The Sumatriptan and Naratriptan Pregnancy Registry

Interim Report

1 January 1996 through 30 April 2007

Issued: August 2007

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

A Project Conducted by GlaxoSmithKline

Project Office: Please contact Kendle International Inc.
Research Park
1011 Ashes Drive
Wilmington, NC 28405

1-800-336-2176 (within North America)
1-910-256-0549 (outside North America)

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 The data contained in this Report will become out-of-date within 9 months of the Report's publication. Please contact the Sumatriptan and Naratriptan Pregnancy Registry to ensure you have obtained the most recent published Report.
2. 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.
3. A statement regarding the Committee Consensus (page 21) must be referenced in any presentation of these data, including emphasis on the limitations of a voluntary prenatal drug exposure Registry such as this.
4. When presenting data from the Pregnancy Registry, please remind the audience that success of the Registry depends on reporting of exposures by health care providers. Registry contact information should be presented.

NOTE:

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

Outside North America, health care providers can enroll pregnancy exposures into the Sumatriptan and Naratriptan Pregnancy Registry:

- Through the medical director of your local GlaxoSmithKline Company
- Or directly to the project office in the USA at:
  910-256-0549 (call collect)
  910-256-0637 (fax)

Within North America, health care providers can enroll pregnancy exposures by calling:
800-336-2176 (call toll-free)
910-256-0549 (call collect)
800-800-1052 (fax)

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

SUMATRIPTAN and NARATRIPTAN

PREGNANCY REGISTRY

INTERIM REPORT

1 January 1996 – 30 April 2007

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FOREWORD

This Report describes the experience of the ongoing study of prospectively reported pregnancy outcomes in the Sumatriptan and Naratriptan Pregnancy Registry for all reporting countries and covers the period 1 January 1996 through 30 April 2007, and replaces the previous Report covering the period 1 January 1996 through 31 October 2006. However, this Report also includes data collected prior to the initiation of the Registry.

Sumatriptan and naratriptan 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 and naratriptan during pregnancy are identified, their pregnancies are followed, and the outcomes are ascertained by voluntary reports from health care providers.

The Registry is 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 what is, as yet, 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:

Roger Cady, MD
Headache Care Center

Janet Cragan, MD, MPH
National Center on Birth Defects and
Developmental Disabilities
Centers for Disease Control and Prevention
US Public Health Service

Marianne Cunnington, PhD
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Shashi Kori, MD
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Richard Lipton, MD
Department of Neurology
Albert Einstein College of Medicine

Marion S. Verp, MD
The University of Chicago
Department of OB/GYN
The Chicago Lying-in Hospital

The Sumatriptan and Naratriptan Pregnancy Registry encourages reporting of all known prenatal exposures as early in the pregnancy as possible to maximize the validity of the data. Such referrals should be directed to:

The medical director of your local GlaxoSmithKline Company
or directly to the Registry at:

Kendle International Inc.
Research Park
1011 Ashes Drive
Wilmington, NC 28405 USA

	In North America:	Outside North America:
Telephone:	800-336-2176	910-256-0549
Fax:	800-800-1052	910-256-0637

http://www.kendle.com/registries/

GlaxoSmithKline Contact: Katherine Firth, Information Manager,
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SUMATRIPTAN and NARATRIPTAN PREGNANCY REGISTRY
INTERNATIONAL INTERIM REPORT
1 JANUARY 1996 THROUGH 30 APRIL 2007

EXECUTIVE SUMMARY

Although there is no evidence of teratogenicity from preclinical studies of sumatriptan or naratriptan, the medical division of GlaxoSmithKline sponsors the Sumatriptan and Naratriptan Pregnancy Registry as part of an ongoing program in epidemiologic safety monitoring. Women with migraines may require or be unintentionally exposed to sumatriptan or naratriptan during pregnancy. The Registry is considered essential because of the potential for exposure in the first trimester of pregnancy and the unknown risks in pregnancy for any new chemical entity.

The purpose of the Registry is to detect an early signal of teratogenicity associated with prenatal use of sumatriptan or naratriptan, if it exists, by collecting voluntary prospective reports of sumatriptan and naratriptan prenatal exposures. Sumatriptan (Imitrex®/Imigran®) and naratriptan (Amerge®/Naramig®) 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 are collected, but proportions of birth defects in sumatriptan- and naratriptan-exposed pregnancies are 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.

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. There are 9 (two are lost to follow-up without pregnancy outcome available) reports of exposure to both sumatriptan and naratriptan. At this time, a conservative position has been taken, which is to report (and cross-reference) the dual exposure as both a sumatriptan and a naratriptan exposure.

This Report contains a description of all prenatal exposures to sumatriptan or naratriptan 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 is unknown when the prenatal exposure is reported, follow-up to determine the pregnancy outcome is required. Prospective reporting of ongoing pregnancies prior to knowledge of the pregnancy outcome reduces bias and permits estimation of the proportion of birth defects.

Retrospective reports where the pregnancy outcome is known at the time of reporting are 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 exist 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 reviews each pregnancy outcome, calculation of risk of spontaneous pregnancy losses overall should not be attempted and cannot be compared to background rates because pregnancies in the Registry are reported at variable and, at times, imprecise times. For example, if a pregnancy is registered at 10 weeks, only a spontaneous loss after this time can be detected and included in the prospective reports. Similarly, pregnancy losses occurring early in gestation may not be recognized and/or reported.

As of 30 April 2007, the Sumatriptan and Naratriptan Pregnancy Registry had a total of 557 pregnancy exposures to sumatriptan and/or naratriptan with outcome information reported, 504 with pregnancy exposures to sumatriptan (4 sets of twins and 1 set of triplets), 46 with pregnancy exposures to naratriptan, and 7 exposures to both sumatriptan and naratriptan. Six of the exposures to both sumatriptan and naratriptan occurred in the 1st trimester. One was an exposure to naratriptan in the 2nd trimester and sumatriptan in the 3rd trimester (see Table 1b).

Sumatriptan - As of 30 April 2007, 517 pregnancy outcomes have been obtained from 511 pregnancies (includes 4 sets of twins and 1 set of triplets) involving exposure to sumatriptan. Of the 445 outcomes reported involving earliest prenatal exposure in the first trimester, there were 395 live-born infants, 31 spontaneous pregnancy losses, 14 induced abortions, and 5 stillbirths. Of these, there were 18 reports of birth defects, 14 live-born infants (one also with a first trimester exposure to naratriptan), 1 stillbirth, and 3 induced abortions with reported birth defects. Of the 57 pregnancy outcomes following earliest prenatal exposure in the second trimester, there were 57 live-born infants. Of these, there were 3 infants with birth defects. There have been 11 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 22 birth defect reports are summarized in Table 3.

The observed proportion with birth defects (n=18) for outcomes following earliest exposure in the first trimester (n=399, excluding fetal deaths and induced abortions without reported defects and all spontaneous pregnancy losses) is 4.5% (95% Confidence Interval (CI): 2.8%-7.2%). The observed proportion with birth defects (n=22) for outcomes with any trimester of exposure (n=471, excluding fetal deaths and induced abortions without reported defects and all spontaneous pregnancy losses) is 4.7% (95% CI: 3.0%-7.1%) (Fleiss 1981).

Naratriptan – As of 30 April 2007, 53 pregnancies with known outcomes have been reported. Of the 48 with first trimester exposures, there were 42 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.

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 currently 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 and Naratriptan Pregnancy Registry uses the inclusion and exclusion criteria of the U.S. Metropolitan Atlanta Congenital Defects Program (MACDP) for 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). 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). No consistent pattern of defects has been observed to date among the birth defects reported to the Registry.

1 INTRODUCTION

The purpose of the Registry is to detect any major teratogenic effect in pregnancies inadvertently or intentionally exposed to IMITREX®/IMIGRAN® (sumatriptan) or AMERGE®/NARAMIG® (naratriptan). The combination of the large number of women with migraines who are of reproductive capacity and the lack of data concerning sumatriptan or naratriptan use during pregnancy makes such a Registry an essential component of the ongoing program of epidemiologic studies of the safety of sumatriptan and naratriptan. This Registry is 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 24). 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 has submitted and received a HIPAA (Health Insurance Portability and Accountability Act) full waiver through the IRB. Patient confidentiality is strictly upheld. The intent of the Registry is to prospectively collect data concerning exposure to sumatriptan or naratriptan 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 and Naratriptan Pregnancy Registry is 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 constitute an Advisory Committee for the Registry and provide independent review of the data. The Sumatriptan Pregnancy Registry began in January 1996 and the Naratriptan Pregnancy Registry began in October 1997. Up until April 2001 they were managed as separate Registries. However, they have now been combined to better address pregnancy exposures to both sumatriptan and naratriptan. To date, there are 7 reports of exposures with outcomes with known exposure to both sumatriptan and naratriptan in the analysis.

2 PROSPECTIVE REGISTRY

This Interim Report is issued semiannually following the Registry Advisory Committee's review of new and previously received data. Each issue contains historical information, as well as new data received by the Registry, and therefore supercedes all previous Reports. The new information in this Report includes data from all cases closed between 1 November 2006 and 30 April 2007.

This Registry is an international registry. To date, there are 557 sumatriptan and/or naratriptan exposures in pregnancy with outcomes which were registered from 17 different countries (Table 1a).

Reports of Infants with Conditions Other Than Birth Defects – As described in the Introduction, the purpose of the Registry is to detect any major teratogenic effect following a pregnancy exposure to sumatriptan or naratriptan. As described in the Methods section, live-born infants with only transient or infectious conditions or biochemical abnormalities are classified as being without birth defects unless there is a possibility that the condition(s) reported may indicate an unrecognized birth defect. These conditions though sometimes reported, are not systematically collected and therefore not within the scope of this Registry to evaluate. 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 (Centers for Disease Control 1989).

Table 1.a. Prospective Registry – Exposure in Pregnancy by Country of Origin

1 January 1996 – 30 April 2007

Country	Sumatriptan[a]	Naratriptan[a]
Australia	6	0
Belgium	4	0
Canada	14	6
Denmark	13	2
France	4	7
Germany	23	2
Ireland	1	0
Italy	7	2
Norway	5	0
Peru	0	1
Slovenia	1	0
Spain	3	1
Sweden	24	0
Switzerland	1	0
The Netherlands	10	0
United Kingdom	33	3
United States	362[b]	29[b]
Total	511	53

[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 – 30 April 2007

	Overall
Sumatriptan	
Pregnancies Enrolled	688
Pending Cases [1],[4]	33 (4.8%)
Cases lost to follow-up [2],[5]	144 (22.0%)
Reports included in analysis [3],[4]	511 (74.3%)
Naratriptan	
Pregnancies Enrolled	80
Pending Cases [1],[4]	0 (0.0%)
Cases lost to follow-up [2],[5]	27 (33.8%)
Reports included in analysis [3],[4]	53 (66.2%)

[1] Cases where the outcome of pregnancy is not yet known (includes 0 reports with exposure to both sumatriptan and naratriptan)
[2] Cases where the outcome of pregnancy has never been received despite requests (includes 2 reports with exposure to both sumatriptan and naratriptan)
[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 2006 through 30 April 2007)

During this period, 20 additional pregnancies involving exposure to sumatriptan were prospectively registered. Three outcomes were obtained and 1 was lost to follow-up because the reporter left the practice from which report was made. Sixteen pregnancies are pending outcome. There were also 21 previously registered pregnancies closed. Of these 21, 14 were closed with known outcomes and 7 were lost to follow-up (for 5 there was no response from the reporting health care provider, for 1 the reporter could not identify patient at time of follow-up, and for 1 the reporter left the practice from which report was made). There were 17 pregnancies with outcomes reported this period added to Table 2.

Outcomes from pregnancies with earliest exposure in the first trimester:

Of the 17 outcomes obtained, 15 involved earliest exposure in the first trimester. Of these 15, there were 13 live-born infants without reported birth defects. There were 2 infants with reported birth 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 defect.

Outcomes from pregnancies with earliest exposure in the third trimester:

There was 1 live birth outcome obtained involving earliest exposure in the third trimester, with no reported birth defect.

All prospectively reported birth defects are described in Table 3.

2.1.2 Summary of Data

Through 30 April 2007, 688 reports of women exposed to sumatriptan during pregnancy have been registered prospectively. Of the 688 reports, 33 are pending outcome information. Of the remaining 655, 144 (144/655= 22.0%) were lost to follow-up. The 144 reports were lost to follow-up for the following reasons:

74 there was no response from the reporting health care provider
36 the patient did not remain under the reporting health care provider's care
14 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
4 there was no response to the reporter from the patient
3 patient refused release of information

Of the 511 pregnancies with outcomes reported (Table 1.b), 517 outcomes (includes 4 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 445 outcomes reported involving earliest prenatal exposure in the first trimester, there were 381 live-born infants without reported birth defects (3 sets of twins). There were 18 reports of birth defects, 14 were live-born infants (1 of which also had a first trimester exposure to naratriptan), 1 stillbirth, and 3 induced abortions. There were also 11 induced abortions and 4 stillbirths (includes 1 member of a set of twins) all without birth defects reported. In addition, there were 31 spontaneous pregnancy losses (includes 1 member of a set of twins).

Outcomes from pregnancies with earliest exposure in the second trimester:

Of the 57 outcomes reported involving earliest exposure in the second trimester, there were 54 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 11 outcomes obtained from pregnancies involving earliest exposure in the third trimester. All 11 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 22 reports of birth defects (Table 2). Of these 22, there were 17 live-born infants, 4 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 2006 through 30 April 2007)

During this period, there were no additional pregnancies involving exposure to naratriptan prospectively registered. There were 2 previously registered pregnancies closed. Of these 2, 1 was closed with known outcome and 1 was lost to follow-up because the reporter could not identify the patient at time of follow-up. There was 1 pregnancy with outcome reported this period added to Table 2.

2.2.2 Summary of Data

Through 30 April 2007, 80 reports of women exposed to naratriptan during pregnancy have been registered prospectively. Of the 80 pregnancies registered, none are pending delivery, 27 (27/80=33.8%) cases were lost to follow-up (for 16 there was no response from the reporting health care provider, for 7 the patient did not remain under the reporting health care provider's care, and for 4 the reporting health care provider could not identify the patient at time of follow-up from information provided at time of enrollment) (Table 1.b). There are 53 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 48 pregnancies with outcomes reported involving earliest exposure in the first trimester, there were 41 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 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.

Table 2. Prospective Registry – Exposure in Pregnancy by Earliest Trimester of Exposure and Outcome

1 January 1996 – 30 April 2007

All Sumatriptan Exposures

Earliest Trimester of Exposure	Birth Defects			No Birth Defects Reported[a]			Spontaneous Pregnancy Loss[b,d,f]	Total Outcomes
	Live Birth	Fetal Death[c]	Induced Abortion	Live Birth	Fetal Death[c,d]	Induced Abortion[d]		
First	14[e]	1	3	381[e]	4	11	31	445
Second	3	0	0	54	0	0	0	57
Third	0	0	0	11[e]	0	0	0	11
Unspecified	0	0	1	3	0	0	0	4
Total	17	1	4	449	4	11	31	517

All Naratriptan Exposures

Earliest Trimester of Exposure	Birth Defects			No Birth Defects Reported[a]			Spontaneous Pregnancy Loss[b,d,f]	Total Outcomes
	Live Birth	Fetal Death[c]	Induced Abortion	Live Birth	Fetal Death[c,d]	Induced Abortion[d]		
First	1[e]	0	0	41[e]	0	1	5	48
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	46	0	1	5	53

[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 misclassification, spontaneous losses < 20 weeks gestation are excluded from the calculation of the risk of birth defects.

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

1 January 1996 – 30 April 2007

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.
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.

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

1 January 1996 – 30 April 2007

First-Trimester Sumatriptan Exposure (continued):

#	Maternal Age	Route	Dose	Indication	Country	Infant Sex	Gestational Weeks at Outcome	Outcome
10.	32	Oral Oral Oral Oral Oral Oral Oral	25 mg/day in week 3 50 mg/day in week 4 25 mg/day in week 17 25 mg/day in week 21 25 mg/day in week 28 25 mg/day in week 31 25 mg/day in week 36	Migraine	Australia	M	40	Live infant. Partial small cleft lip.
11.**	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.
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 50 mg/day in week 2 50 mg/day in week 3 50 mg/day in week 5 50 mg/day in week 6 50 mg/day in week 7 50 mg/day in week 8 50 mg/day in week 9 50 mg/day in week 10 50 mg/day in week 12	Migraine	Sweden	?	21	Induced abortion. Abortion was based on a prenatal test result indicating Down Syndrome.
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 5 100 mg/day in week 6 6 mg/day in week 6 6 mg/day in week 7 100 mg/day in week 7	Migraine	USA	M	34	Live infant. Pyloric stenosis requiring surgery.

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

1 January 1996 – 30 April 2007

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.

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.

*Denotes cases that are new since the last Report

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

Table 4. Prospective Registry – Exposure in Pregnancy by Reason for Treatment and Outcome

1 January 1996 – 30 April 2007

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	18[c]	343[b,c]	4[b]	9	27
Naratriptan	1[c]	40[c]	0	1	5
Non-Migraine Headache					
Sumatriptan	0	11	0	0	2
Unspecified					
Sumatriptan	0	27	0	2	2
Naratriptan	0	1	0	0	0
Second-Trimester:					
Migraine					
Sumatriptan	3	48[b]	0	0	0
Naratriptan	0	4[c]	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	10[c]	0	0	0
Non-Migraine Headache					
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 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 pregnancy is collected prospectively by the attending midwife or physician starting with an interview at the first antenatal visit, most commonly at 10-12 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.

Kallen 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 between infants exposed to sumatriptan and those exposed to other drugs for migraine. No increase in the rate of congenital malformations was seen. Among the 905 infants in the study, 28 (3.1%, 95% CI: 2.1 to 4.4) had a congenital malformation; among the 658 infants exposed to sumatriptan only, 18 (2.7%, 95% CI: 1.6 to 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 Register have been made available to GlaxoSmithKline and data up until June 2004 are described below. Drug exposure data are collected at the first antenatal visit (usually week 10-12) 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 2003 (n=732,509).

The Swedish Medical Birth Register				
	Observed number	%	Expected number	%
	Total number of infants: 1513			
Known sex:				
male	777	(51.5)	775.4	(51.4)
female	732	(48.5)	733.6	(48.6)
Multiple births	39	(2.6)	44.2	(3.1)
Singleton births	1474	(97.4)	1430.9	(96.9)
Among them:				
Birth weight				
<1500 grams	5	(0.3)	8.5	(0.6)
<2500 grams	49	(3.3)	47.0	(3.2)
>4999 grams	54	(3.7)	61.5	(4.2)
Gestational Age				
<32 weeks	5	(0.3)	10.7	(0.7)
<37 weeks	84	(5.7)	75.0	(5.1)
Among all infants:				
Stillborn	7	(0.5)	5.5	(0.4)
Liveborn, dead	2	(0.1)	3.2	(0.2)
With any malformation	52	(3.4)	52.6	(3.5)

Data on malformation outcomes are available to the end of 2005 (data from 2005 not quite complete). The following 45 malformations were recorded among 1877 sumatriptan exposures:

ICD code	Malformation	number
Q05,741X+742B	Spina bifida+microcephaly	1
Q170	Prauricular appendix	3
Q180	Branchial sinus or fistula	1
Q210, 745E	Ventricular septum defect	7
Q210+Q211	Ventricular and atrium septum defect	2
Q211	Atrium septum defect	1
Q213	Tetralogy of Fallot	1
Q234+Q211	HLHS+atrium septum defect	1
Q249	Unspecified cardiac defect	1
Q250	Persistent ductus arteriosus	1
Q257+Q211	Pulmonary artery anomaly+atrium septum defect	1
Q309	Unspecified nose malformation	1
Q391	Oesophageal atresia	2
Q391+Q600+Q627	Oesophageal atresia+unilat. renal oagenesis+vesico-uretero-renal reflux	1
Q411	Jejunal atresia	1
Q513	Bicornuate uterus	1[a]
Q53x	Undescended testicle	5
Q540	Hypospadias, glandular	1
Q620	Hydronephrosis	1
Q619+Q627	Cystic kidney+vesico-uretero-renal reflux	1
Q65x	Instable hip	8
754C	Spine malformation	1
756A	Facial/skull malformation	1
Q660	Pes equinovarus	1
Q680	Deformity of sternocleido muscle	1
Q69x	Polydactyly	4

The Swedish Medical Birth Register – Malformations continued

ICD code	Malformation	number
748C	Congenital laryngeal stridor	1
749x	Cleft lip/palate	1
	Unspecified musculoskeletal malformation	1[b]
Q713	Absence of hand/fingers	1
Q825	Nevus	2
Q870	Syndrome affecting facial appearance	1

Note that in the Swedish version of ICD9, the decimal is replaced with a letter (0=A, 1=B, etc.)

HLHS = hypoplastic left heart syndrome
[a] probably miscoding for maternal malformation.
[b] Also exposed to naratriptan

The authors concluded, "the general pregnancy outcome after exposure to sumatriptan is close to normal and no increased risk for congenital malformations is seen. There are, however, three infants with oesophageal and one with jejunal atresia which is a high number. The expected number of any intestinal atresia is 0.9 and the found number of 4 is thus high, especially as 3 of them were oesophageal atresia (with a normal rate of about 1/5000 births). This finding could be random but suggests further observations. At present, an association with intestinal atresias (and especially oesophageal atresia) cannot be ruled out but support for an association has to come from independent data, either from other sources or from a continued follow-up of Swedish data". There were only 18 exposures to naratriptan with one recorded malformation. Numbers are too small to draw conclusions.

3.2 Retrospective Reports

In addition to reports received directly by the Registry, GlaxoSmithKline's spontaneous reporting system provides the Registry with retrospective notification of sumatriptan- and naratriptan-exposed pregnancies when outcomes with birth defects are reported. Reports are considered retrospective when pregnancies involving sumatriptan and/or naratriptan exposure are reported after the pregnancy outcome is already known. Retrospective reports may be biased toward the reporting of more abnormal outcomes, and are much less likely to be representative of the general population experience. These outcomes are reviewed because they may be helpful in detecting a possible pattern of birth defects suggestive of common etiology. Retrospective reports of birth defects are presented below.

Health Care Provider Reports:

Sumatriptan

Through 30 April 2007, 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 30 April 2007, there have been 3 birth defects reported retrospectively. They both 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.

*New reports in this period

3.3 Literature Review

3.3.1 Migraine and Pregnancy Outcomes

A literature review revealed only one published study of the prevalence of birth defects among migraineurs. 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.

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). 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 four 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 not-exposed migraine comparison group.

4) Fox *et al* (2002) conducted an evidenced-based evaluation of pregnancy outcome after exposure to sumatriptan based on 3 of the 4 studies above, plus the registry data, and two case reports. However, the 2 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.

To date, there is no published literature on naratriptan and pregnancy outcomes.

3.3.3 Case Reports in the Literature

On an ongoing basis, the published medical literature is reviewed for case reports with outcomes of pregnancies exposed to sumatriptan or naratriptan. As relevant articles are found, they will be 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 simplifies the Report and provides a means to describe pregnancy exposures to both sumatriptan and naratriptan.

The Advisory Committee reviewed the accumulated data for the 557 pregnancy exposures (504 sumatriptan, 46 naratriptan, and 7 to both sumatriptan and naratriptan). This represents 563 prospectively reported pregnancy outcomes in the Sumatriptan and Naratriptan Pregnancy Registry (510 sumatriptan and 46 naratriptan, and 7 outcomes with exposures to both sumatriptan and naratriptan). See Section 6, METHODS, page 23 for classification criteria.

4.1 Sumatriptan

Review of the composite data:

Reports of First-Trimester Exposure:

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=18/399) was 4.5% (95% CI: 2.8%-7.2%) (Bhattacharyya *et al*, 1977). Note: In the Registry, 1 of the 18 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 ventricular septal defect (VSD) in 4 of the 399 (1.0%) prospective first trimester exposures to sumatriptan. Two of the four VSDs were clinically insignificant. The Advisory Committee continues to monitor the occurrence of VSDs, as well as all other reported defects, in the Registry.

Reports from All Trimesters of Exposure:

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=22/471) was 4.7% (95% CI: 3.0%-7.1%) (Bhattacharyya *et al,* 1977). Note: One of the 22 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 53 outcomes involving naratriptan exposure during pregnancy, 42 were live born infants with earliest exposure in the first trimester. Of the 42, 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. The proportion of birth defects (excluding fetal deaths and induced abortions without reported birth defects and all spontaneous pregnancy losses) in pregnancies exposed to naratriptan in the first trimester (n=1/42) was 2.4% (95% CI: 0.1%-

14.1%). Based on the insufficient number of outcomes following a pregnancy exposure to naratriptan in the Registry to date, the risk calculation, and its corresponding confidence interval does not provide informative or reliable data regarding the risk of birth defects in this population.

5 COMMITTEE CONSENSUS

The Sumatriptan and Naratriptan Pregnancy Registry is a prospective, observational study which aims to detect a signal of any large risk of major malformations following exposure to sumatriptan or naratriptan 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 and Naratriptan Pregnancy Registry, the voluntary nature of the recruitment, and other methods used, there is no directly comparable group of unexposed pregnant women against which to compare the observed prevalence of birth defects in the Registry.

The Sumatriptan and Naratriptan Pregnancy Registry uses 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 (Centers for Disease Control 1989). 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). The prevalence of such "early diagnoses" is important for Registry comparisons since the majority of outcome reports received are from clinicians, such as obstetricians or adult subspecialists, who may have limited access to pediatric diagnoses made after the newborn hospitalization. Another study in a northeastern US hospital from a different time period has reported a frequency of 1.6%-2.2% at birth, depending on whether chromosomal anomalies and other genetic disorders are included (Nelson *et al*, 1989).

Several factors may introduce bias into the calculation of the risk of major defects in data from the Sumatriptan and Naratriptan Registry. As reporting of exposed pregnancies is totally voluntary, it is possible that even among prospectively reported pregnancies there could be differential reporting of high-risk or low-risk pregnancies. In addition, reporting of defects from maternal, rather than pediatric, health care providers may limit detection of defects not immediately apparent at birth. It is also possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Voluntary terminations and fetal deaths for which no defects have been detected and all spontaneous abortions are excluded from the risk calculations. However, in reality, it is unknown what proportion of these pregnancies actually have defects. While the data

collection form attempts to obtain information on birth defects detected at the time of the outcome, the reporting physician may not always know 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 are enrolled in the Sumatriptan and Naratriptan Pregnancy Registry at different times in gestation, calculation of the risk of spontaneous abortion with exposure is beyond the scope of the activities of the Registry. However, despite these factors, the Registry provides a useful tool for supplementing animal toxicology studies, other epidemiologic studies, and clinical trials to assist clinicians in weighing the risks and benefits of treatment for individual patients.

Sumatriptan: If the baseline frequency of total birth defects is 2-3 in 100 live births, a sample size of 399 for first trimester sumatriptan exposures has an 80 percent chance (80% power) of correctly detecting at least a 1.8 to 2.0-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 399 for first trimester exposure has an 80 percent chance (80% power) of correctly detecting at least a 7.2-fold increase from baseline in the frequency of a specific birth defect. Currently, the frequency of major birth defects for first trimester sumatriptan exposures in the Registry is 4.5% (95% Confidence Interval for observed proportion: 2.8%-7.2%). 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 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 notes the occurrence of ventricular septal defect (VSD) in 4 of the 399 (1.0%) prospective first trimester sumatriptan exposures. The Swedish Medical Birth Registry (Kallen *et al*, 2001) reported a similar occurrence of VSDs in 7 of 658 (1.1%) mostly first trimester sumatriptan exposures. The occurrence of VSDs in the Registry is higher than the 0.25% reported in the population-based Metropolitan Atlanta Congenital Defects Program (Botto *et al*, 2001), but lower than the 5.3% reported in a clinical study using echocardiography to screen for VSDs in 1053 consecutive neonates (Roguin *et al*, 1995). It is difficult to compare the findings from such studies because variations in the frequency of VSD may result from differences in the use of newborn echocardiography and the inclusion or exclusion of clinically insignificant defects. The Registry will continue to monitor the reported frequency of VSD after first trimester exposure to sumatriptan.

Naratriptan: If the baseline frequency of total birth defects is 2-3 in 100 live births, a sample size of 42 for first trimester naratriptan exposures has an 80 percent chance (80% power) of correctly detecting at least a 4.0 to 4.8-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 42 for first trimester exposure has an 80 percent chance

(80% power) of correctly detecting at least a 32.4-fold increase from baseline in the frequency of a specific birth defect. Currently, the frequency of major birth defects for first trimester naratriptan exposures in the Registry is 2.4% (95% Confidence Interval for observed proportion: 0.1%-14.1%). 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 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.

NOTE: This Interim Report is issued semiannually following the independent review of new data. Each Report includes the historical information as well as new data known to the Registry and, therefore, supercedes all previous Reports. If your current Report is older than 9 months, please request the updated Interim Report from your local GlaxoSmithKline Company, or directly from the Registry.

6 METHODS

6.1 Registration and Follow-up

Reporting of exposed pregnancies is voluntary. Pregnancies are registered following prenatal exposure to sumatriptan or naratriptan and prior to knowledge of the pregnancy outcome. The Registry considers any report of an exposure received, whether written or verbal, to be entered even if the initial report provides insufficient baseline data to allow for adequate follow-up. At the patient's estimated date of delivery, follow-up is initiated to obtain and assess the pregnancy outcome. Registration of pregnancies exposed to sumatriptan or naratriptan must be prospective – that is, reported during pregnancy before the pregnancy outcome is known. Retrospective reports, those where the outcome is already known, are also reviewed by the Registry, although they may be biased toward the reporting of more abnormal outcomes and are much less likely to be representative of the general population experience, and therefore cannot be used for risk assessment or analysis. Health care providers with patients exposed to sumatriptan or naratriptan during pregnancy who are willing to provide follow-up information at outcome are 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 is reported prospectively, the Registry collects registration data from the treating health care provider through telephone interview or a short registration form. In this study, there are minimum requirements for how much and what kind of data must be collected before considering a pregnancy eligible for registration. The minimum data points required include: 1) country of origin of report, 2) documentation that the Registry drug was taken during pregnancy, 3) enough information to confirm that the pregnancy is 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 is already known or is 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 is sent to the health care provider requesting information on maternal risk factors throughout the pregnancy, pregnancy outcome, and neonatal health. Additional follow-up is not sought from subsequent health care providers.

A report of an exposure is closed when the following information has been obtained: clear information on the sumatriptan or naratriptan exposure and pregnancy outcome determination. A report may be closed as "lost to follow-up" when the Registry does 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 are closed as "lost to follow-up" only after the reporting health care provider has been repeatedly contacted for follow-up information well beyond the expected delivery date, or if the reporting health care provider can no longer locate the patient. Only data from "closed" reports of exposed pregnancies with known outcomes are summarized in this Report.

6.2 Patient Confidentiality

The Registry on a regular basis makes efforts to assure patient confidentiality, including review of data privacy issues. For this reason, an additional patient confidentiality measure was established. Each registered patient receives a Registry-assigned patient identification number provided to the reporter at the time of patient registration. This number is used in all subsequent communication with the health care provider. (See Appendix C for instructions on how to obtain patient identification numbers.)

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 conducts an annual review with requests for quarterly 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 satisfies the requirements for a waiver of authorization (*Standards for Privacy of*

Individually Identifiable Health Information CRF 45, Part 160, Part 164 A-E, http://www.hhs.gov/ocr/hipaa; *Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule,* http://privacyruleandresearch.nih.gov.).

6.3 Classification of Outcomes

The Registry adopts the term "birth defect" for abnormalities usually referred to as "congenital abnormality". For purposes of data reporting, pregnancy outcomes are categorized as one of the following: 1) outcomes with birth defects, 2) outcomes without reported birth defects, or 3) spontaneous pregnancy losses. The second category is further classified as, a) live births, b) fetal deaths, and c) induced abortions. The Registry adopts 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 adopts the list of birth defects recognized by the CDC MACDP (Centers for Disease Control 1989; Correa-Villaseñor *et al,* 2003, Correa *et al*, 2007). All defects are classified in consultation with the CDC Division of Birth Defects and Developmental Disabilities. The Registry adopts the consensus approach of being more conservative and including all defects, including on a case-by-case basis 3 or more minor/conditional birth defects as classified in the CDC MACDP as conditional exclusions in the absence of a major defect (Centers for Disease Control 1989). The Registry Advisory Committee reviews reports of combinations of three or more minor/conditional birth defects to determine if the combination could indicate a major defect, even though the occurrence of each minor/conditional defect alone might be excluded by the CDC MACDP guidelines (Centers for Disease Control 1989; Correa-Villaseñor *et al,* 2003, Correa *et al*, 2007). All defects are included in the "outcomes with birth defects" category, whether or not the infant is born alive, (including any structural defect in an infant born prior to 20 gestation weeks or weighing <500 gm). The Registry, however, does conform to the CDC MACDP guidelines in disqualifying as defects those findings that are present in infants born at less than 36 weeks of gestation and are attributable to prematurity itself, such as patent ductus arteriosus or inguinal hernias. The CDC MACDP classification does include chromosomal defects. Though these defects are not likely to contribute to a risk for a drug exposure, the Registry includes these defects to maintain this consistency with the CDC MACDP.

Live-born infants with only transient or infectious conditions, or biochemical abnormalities, are classified as being without reported birth defects unless there is a possibility that the condition reflects an unrecognized birth defect. Detected and reported transient or infectious conditions or biochemical abnormalities in infants without reported birth defects and defects that are excluded by the CDC guidelines are noted in Appendix A.

6.4 Exclusions

For the Registry, emphasis is placed on prospective registration of pregnancies involving use of sumatriptan and/or naratriptan during pregnancy. However, the Registry encourages reporting of all known prenatal exposures to sumatriptan or naratriptan, though not all reports are appropriate for inclusion in the analysis of data. Pregnancies included in the data analysis are those prospectively registered by health care providers.

Occasionally, the Registry receives prospective or retrospective notification of prenatal exposures and pregnancy outcomes from patients, which are never verified by a health care provider. The Advisory Committee also reviews these outcomes as they may be helpful for detecting a possible pattern of defects. Since there is no denominator from which risk can be calculated, these reports are excluded from the data analysis. They are summarized in Appendix B of this Interim Report.

6.5 Analysis

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

The calculations of risk to sumatriptan or naratriptan for birth defects are 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 is calculated separately for sumatriptan and naratriptan, with reports of exposures to both sumatriptan and naratriptan 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 and all spontaneous pregnancy losses are excluded from this calculation. A 95% confidence interval is calculated using the Fleiss method (Fleiss 1981). Fundamental to the assessment process the Advisory Committee uses to review data are the following concepts. The overall frequency of major malformations in metropolitan Atlanta reported by the MACDP from 1968 through 2003 was 2.67%. (Correa *et al*, 2007). The estimated risk quoted in the literature may vary due to differences in case definition, population sampled, and ascertainment methods. The Collaborative Perinatal Project, using a broader case definition and prospective ascertainment, reported a frequency of 5%-7% (Chung *et al,* 1975). The baseline risk of individual 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 are included in the Interim Reports for the Registry.

The basic criteria for review of data for a specific case are: 1) was the timing of the exposure to sumatriptan or naratriptan 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 reviews 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 are reported at variable and, at times, imprecise times. For example, if a pregnancy is registered at 10 weeks, only a spontaneous loss after this time can be detected and included in the prospective reports. Similarly, pregnancy losses occurring early in gestation may not be recognized and/or reported.

While the Registry is limited to prospective reports, some pregnancy exposures are reported only following pregnancy outcome (retrospective reports). The Registry also reviews 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 is the Advisory Committee formed to oversee the process and results. The Advisory Committee is 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 reviews all data in the Registry on an ongoing basis, and meets twice a year to review the aggregate data. Members of the Advisory Committee agree on an interpretation of the data, and provide strategies for the dissemination of information regarding the Registry. An Interim Report is prepared after each meeting to summarize these aggregate data. Since the Report contains historical information as well as the new data, it completely supercedes all previous Reports. This Report is available to health care providers who treat this specialized population.

6.6 Potential Biases

As reporting of pregnancies is totally voluntary, it is possible that even in prospectively reported pregnancies there could be bias in the type of pregnancies reported. For example, high-risk or low-risk pregnancies may be 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 attempt 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 be known to the reporting physician.

Those pregnancies that have reached estimated dates of delivery but for which outcome information was unobtainable are considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. All attempts are 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 are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized birth defect. Detected and reported transient or infectious conditions or biochemical abnormalities in infants without birth defects and defects that are excluded by the CDC guidelines 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 – 30 April 2007

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.
27. *	Live infant: Jaundice a few days after birth.

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

Sumatriptan

Report #	2nd Trimester Exposure
1.	Live infant: Physiologic hyperbilirubenemia, prematurity – events resolved.

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).

* Denotes cases that are new since the last Report

Appendix B: Patient Reported Prenatal Sumatriptan and Naratriptan Exposures

Prospective:

Criteria for inclusion in the prospective Registry require 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 continues to accept reports of exposures from patients, without confirmation by health care providers, but they are not included in the prospective Registry section of the Interim Report. All patient-reported prenatal exposures are accounted for here.

Through 30 April 2007, there are 82 reports of prenatal exposure to sumatriptan prospectively made to the Registry by patients who have never been confirmed by a health care provider. Of these 82 reports, 73 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. 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 30 April 2007, there are 8 reports of prenatal exposure to naratriptan prospectively made to the Registry by patients who have never been confirmed by a health care provider. All 8 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.

1 January 1996 – 30 April 2007

Sumatriptan

(a) Live infant: Dislocated hip.

Retrospective:

Through 30 April 2007, there have been 3 birth defects retrospectively reported by a patient exposed to sumatriptan without confirmation from a health care provider. There are no retrospective defects reported by patients exposed to naratriptan.

1 January 1996 – 30 April 2007

Sumatriptan

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

(b) Spontaneous loss: Heart problem.

(c) Live infant: Microcephaly-slower development.

* Denotes cases that are new since the last Report

Appendix C: Background - Sumatriptan and Naratriptan

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

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®)

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

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 cervico-thoracic 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.

Appendix D: Registry Enrollment and Data Forms

The Registry is a voluntary enrollment program. Such a case-registration approach only works with the continued participation of health care providers who register patients and assist in providing follow-up information postpartum. The assistance of health care providers who have provided information to the Registry is greatly appreciated, and the help of others is eagerly sought. The Registry strongly encourages registration as early in pregnancy as possible, before any tests to determine the presence of defects are conducted to strengthen the validity of the study.

Registry enrollment and Follow-up forms may be obtained by contacting the Sumatriptan and Naratriptan Pregnancy Registry or the data forms may be copied from the included samples to prospectively report prenatal exposures to sumatriptan or naratriptan. Patient registration may be accomplished by sending the registration forms via mail or FAX transmission at 800-800-1052 or 910-256-0637, by calling the Registry at 800-336-2176 or 910-256-0549 (call collect), or printing the data forms off the website http://www.kendle.com/registries

Instructions for completing forms:

Patient Anonymity and Patient Identifiers

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

Patient IDs can be obtained by calling or faxing the Registry for a number (or a block of numbers, for providers who register patients on a regular basis). The Registry also provides a **Patient Log** as a tool for cross-referencing the patient with the Registry Patient (Log) ID number if necessary. Whatever method is used, it is very important to keep the cross-reference record in a secure place to protect patient confidentiality at your site.

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

- Copy all pages of the Registration Form
- Fill in as much information as is available at the time of reporting
- Report as early as possible after the exposure is known to you

Return the form to the Registry. In the month of the patient's estimated date of delivery, a short Follow-Up Form will be sent to the health care provider to report the pregnancy outcome information.

In the USA, mail the completed form(s) to:

Sumatriptan and Naratriptan Pregnancy Registry
Research Park
1011 Ashes Drive
Wilmington, NC 28405 USA

OR

Register via FAX transmittal by dialing:

800-800-1052 (toll-free in North America) or 910-256-0637

OR

Register via phone by dialing 800-336-2176 or 910-256-0549 (call collect)

Outside the US, contact the Medical Director of the GlaxoSmithKline Company in your country.

Keep in a secure place to protect patient confidentiality

SUMATRIPTAN AND NARATRIPTAN 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 is 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 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 2007***	***15 Jan 2007***

CONFIDENTIAL

SUMATRIPTAN AND NARATRIPTAN 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 AND/OR NARATRIPTAN DOSES DURING THIS PREGNANCY

Enter the ***sumatriptan and/or naratriptan 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 and/or naratriptan*** 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 and/or naratriptan*** 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 and naratriptan, 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 AND NARATRIPTAN 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

Patient Age _____

Is there evidence of a defect from a prenatal test? ☐ Yes ☐ No

Last Menstrual Period _____ _____ _____ (day month year)

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

☐ Ultrasound ☐ Amniocentesis ☐ MSAFP ☐ Other: _____

Estimated Date of Delivery _____ _____ _____ (day month year)

How was the Estimated Date of Delivery determined?

☐ by Last Menstrual Period ☐ by Ultrasound ☐ Unknown ☐ by Other Method: _____

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

	Date of Treatment *(d/m/y)*	# of Days	Total Daily Dose *(total mg/day)*	Gestation Week *(from LMP)* Course Began*	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						

- *If Course 1 occurred prior to conception, enter 0*

The above treatment dates are based upon (check one):

☐ **Medical Chart** ☐ **Patient Diary** ☐ **Best Recollection** ☐ **Other** _____ **(specify)**

3. HEALTH CARE PROVIDER INFORMATION

Name _____ Specialty _____

Address _____ Phone _____

_____ Fax _____

_____

Alternate Contact _____

Provider's Signature _____ Date _____ _____ _____ (day month year)

SUMATRIPTAN AND NARATRIPTAN 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 AND/OR NARATRIPTAN DOSES DURING THIS PREGNANCY

Enter the ***sumatriptan and/or naratriptan 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 or naratriptan 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 or naratriptan 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 and naratriptan 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 AND NARATRIPTAN 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

1. MATERNAL DATA

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

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

	Date of Treatment *(d/m/y)*	# of Days	Total Daily Dose *(total mg/day)*	Gestation Week *(from LMP)* Course Began*	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						

- *If Course 1 occurred prior to conception, enter 0*

3. 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: _____	_____	_____	_____

4. 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***

5. 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: _____	☐	☐	☐	☐

Registry Patient ID_____

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910-256-0637 (All International Faxes)

(FOR OFFICE USE ONLY)

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

6. 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)?

7. HEALTH CARE PROVIDER INFORMATION

Name _____ Specialty _____

Address _____ Phone _____

_____ Fax _____

_____

Alternate Contact _____

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