only transient or infectious conditions, or biochemical abnormalities, were classified as being without reported 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 reported birth defects and defects that are excluded by the CDC guidelines are noted in Appendix A.

6.4 *Exclusions*

For the Registry, emphasis was placed on prospective registration of pregnancies involving use of sumatriptan, naratriptan, and/or Treximet during pregnancy. However, the Registry encouraged reporting of all known prenatal exposures to sumatriptan, naratriptan, or Treximet, 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 prospective or retrospective notification of prenatal exposures and pregnancy outcomes from patient reports that were never verified by a health care provider. The Advisory Committee also reviewed these outcomes as they may have been helpful for detecting a possible pattern of defects. Since there was no denominator from which risk could be calculated, these reports were excluded from the data analysis. They are summarized in Appendix B of this Report.

6.5 *Analysis*

Pregnancy outcomes were stratified by the earliest trimester of exposure to sumatriptan, naratriptan, and/or Treximet. Gestational weeks were counted from the date of the last menstrual period, with the second trimester beginning at week 14, and the third trimester beginning at week 28.

The calculations of risk to sumatriptan, naratriptan, or Treximet for birth defects were made by dividing the number of outcomes with birth defects by the combined number of live-born infants with and without reported birth defects and outcomes other than live births with birth defects. Note that the calculation of risk was calculated separately for sumatriptan, naratriptan, and Treximet, with reports of exposures to more than one of these medications being represented in each calculation as the earliest trimester of

exposure to that product (i.e., reports of combination treatments are reported in both analyses). Fetal deaths and induced abortions without reported defects were excluded from this calculation. Due to the likelihood of inconsistent identification of defects in spontaneous pregnancy losses < 20 weeks gestation, these cases were also excluded from this calculation regardless of birth defect status. A 95% confidence interval was calculated using the Fleiss method (Fleiss, 1981).

Fundamental to the assessment process the Advisory Committee used to review data were the following concepts. The overall frequency of major malformations in metropolitan Atlanta reported by the MACDP from 1968 through 2003 was 2.67%. (Correa *et al*, 2007, Correa *et al*, 2008). The estimated risk quoted in the literature may vary due to differences in case definition, population sampled, and ascertainment methods. The Collaborative Perinatal Project, using a broader case definition and prospective ascertainment, reported a frequency of 5%-7% (Chung and Myrianthropoulos, 1975). The baseline risk of individual defects is thought to be considerably lower, generally less than 1 per 1000 live births. Most major structural defects have their origins in the first trimester of pregnancy, the time of major organogenesis. For such defects, exposures occurring in the second or third trimester are not likely to be causally associated. However, for the sake of completeness, and to enable the Advisory Committee to assess possible increases in the frequency of birth defects, all defects meeting the CDC criteria were included in the Interim Reports and Final Report for the Registry.

The basic criteria for review of data for a specific case were: 1) was the timing of the exposure to sumatriptan, naratriptan, or Treximet relevant to the origins of the defect; 2) was there another known or likely cause (e.g., recognized genetic or chromosomal defect or exposure to a known teratogen); 3) was the defect totally unknown or a previously unseen event; 4) was there a unique combination of defects; 5) in review of the composite data, was there a deviation from the baseline expectation of defects indicating an increase in the overall frequency of defects; 6) was there a deviation from the baseline of specific defects; 7) in the review of all the reported defects, was there diversity in the defects, suggesting no apparent single cause, or was there uniqueness (e.g., a pattern) of the defects that might suggest a common etiology? The Data Summary sections of this Report describe the Advisory Committee's assessment of the data according to these criteria.

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

While the Registry was limited to prospective reports, some pregnancy exposures were reported only following pregnancy outcome (retrospective reports). The Registry also reviewed each retrospective report involving a birth defect. In general, retrospective notification of outcomes following exposures to drugs is biased toward reporting the severe and unusual cases, and is not reflective of the general experience with the drug. Moreover, information about the total number of exposed persons is unknown. Therefore, rates of outcomes cannot be calculated from these data. However, a series of reported birth defects can be analyzed to detect patterns of specific defects and can identify early signals of new drug risks. Separate sections of this Report describe all abnormal outcomes of retrospectively reported cases.

An important aspect of the Registry was the Advisory Committee formed to oversee the process and results. The Advisory Committee was composed of representatives from GlaxoSmithKline, with specialists in obstetrics, neurology, internal medicine, epidemiology, pediatrics, clinical research, genetics, family practice, and teratology from academic centers and the CDC. This Committee reviewed all data in the Registry on an ongoing basis, and met twice a year to review the aggregate data. Members of the Advisory 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 this Final Report contains historical information as well as new data, it completely supersedes all previous Reports. This Report is available to health care providers who treat this specialized population.

6.6 Potential Biases

As reporting of pregnancies was totally voluntary, it is possible that even in prospectively reported pregnancies there could have been bias in the type of pregnancies reported. For example, high-risk or low-risk pregnancies may have been more likely to be reported.

The calculation of risk, which excludes voluntary terminations and fetal deaths not involving major birth defects and all spontaneous pregnancy losses, may introduce some bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or birth defects. The data collection forms for this Registry attempted to obtain information on birth defects detected at the time of the outcome, but in all likelihood, the condition of the aborted fetus may not always have been known to the reporting physician.

Those pregnancies that have reached estimated dates of delivery but for which outcome information was unobtainable were considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could have differed from those with documented outcomes. All attempts were made to minimize this potential source of bias.

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Appendix A: Reports of Infants with Conditions Other than Birth Defects

Live-born infants with only transient or infectious conditions or biochemical abnormalities were classified as being without birth defects unless there was a possibility that the condition reflected an unrecognized birth defect. Detected and reported transient or infectious conditions or biochemical abnormalities in infants without birth defects and defects that are excluded by the CDC guidelines are noted in the following table of reports of infants with conditions other than birth defects. However, though this information is sometimes reported, it is not systematically collected and therefore not evaluable and not within the scope of this Registry, but is reported here to provide the information available.

1 January 1996 – 19 September 2012

Sumatriptan

Report #	1st Trimester Exposure
1.	Live infant: Shoulder dystocia due to macrosomia.
2.	Live infant: Mild jaundice.
3.	Live infant: Pre-auricular skin tag located before the tragus of the ear.
4.	Live infant: Mild jaundice.
5.	Live infant: Neonatal jaundice.
6.	Live infant: Neonatal jaundice, Stills murmur diagnosed at 4 months of age.
7.	Live infant: Systolic murmur (“innocent”) did not persist.
8.	Live infant: Meconium staining, fetal distress.
9.	Live infant: Slight rise in bilirubin.
10.	Live infant: Thick meconium.
11.	Live infant: Irritability.
12.	Live infant: Crying possible colic.
13.	Live infant: Jaundice, nuchal cord x 2 – reduced.
14.	Live infant: Amniotic fluid aspiration.
15.	Non-viable fetus.
16.	Spontaneous loss: Maternal uterine septum noted.
17.	Stillbirth: Generalized edema, serous pleural and abdominal effusions, bilateral lung hypoplasia and polyhydramnios. No definitive cause at autopsy.
18.	Live infant: Neonatal jaundice, cord blood A+, direct coombs negative.
19.	Live infant: Small birth mark – hemangioma.
20.	Live infant: Pyelectasis renal pelvis 6 mm bilaterally noted on ultrasound at 20 weeks gestation.
21.	Live infant: Possible premature closure of one or more sutures of the skull (craniosynstosis). On follow-up, the physician reported that there had been no premature closure of cranial sutures.
22.	Live infant: Intrauterine growth retardation and hypotrophy.
23.	Live infant: Respiratory syncytial virus.
24.	Live infant: Peripheral pulmonary stenosis.
25.	Live infant: Nuchal cord.
26.	Live infant: Swallowed meconium and oxygen saturation was low at delivery.

Appendix A: Reports of Infants with Conditions Other than Birth Defects (continued)

Sumatriptan

Report #	1st Trimester Exposure (continued)
27.	Live infant: Jaundice a few days after birth.
28.	Live infant: Premature birth.
29.	Live infant: Premature birth, intrauterine growth retardation.
30.	Live infant: Congenital testicular torsion. One testicle was removed during the month after birth.
31.	Live infants: Infants in Neonatal Intensive Care Unit; likely narcotic addiction and potential Prozac withdrawal issues.
32.	Live infant: Abnormal newborn screen for CPT-1.
33.	Live infant: Born with pneumothorax.

Report #	2nd Trimester Exposure
1.	Live infant: Physiologic hyperbilirubinemia, prematurity – events resolved.
2.	Live infant: Cord wrapped around neck.
3.	Live infant: Mild neonatal jaundice, recovered spontaneously.

Naratriptan

Report #	1st Trimester Exposure
1.	Live infant: Jaundice-under lights x 24 hours, home at 4 days old, readmitted with jaundice day 6, discharged day 7.
2.	Live infant: Ptosis (right eye).

Report #	2nd Trimester Exposure
1.	Live infant: GERD (gastroesophageal reflux disease).

Treximet

There have been no reports of infants with conditions other than birth defects following exposure to Treximet in pregnancy.

* Denotes cases that are new since the last Report

Appendix B: Patient-Reported Prenatal Sumatriptan, Naratriptan, and/or Treximet Exposures

Prospective:

Criteria for inclusion in the prospective Registry required registration and follow-up by a health care professional. There were 34 prospective reports of prenatal sumatriptan exposure made by patients prior to the establishment of the Registry. The Registry accepted reports of exposures from patients, without confirmation by health care providers, but they are not included in the prospective Registry section of the Report. All patient-reported prenatal exposures are accounted for here.

Through 19 September 2012, there were 89 reports of prenatal exposure to sumatriptan prospectively made to the Registry by patients who were never confirmed by a health care provider. Of these 89 reports, 80 were lost to follow-up because there was no additional contact made to the Registry by the patient or her health care provider or were not valid, and none are pending outcome. Of the remaining 9 pregnancies with outcomes, outcomes include 6 live infants born without reported birth defects, 1 live infant with a birth defect (noted below), 1 induced abortion and 1 spontaneous pregnancy loss (no defects reported).

Through 19 September 2012, there were 9 reports of prenatal exposure to naratriptan prospectively made to the Registry by patients who have never been confirmed by a health care provider. All 9 reports are lost to follow-up because there was no additional contact made to the Registry by the patient or her health care provider or were not valid.

Through 19 September 2012, there were no reports of prenatal exposure to Treximet prospectively made to the Registry by patients who have never been confirmed by a health care provider.

1 January 1996 – 19 September 2012

Sumatriptan

(a) Live infant: Dislocated hip.

Retrospective:

Through 19 September 2012, there were 4 birth defects retrospectively reported by a patient exposed to sumatriptan without confirmation from a health care provider. There were no retrospective defects reported by patients exposed to naratriptan or Treximet.

1 January 1996 – 19 September 2012

Sumatriptan

(a) Live infant: Multiple abnormalities, no known cause.

(b) Spontaneous loss: Heart problem.

(c) Live infant: Microcephaly-slower development.

(d) Live infant: Hemihyperplasia

* Denotes cases that are new since the last Report

Appendix C: Background – Sumatriptan, Naratriptan, and Treximet

The desire to continue treating a woman already receiving sumatriptan, naratriptan, or Treximet may lead physicians to prescribe sumatriptan, naratriptan, or Treximet to pregnant women. Inadvertent use of sumatriptan, naratriptan, or Treximet by pregnant women has also been reported. This Registry provided a mechanism to collect data concerning exposures to sumatriptan, naratriptan, or Treximet during pregnancy. A semi-annual Interim Report has been distributed to the medical community on the outcomes of those pregnancies. This Registry was intended to supplement animal toxicology studies and the continuing sumatriptan, naratriptan, and Treximet post-marketing surveillance programs.

SUMATRIPTAN (IMITREX®/IMIGRAN®)

Sumatriptan, a selective 5-hydroxytryptamine receptor subtype agonist, is indicated for the acute treatment of migraine attacks with or without aura and is currently available in injection, tablet, and nasal spray formulations.

Animal Data: Sumatriptan Injection

Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in two gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay). In two cytogenetics assays (the in vitro human lymphocyte assay and the in vivo rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

A fertility study (Segment 1) by the subcutaneous route, during which male and female rats were dosed daily with sumatriptan prior to and throughout the mating period, has shown no evidence of impaired fertility at doses equivalent to approximately 100 times the maximum recommended single human dose of 6 mg on a mg/m^2 basis. However, following administration, a treatment-related decrease in fertility, secondary to a decrease in mating, was seen for rats treated with 50 and 500 mg/kg per day. The no-effect dose for this finding was approximately eight times the maximum recommended single human dose of 6 mg on a mg/m^2 basis. It is not clear whether the problem is associated with the treatment of males or females or both.

Pregnancy: Pregnancy Category C: Sumatriptan has been shown to be embryolethal in rabbits when given daily at a dose approximately equivalent to the maximum recommended single human subcutaneous dose of 6 mg on a mg/m^2 basis. There is no evidence that establishes that sumatriptan is a human teratogen; however, there are not adequate and well-controlled studies in pregnant women. IMITREX/IMIGRAN Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In assessing this information, the following additional findings should be considered:

Embryolethality: When given intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. The mechanism of the embryolethality is not known. These doses were approximately equivalent to the maximum single human dose of 6 mg on a mg/m^2 basis.

The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at doses that are approximately 20 times a human dose of 6 mg on a mg/m^2 basis did not

cause embryolethality. Additionally, in a study of pregnant rats given subcutaneous sumatriptan daily prior to and throughout pregnancy, there was no evidence of increased embryo/fetal lethality.

Teratogenicity: Term fetuses from Dutch Stride rabbits treated during organogenesis with oral sumatriptan exhibited an increased incidence of cervicothoracic vascular and skeletal abnormalities. The functional significance of these abnormalities is not known. The highest no-effect dose for these effects was 15 mg/kg per day, approximately 50 times the maximum single dose of 6 mg on a mg/m^2 basis.

In a study in rats dosed daily with subcutaneous sumatriptan prior to and throughout pregnancy, there was no evidence of teratogenicity.

Animal Data: Oral Sumatriptan

Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in two gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay). In two cytogenetics assays (the in vitro human lymphocyte assay and in the in vivo rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

In a study in which male and female rats were dosed daily with oral sumatriptan prior to and throughout the mating period, there was treatment-related decrease in fertility secondary to a decrease in mating in animals treated with 50 and 500 mg/kg per day. The no-effect dose for this finding was approximately one-half of the maximum recommended single human treatment of the males or females or both combined.

In reproductive toxicity studies in rats and rabbits, oral treatment with sumatriptan was associated with embryolethality, fetal abnormalities, and pup mortality. There is no evidence that establishes that sumatriptan is a human teratogen; however, there are no adequate and well-controlled studies in pregnant women.

When given orally to pregnant rabbits daily throughout organogenesis, sumatriptan caused embryolethality only at a dose that clearly resulted in maternal toxicity, 100 mg/kg per day. The no-effect dose for embryolethality was 50 mg/kg per day, which is approximately nine times the maximum single human dose of 100 mg on a mg/m^2 basis.

A study in which rats were dosed daily with oral sumatriptan prior to and throughout gestation demonstrated fetal toxicity and a small increased incidence of a syndrome of malformations (short tail/short body and vertebral disorganization) after long-term treatment with 500 mg/kg per day. The no-effect dose for this effect was 50 mg/kg per day, approximately five times the maximum single human dose of 100 mg on a mg/m^2 basis.

Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in an increased incidence of cervicothoracic vascular and skeletal abnormalities. The highest no-effect dose established for these effects was 15 mg/kg per day, approximately three times the human dose of 100 mg on a mg/m^2 basis.

Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in a decrease in pup survival between birth and postnatal day 4 at doses of approximately 250 mg/kg per day or higher. The no-effect dose for this effect was approximately 60 mg/kg per day, or six times the maximum single human dose of 100 mg on a mg/m^2 basis.

Oral treatment of pregnant rats with sumatriptan from gestational day 17 through postnatal day 21 demonstrated a decrease in pup survival measured at postnatal days 2, 4, and 20 at the dose of 1,000 mg/kg per day. The no-effect dose for this finding was 100 mg/kg per day, approximately 10 times the human dose of 100 mg on a mg/m^2 basis.

NARATRIPTAN (AMERGE®/NARAMIG®)

Naratriptan, a selective 5-hydroxytryptamine receptor subtype agonist, is indicated for the acute treatment of migraine attacks with or without aura in adults and is currently available in tablet formulation.

Animal Data

The toxicity studies conducted on naratriptan are considered to provide good assurance of safety for its proposed intermittent oral use in the treatment of migraine. Naratriptan has low acute toxicity by the oral and intravenous route and is well tolerated in repeat dose studies in the rat and dog, at dosages, and resulting systemic exposures, considerably higher than those achieved in humans.

In rats, increased mortality was observed following repeat oral administration for up to 29 weeks at a systemic exposure ranging from approximately 400 to 1000 times that seen in humans following an oral (tablet) dose of 5 mg. At the same exposure level, effects on the testes and epididymides, a slight reduction in prostate weight, changes in the female reproductive tract (atrophic or cystic ovaries and vaginal anoestrus), and atrophy of the granular ducts of the submandibular salivary glands (predominantly in females) were observed. The effects in females, together with the changes in oestrus cycles seen in the oral fertility study, are considered indicative of a disturbance in hormonal balance. The effects were mild and with the exception of the testicular/epididymal atrophy, showed recovery after a treatment-free period. At the no effect level for these findings, systemic exposure was approximately 70 to 100 times that seen in humans following an oral (tablet) dose of 5 mg.

In the fertility study in rats, increased pre-implantation loss and maternal toxicity that was accompanied by fetal growth retardation and reduced survival of F_1 pups were seen at the high dosage (340mg/kg/day). However, overall reproductive performance of the F_0 and F_1 generations, and development of the F_1 and F_2 generations, were unaffected by treatment with naratriptan.

Naratriptan was not teratogenic in the rat or rabbit. In the rat, maternal toxicity was seen, which was accompanied by slight increases in early post-implantation loss and minor skeletal effects. In the Dutch rabbit, maternal toxicity was accompanied by increases in pre- and post-implantation loss and, at all dosages, minor skeletal effects and variations in the position of the cervicothoracic vasculature. In the New Zealand White rabbit, however, the embryonic loss and effects on the fetal vasculature were not reproducible, and maternal toxicity was accompanied only by an increased incidence of minor skeletal variants.

In the peri-/post-natal study, maternal toxicity which was accompanied by reduced survival of F_1 pups was seen at the high dosage (340mg/kg/day), together with some transient effects on early post-natal development which reversed after weaning. However, parturition, outcome of pregnancy, reproductive performance of the F_1 generation, and F_2 embryonic development were unaffected by treatment with naratriptan.

SUMATRIPTAN WITH NAPROXEN SODIUM (TREXIMET^{TM})

Treximet contains sumatriptan (as the succinate), a selective 5-hydroxytryptamine receptor subtype agonist, and naproxen sodium, a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Treximet is indicated for the acute treatment of migraine attacks in adults and is currently available in tablet formulation.

Animal Data

Sumatriptan and naproxen sodium tested alone and in combination were negative in an in vitro bacterial reverse mutation assay, and in an in vivo micronucleus assay in mice. The combination of sumatriptan and naproxen sodium was negative in an in vitro mouse lymphoma tk assay in the presence and absence of metabolic activation. However, in separate in vitro mouse lymphoma tk assays, naproxen sodium alone was reproducibly positive in the presence of metabolic activation. Naproxen sodium alone and in combination with sumatriptan was positive in an in vitro clastogenicity assay in mammalian cells in the presence and absence of metabolic activation. The clastogenic effect for the combination was reproducible within this assay and was greater than observed with naproxen sodium alone. Sumatriptan alone was negative in these assays.

Chromosomal aberrations were not induced in peripheral blood lymphocytes following 7 days of twice-daily dosing with Treximet in human volunteers.

The effect of Treximet on fertility in animals has not been studied.

In developmental toxicity studies in rabbits, oral treatment with sumatriptan combined with naproxen sodium (5/9, 25/45, or 50/90 mg/kg/day sumatriptan/naproxen sodium) or each drug alone (50/0 or 0/90 mg/kg/day sumatriptan/naproxen sodium) resulted in decreased fetal body weight in all treated groups and in increased embryofetal death at the highest dose of naproxen, alone and in combination with sumatriptan. Naproxen sodium, alone and in combination with sumatriptan, increased the total incidences of fetal abnormalities at all doses and increased the incidence of specific malformations (cardiac interventricular septal defect in the 50/90-mg/kg/day group, fused caudal vertebrae in the 50/0- and 0/90-mg/kg/day groups) and variations (absent intermediate lobe of the lung, irregular ossification of the skull, incompletely ossified sternal centra) in the 50/0- and 0/90-mg/kg/day groups. A no-effect dose for development toxicity in rabbits was not established. The lowest effect dose was 5/9 mg/kg/day sumatriptan/naproxen sodium, which was associated with plasma exposures (AUC) to sumatriptan and naproxen that were 1.4 and 0.14 times, respectively, those attained at the maximum recommended human oral daily dose of 85 mg sumatriptan and 500 mg naproxen sodium.

Naproxen is an inhibitor of prostaglandin synthesis. This class of compounds is known to delay parturition. Because of this and the known effects of drugs of this class on the human fetal cardiovascular system (closure of the ductus arteriosus), use of naproxen containing treatments during third trimester should be avoided.

Appendix D: Registry Enrollment and Data Forms

The Registry was a voluntary enrollment program, and the assistance of health care providers who have provided information to the Registry is greatly appreciated.

Instructions for completing forms:

Patient Anonymity and Patient Identifiers

As of May 2002, the Registry no longer collected any identifiers that might inadvertently compromise patient confidentiality. The patient identifier used was a Registry assigned log number provided to the reporter at the time the patient was registered.

Although Registry enrollment ended on 31 January 2012, and follow up ended on 19 September 2012, this report includes data collection forms for reference only.

Keep in a secure place to protect patient confidentiality

SUMATRIPTAN/NARATRIPTAN/TREXIMET PREGNANCY REGISTRY PATIENT LOG

Call the Registry Office for Patient ID Numbers
800-336-2176 or 910-256-0549 (phone)
800-800-1052 or 910-256-0637 (fax)

In an effort to assure patient confidentiality and anonymity, identifiers (e.g., initials, chart number, date of birth) on patients enrolled in the Registry are not collected. The number we use to refer to your patient for further follow-up on the outcome of this pregnancy is a Patient (Log) ID number.

This log is provided for your convenience. You may want to use this form to track your Registry patients and to easily cross-reference the Sumatriptan/Naratriptan/Treximet Registry Patient (Log) ID number with your patient.

THIS LOG IS FOR YOUR USE ONLY, DO NOT RETURN THIS TO THE REGISTRY
FOR QUICK REFERENCE, KEEP SEPARATE FROM PATIENT'S CHART

Please call the Registry Office at 1-800-336-2176 if you have questions.

Patient **(Log)** ID *assigned by the Registry*	Suggested information to use to reference this patient when Registry follow-up is necessary			
	Patient Name	Chart number	EDD	Date Registry form completed
00001	***Jane Doe***	***123656***	***1 Jul 2009***	***15 Jan 2009***

SUMATRIPTAN/NARATRIPTAN/TREXIMET PREGNANCY REGISTRY

Instructions for completing the REGISTRATION FORM

1. MATERNAL DATA

Patient (Log) ID: Call, fax, or email the Registry for a Registry assigned number, with which to identify this patient.

Race: Check the appropriate box for the pregnant woman's ethnicity.

Prenatal test done: Indicate if a defect was noted on a prenatal test.
If yes, please provide the test on which the defect was noted.

Patient Age: Provide age of the pregnant woman at conception.

Last Menstrual Period (LMP): Provide the date of the pregnant woman's last menstrual period.

Estimated Date of Delivery (EDD): Provide the estimated date of delivery.

How was the EDD determined: Check the box appropriate for how the EDD was calculated.

2. All SUMATRIPTAN, NARATRIPTAN, AND/OR TREXIMET Doses During This Pregnancy

Enter the ***sumatriptan, naratriptan, and/or Treximet treatment information*** in the appropriate section. For each course of treatment indicate as much of the information as possible:

- **Date of Treatment:** If the exact date of treatment is not known, please indicate the gestation week of treatment.
- **# of Days on Treatment:** If the same dosage was taken for several days during a week, please indicate.
- **Total Daily Dose (mg/day):** If there was more than one dose of ***sumatriptan, naratriptan, and/or Treximet*** in one day, please provide the total daily dose (i.e., total the individual doses).
- **Gestation Week (from LMP) Course Began*:** Indicate the gestation week of exposure. If the date treatment began is known the gestation week does not need to be calculated. However, if the exposure occurred within one month of LMP, indicate by entering a "0".
- **Route:** Indicate the route of administration.
- **Reason for Use:** Indicate the reason code that ***sumatriptan, naratriptan, and/or Treximet*** was taken or specify if different from the indications provided.

Treatment date(s) are based upon (check one): Indicate by checking one box that best fits the way the treatment dates were determined. Check "other" and specify if one of the listed items does not fit.

3. HEALTH CARE PROVIDER INFORMATION

Complete the contact information on the bottom of the form, including the date that the data form was completed.

NOTE: The Registry is not designed to monitor all types of events that might occur during pregnancy, labor and delivery, or other neonatal or post-natal events other than defects. If such events occur the provider is encouraged to contact GlaxoSmithKline at 888-825-5249, the manufacturer of sumatriptan, naratriptan, and Treximet, and/or FDA (Food and Drug Administration). The FDA can be reached by faxing the information to 800-FDA-0178 or online at http://www.fda.gov/medwatch/.

SUMATRIPTAN/NARATRIPTAN/TREXIMET PREGNANCY REGISTRY REGISTRATION FORM

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

FOR OFFICE USE ONLY

Registry Patient ID_____ HCP ID _____

WPSP ID _____ Country_____

Registry date of notification _____ _____ _____ ☐ Phone
day month year ☐ Transcribed

1. MATERNAL DATA

Patient (Log) ID: _____

Registry-assigned ID number. Call / Fax the Registry Office for a non-patient identifying number (800-336-2176 US / Canada, 910-256-0549 Int'l, phone) 800-800-1052 US / Canada, 910-256-0637 Int'l, Fax)

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

Race: ☐ White ☐ Black ☐ Hispanic ☐ Asian ☐ Other (specify): _____

Patient Age _____

Last Menstrual Period ____ ____ ____
day month year

Estimated Date of Delivery ____ ____ ____
day month year

How was the Estimated Date of Delivery determined?

☐ by Last Menstrual Period ☐ by Ultrasound ☐ by Other Method (specify): _____ ☐ Unknown

Is there evidence of a defect from a prenatal test?

☐ Yes ☐ No

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

☐ Ultrasound ☐ Amniocentesis ☐ MSAFP ☐ Other (specify): _____

2. HEALTH CARE PROVIDER INFORMATION

Name _____ Specialty _____

Address _____ Phone _____

_____ Fax _____

_____

Alternate Contact _____

Provider's Signature _____ Date ____ _____ ___
day month year

Pregnancy Registry — Registration Form

Registry Patient ID_____

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

FOR OFFICE USE ONLY

Patient (Log) ID: _____ ***Registry-assigned ID number***

3. ALL SUMATRIPTAN/NARATRIPTAN/TREXIMET DOSES DURING THIS PREGNANCY

	Date of Treatment *(d/m/y)*	# of Days	Total Daily Dose *(total mg/day)*	Gestation Week *(from LMP)* Course Began (if Course 1 began prior to conception, enter 0)	Route *(enter code)* 1 = Oral 2 = Subcutaneous 3 = Intranasal 4 = Other (specify) _____	Reason for Use *(enter code)* 1 = Migraine 2 = Cluster Headache 3 = Non-Migraine Headache 4 = Other (specify) _____
SUMATRIPTAN COURSES						
Course 1						
Course 2						
Course 3						
Course 4						
Course 5						
Course 6						
The above treatment dates are based upon (check one): ☐ Medical Chart ☐ Patient Diary ☐ Best Recollection ☐ Other _____ (specify)						
NARATRIPTAN COURSES						
Course 1						
Course 2						
Course 3						
Course 4						
Course 5						
Course 6						
The above treatment dates are based upon (check one): ☐ Medical Chart ☐ Patient Diary ☐ Best Recollection ☐ Other _____ (specify)						
TREXIMET COURSES						
Course 1						
Course 2						
Course 3						
Course 4						
Course 5						
Course 6						
The above treatment dates are based upon (check one): ☐ Medical Chart ☐ Patient Diary ☐ Best Recollection ☐ Other _____ (specify)						

SUMATRIPTAN/NARATRIPTAN/TREXIMET PREGNANCY REGISTRY

Instructions for completing the FOLLOW-UP FORM

1. MATERNAL DATA *(page 1)*

Patient (Log) ID: Call or fax the Registry for a Registry assigned number, with which to identify this patient.

2. ALL SUMATRIPTAN, NARATRIPTAN, AND/OR TREXIMET DOSES DURING THIS PREGNANCY

Enter the ***sumatriptan, naratriptan, and/or Treximet treatment information*** in the appropriate section. For each course of treatment indicate as much of the information as possible:

- **Date of Treatment:** If the exact date of treatment is not known, please indicate the gestation week of treatment.
- **# of Days on Treatment:** If the same dosage was taken for several days during a week, please indicate.
- **Total Daily Dose (mg/day):** If there was more than one dose of sumatriptan, naratriptan, or Treximet in one day, please provide the total daily dose (i.e., total the individual doses).
- **Gestation Week (from LMP) Course Began*:** Indicate the gestation week of exposure. If the date treatment began is known the gestation week does not need to be calculated. However, if the exposure occurred within one month of LMP, indicate by entering a "0".
- **Route:** Indicate the route of administration.
- **Reason for Use:** Indicate the reason codes that sumatriptan, naratriptan, or Treximet was taken or specify if different from the codes provided.

3. HEADACHE HISTORY DURING PREGNANCY

Indicate the ***"Average Number of Headaches Per Trimester"*** for the appropriate types of headaches occurring during this pregnancy, in the appropriate pregnancy trimester column. If the type is not listed, specify it in the space allocated and indicate the number per trimester.

4. HISTORY OF CIGARETTE SMOKING

- **Has the patient smoked cigarettes within 1 month of conception or during this pregnancy:** Indicate "Yes" or "No". If no, go to the next page.
- **Did the patient quit smoking?:** Indicate "Yes", "No", "Don't know". ***If yes***, provide the gestation week the patient stopped smoking.
- **Did the patient resume smoking:** Indicate "Yes" or "No". ***If yes***, what was the gestation week during the pregnancy that the patient resumed smoking?

5. OTHER HEADACHE DRUGS *(page 2)*

Indicate the medications/drugs taken by the patient <u>for headache</u>:

- Check "Prior to Conception" if medication was taken within 1 month of conception.
- Check the trimester that the medication was taken <u>for headache</u>. Specify other medications, as needed, in the space(s) provided and check the trimester that the medication was taken <u>for headache</u>.

6. PREGNANCY OUTCOME *(page 3)*

All information in this section is targeted for assessment at the time of delivery.

- **Date of Outcome:** Indicate the date of the outcome (live birth or fetal loss).
- **Gender:** Check the appropriate gender for the infant/fetus.
- **Length / head circumference:** Indicate the length and head circumference in either inches or centimeters, circle which measure was used.
- **Outcome:** Indicate both the outcome (check outcome) and whether or not a birth defect was noted (check "yes or "no"). *If "yes",* list in the space provided the birth defects and any factors that may have had an impact on this outcome, as well as any information on birth defect attribution.
- **Gestational Age:** Indicate the gestational age of the infant/fetus at outcome.
- **Birth Weight:** Indicate the weight (in grams) of the infant/fetus at outcome.
- **Method of Delivery:** Check the method of delivery.

7. HEALTH CARE PROVIDER INFORMATION

Complete the contact information on the bottom of the form, including the date that the data form was completed.

NOTE: The Registry is not designed to monitor all types of events that might occur during pregnancy, labor and delivery, or other neonatal or post-natal events other than defects. If such events occur the provider is encouraged to contact GlaxoSmithKline at 888-825-5249, the manufacturer of the sumatriptan, naratriptan, and Treximet and/or FDA (Food and Drug Administration). The FDA can be reached by faxing the information to 800-FDA-0178 or online at http://www.fda.gov/medwatch/.

SUMATRIPTAN/NARATRIPTAN/TREXIMET PREGNANCY REGISTRY FOLLOW–UP FORM

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

FOR OFFICE USE ONLY

Registry Patient ID_____ HCP ID _____

WPSP ID _____ Country_____

Date case closed _____ _____ _____ ☐ Phone
day month year ☐ Transcribed

Patient (Log) ID: _____ ***Registry-assigned ID number***

1. ALL SUMATRIPTAN/NARATRIPTAN/TREXIMET DOSES DURING THIS PREGNANCY

	Date of Treatment *(d/m/y)*	# of Days	Total Daily Dose *(total mg/day)*	Gestation Week *(from LMP)* Course Began (if Course 1 began prior to conception, enter 0)	Route *(enter code)* 1 = Oral 2 = Subcutaneous 3 = Intranasal 4 = Other (specify) _____	Reason for Use *(enter code)* 1 = Migraine 2 = Cluster Headache 3 = Non-Migraine Headache 4 = Other (specify) _____
SUMATRIPTAN COURSES						
Course 1						
Course 2						
Course 3						
NARATRIPTAN COURSES						
Course 1						
Course 2						
Course 3						
TREXIMET COURSES						
Course 1						
Course 2						
Course 3						

2. HEADACHE HISTORY DURING THIS PREGNANCY

	Trimester of Pregnancy		
	First	**Second**	**Third**
Average Number of Headaches Per Trimester:			
Migraine with aura	_____	_____	_____
Migraine without aura	_____	_____	_____
Migraine with and without aura	_____	_____	_____
Non migraine headaches	_____	_____	_____
Other: _____	_____	_____	_____

3. HISTORY OF CIGARETTE SMOKING

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

Did patient quit smoking? ☐ Yes ☐ No ☐ Don't Know If yes, when? _____ (gestation week)

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

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

Registry Patient ID _____
FOR OFFICE USE ONLY

Patient (Log) ID: _____ ***Registry-assigned ID number*** **_____**

4. OTHER HEADACHE DRUGS (medications/drugs received within 1 month of conception or during this pregnancy)

	Prior to Conception (√)	Trimester of Pregnancy First (√)	Second (√)	Third (√)
Aspirin	☐	☐	☐	☐
Codeine	☐	☐	☐	☐
Ergotamine tartrate (Ergostat)	☐	☐	☐	☐
Dihydroergotamine mesylate (D.H.E. 45)	☐	☐	☐	☐
butalbital (Esgic, Fioricet, Fiorinal)	☐	☐	☐	☐
Diazepam	☐	☐	☐	☐
Anti-Depressants				
Nortriptyline HCl (Pamelor)	☐	☐	☐	☐
Amitriptyline (Elavil, Endep)	☐	☐	☐	☐
doxepin HCl (Adapin, Sinequan)	☐	☐	☐	☐
Other (specify): _____)	☐	☐	☐	☐
Anti-Convulsants				
Carbamazepine	☐	☐	☐	☐
Lamotrigine	☐	☐	☐	☐
Valproic acid	☐	☐	☐	☐
Other (specify): _____)	☐	☐	☐	☐
NSAIDS				
Specify: _____)	☐	☐	☐	☐
Other Triptans				
Almotriptan	☐	☐	☐	☐
Eletriptan	☐	☐	☐	☐
Frovatriptan	☐	☐	☐	☐
Rizatriptan	☐	☐	☐	☐
Zolmitriptan	☐	☐	☐	☐
Other (specify): _____)	☐	☐	☐	☐
Beta-Blockers				
(specify: _____)	☐	☐	☐	☐
Calcium-channel blockers				
(specify: _____)	☐	☐	☐	☐
Other: _____	☐	☐	☐	☐

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910-256-0637 (All International Faxes)

Registry Patient ID_____
FOR OFFICE USE ONLY

Patient (Log) ID: _____ ***Registry-assigned ID number*** **_____**

5. PREGNANCY OUTCOME

Date of Outcome: _____ _____ _____
day month year

Gestational Age: _____ weeks

Gender: ☐ Male ☐ Female

Birth Weight: _____ grams

Length: _____cm/in. *(circle one)*

Head Circumference: _____ cm/in. *(circle one)*

Outcome:

	Birth Defect Noted?	
☐ Live Infant	☐ Yes	☐ No
☐ Abortion, Spontaneous	☐ Yes	☐ No
☐ Abortion, Induced	☐ Yes	☐ No
☐ Stillbirth	☐ Yes	☐ No

Method of Delivery:
☐ Normal Vaginal ☐ Caesarean Section
☐ Forceps ☐ Other

If any birth defects were noted, please list the birth defect(s) and any factors that may have had an impact on this outcome:

To what do you attribute the defect(s)?

6. HEALTH CARE PROVIDER INFORMATION

Name _____ Specialty _____
Address _____ Phone _____
_____ Fax _____
_____
Alternate Contact _____

Provider's Signature _____ Date ____ ____ ____
day month year