

GSK Medicine: Sumatriptan, naratriptan, sumatriptan-naproxen combination (Treximet™)
Study No.: WWE112914/ EPIP082/EPI40050
Title: The Sumatriptan, Naratriptan and Treximet Pregnancy Registry
<p>Rationale: GlaxoSmithKline sponsors the Sumatriptan, Naratriptan and Treximet 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.</p> <p>The purpose of the Registry is to collect voluntary prospective reports of sumatriptan, naratriptan and sumatriptan/naproxen combination prenatal exposures. 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. From 2008 exposures to the sumatriptan/naproxen combination product (Treximet) have also been collected.</p> <p>Data from the registry are reviewed and conclusions developed by an independent scientific advisory committee, comprised of experts in headache, neurology, teratology, obstetrics and epidemiology on a semi-annual basis. The resulting reports are published at http://pregnancyregistry.gsk.com/index.html and made available to regulators.</p>
<p>Objectives:</p> <ul style="list-style-type: none"> a) to assess the risk of major birth defects (MBDs) following exposure to sumatriptan, naratriptan or the sumatriptan/naproxen combination in pregnancy and b) to provide information on outcomes following pregnancy exposure to sumatriptan, naratriptan and sumatriptan/naproxen combination and c) to generate hypotheses concerning potential associations with specific defect types, to be tested through appropriately designed studies.
Indication: Migraine
Study Investigators/Centers: The International Registry is managed by Kendle International Inc.
<p>Research Methods:</p> <p>Data Source: Primary data collection (January 1, 1996 to 31 October, 2009).</p> <p>Study Design: An observational, exposure-registration follow-up study.</p> <p>Study Population: Women exposed to sumatriptan, naratriptan or the sumatriptan/naproxen combination during pregnancy across 18 countries.</p> <p>Recruitment and Data Collection: Healthcare professionals with patients exposed to sumatriptan, naratriptan or the sumatriptan/naproxen combination during pregnancy are encouraged to prospectively enroll each patient in the registry. Reporting of exposed pregnancies is voluntary. Pregnancies must be registered prospectively following prenatal exposure to sumatriptan or naratriptan and prior to knowledge of the pregnancy outcome. Health care providers with patients exposed to sumatriptan, naratriptan or the sumatriptan/naproxen combination 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.</p> <p>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 with the healthcare provider to obtain and assess the pregnancy outcome. 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. They therefore cannot be used for risk assessment or analysis.</p> <p>When the pregnancy is reported prospectively, the Registry collects registration data from the treating health care provider through a telephone interview or a short registration form. In this study, there are minimum requirements for</p>

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 (i.e. if the mother has changed healthcare provider).

A report of an exposure is closed when the following information has been obtained: clear information on the sumatriptan, naratriptan or sumatriptan/naproxen combination 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.

The study has undergone Institutional Review Board (IRB) review and approval. 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.

Study Outcomes:

The primary outcome is all major congenital malformations. The Registry adopts the following definition for birth defect 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 Metropolitan Atlanta Congenital Defects Surveillance Program (MACDP) (Centers for Disease Control; Correa-Villaseñor *et al*, 2003). All defects are classified in consultation with an expert in pediatrics and birth defects from the CDC Division of Birth Defects and Developmental Disabilities. The Registry conforms 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.

Study Exposures

All pregnancies included in the registry have been exposed to sumatriptan, naratriptan or the sumatriptan/naproxen combination in pregnancy. Exposure is classified by trimester (second trimester begins at 14 weeks gestations and third trimester at 28 weeks gestation), and by birth outcome (live birth, induced abortion, spontaneous loss (<20 weeks), fetal loss (>20 weeks).

Study comparator groups

There is no internal control/comparator group as this is a drug specific pregnancy registry. The risk of major birth defects in sumatriptan, naratriptan or sumatriptan/naproxen combination exposed pregnancies is descriptively compared with risk estimates from general population surveillance programs (CDC MACDP and the Brigham and Women's Hospital Surveillance program) and from reports in the literature from cohorts of women with migraine.

Data Analysis Methods:

The percentage of infants with major birth defects and 95% confidence intervals (Wilson score method with continuity correction) are calculated by trimester of exposure to sumatriptan, naratriptan or the sumatriptan/naproxen combination as:

$$\frac{\text{the total number of outcomes with major birth defects}}{\text{the number of outcomes with major birth defects} + \text{the number of live births without major birth defects}}$$

(the number of outcomes with major birth defects + the number of live births without major birth defects).

All spontaneous pregnancy losses, as well as elective terminations and fetal deaths without reported defects and pregnancies lost to follow up, are excluded from the denominator due to the likelihood of inconsistent identification of defects in those situations.

The risk of major birth defects following first trimester exposure to sumatriptan, naratriptan or the sumatriptan/naproxen combination is of primary interest as this represents the period of organogenesis.

For those pregnancies exposed to a combination of the products of interest (e.g. sumatriptan and naratriptan), a conservative approach is adopted and exposures are included in risk calculations for the individual drugs involved.

Descriptive comparisons are made with estimates of the risk of major birth defects from general population surveillance programs (2.1 – 2.7% from MACDP depending on time of observation after birth (birth to one year) (Correa *et al.* 2007) and 1.6 – 2.2% from Brigham and Women's Hospital (Nelson *et al.* 1989) and with risks reported in the literature from cohorts of women with migraine (3.4%, 95% CI: 2.1%-4.6% Wainscott *et al.*, 1978).

Limitations:

As reporting of pregnancies is 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.

The Registry has no internal control group. Therefore descriptive comparisons are made with several external groups to assess consistency in risk patterns. However, the underlying differences in data collection between studies, as well as potential underlying differences between the migraine and general population groups limits conclusions that can be drawn.

Study Results:**Total N**

	Sumatriptan	Naratriptan	Sumatriptan/naproxen
Total number of pregnancies registered	772	92	4
No. closed with known outcome	580	57	1
No. pending	21	4	3
No. lost to follow up	171 (22.8%)	31 (35.2%)	0 (0%)

Of the 580 pregnancies with known outcome exposed to sumatriptan, 73% were registered from the US.

Of the 57 pregnancies with known outcome exposed to naratriptan, 54% were registered from the US.

Exposure in Pregnancy by earliest trimester of pregnancy								
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	16 ^e	1	3	433 ^e	4	11	32	500
Second	3	0	0	66	0	0	0	69
Third	0	0	0	15 ^e	0	0	0	15
Unspecified	0	0	1	3	0	0	0	4
Total	19	1	4	517	4	11	32	588
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	45 ^e	0	1	5	52
Second	0	0	0	5 ^e	0	0	0	5
Third	0	0	0	0	0	0	0	0
Unspecified	0	0	0	0	0	0	0	0
Total	1	0	0	50	0	1	5	57
All Sumatriptan/Naproxen combination 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	0	0	0	0	0	0	1	1
Second	0	0	0	0	0	0	0	0
Third	0	0	0	0	0	0	0	0
Unspecified	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	0	1	1
^a Birth defect not reported but cannot be ruled out ^b Pregnancy loss occurring < 20 weeks gestation ^c Pregnancy loss occurring ≥ 20 weeks gestation ^d Not included in the risk calculation ^e Includes reports of exposure to both sumatriptan and naratriptan ^f Includes defect and non-defect reports. Due to the likelihood of inconsistent identification of defects, spontaneous losses < 20 weeks gestation and fetal deaths and induced abortions without reported defects are excluded from the calculation of the risk of birth defects.								
Data Summary: Risk of major birth defects (MBDs) by earliest trimester of exposure								
Sumatriptan								
First trimester:	20 MBDs among 453 outcomes: 4.4% (95% CI 2.8% - 6.9%)							
Second trimester:	3 MBDs among 69 outcomes: 4.3% (95% CI 1.1% - 13.0%)							
Third trimester:	0 MBDs among 15 outcomes: no risk and 95% CI due to small numbers							
Unspecified trimester:	1 MBD among 4 outcomes: no risk and 95% CI due to small numbers							
All trimesters	24 MBDs among 541 outcomes: 4.4% (95% CI 2.9% - 6.6%)							
Naratriptan								
First trimester	1 MBD among 50 outcomes: 2.0% (95% CI 0.1% - 12.0%)							

Description of major birth defects by trimester of exposure to sumatriptan	
Description of major birth defect	Maximal dose in exposed trimester (milligrams/day)
First trimester	
Cerebral abnormality/developmental delay	100
Moderate craniostenosis in twin infant	20
Partial small cleft lip	25
Ventricular septal defect (4)*	50, 100, unknown (2)
Systolic murmur (also abnormal head circumference)	100
Biliary atresia	100
Diaphragmatic hernia	24
Pyloric stenosis (3)	100, 200, 100
Anterior displacement of anus	25
Malformation of left hand	6
Polydactyly	100
Hip dysplasia	100
Down Syndrome (2)	50, 100
Trisomy 18	50
Second trimester	
Congenital hyperthyroidism	Unknown
Trisomy 21	50
Webbing of first joint of three toes on left foot	200
Unspecified trimester	
Down syndrome	Unknown
* Also exposed in first trimester to naratriptan (dose unknown)	
A description of all retrospectively reported birth defects can be found in the latest sumatriptan and naratriptan pregnancy registry report at http://pregnancyregistry.gsk.com/index.html	
There is currently outcome information available on one first trimester exposure to the sumatriptan/naproxen combination: a spontaneous pregnancy loss.	
Conclusion:	
Sumatriptan: Currently, the frequency of major birth defects for first trimester sumatriptan exposures in the Registry is 4.4% (95% Confidence Interval for observed proportion: 2.8%-6.9%). The overall frequency of major birth defects reported by the MACDP, using the same defect classification, ranges from 2.1% to 2.7% depending on the length of the	

period of ascertainment (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). While this frequency of birth defects in sumatriptan exposed pregnancies 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.

If the baseline frequency of total birth defects is 2-3 in 100 live births, a sample size of 453 for first trimester sumatriptan exposures has an 80 percent chance (80% power) of correctly detecting at least a 1.75 to 1.94-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 453 for first trimester exposure has an 80 percent chance (80% power) of correctly detecting at least a 6.68-fold increase from baseline in the frequency of a specific birth defect.

The Advisory Committee notes the occurrence of ventricular septal defect (VSD) in 4 of the 453 (0.88%) prospective first trimester sumatriptan exposures. The Swedish Medical Birth Registry (Kallen *et al*, 2001) reported a slightly higher 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 VSDs after first trimester exposure to sumatriptan. No other consistent pattern of defects has been observed to date among the birth defects reported to the Registry.

Naratriptan: Currently, the registry reports 1 major birth defect among 46 first trimester naratriptan exposures. While this frequency is encouraging, the number of exposed pregnancy outcomes accumulated to date represents a sample of insufficient size for making comparisons of the frequency of specific birth defects or for reaching definitive conclusions regarding the possible teratogenic risk of naratriptan. It is expected that a teratogenic exposure in the first trimester would result in an increased frequency of one or a combination of individual defects or types of defects, but not necessarily in all defects.

If the baseline frequency of total birth defects is 2-3 in 100 live births, a sample size of 46 for first trimester naratriptan exposures has an 80 percent chance (80% power) of correctly detecting at least a 3.80 to 4.60-fold increase from baseline in the frequency of total birth defects. If the baseline frequency for a specific birth defect is 1 in 1000 live births, a sample size of 46 for first trimester exposure has an 80 percent chance (80% power) of correctly detecting at least a 30.25-fold increase from baseline in the frequency of a specific birth defect.

Sumatriptan/naproxen combination: Outcome data are available for only one first trimester exposure to the sumatriptan/naproxen combination enrolled in the Registry, a spontaneous pregnancy loss.

References:

Botto LD, Correa A, Erickson JD. Racial and temporal variations in the prevalence of heart defects. *Pediatrics* 2001;107:E32.

Centers for Disease Control and Prevention. Metropolitan Atlanta Congenital Defects Program 6-Digit code defect list. To access an electronic copy of the code list, go to http://www.cdc.gov/ncbddd/bd/macdp_resources.htm and click on the 3rd bullet.

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

Correa A, Cragan JD, Kucik JE, *et al.* Metropolitan Atlanta Congenital Defects Program 40th Anniversary Edition Surveillance Report: Reporting Birth Defects Surveillance Data 1968-2003. *Birth Defects Research (Part A)* 2007; 79 (2):65-186.

Kallen B, Lygner PE. Delivery outcome in women who used drugs for migraine during pregnancy with special reference to Sumatriptan. *Headache* 2001;41:351-356.

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

Roguin N, Du ZD, Barak M, Nasser N, Hershkowitz S, Milgram E. High prevalence of muscular ventricular septal defect in neonates. *J Am Coll Cardiol* 1995;26:1545-1548.

Wainscott G, Volans GN, Sullivan FM, Wilkinson M. The outcome of pregnancy in women suffering from migraine. *Postgrad Med J* 1978;54:98-102.