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Triptans in Pregnancy

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Abstract

The triptans are a class of tryptamine-based drugs indicated for in the treatment of migraine headaches. The triptans act as serotonin (5-hydroxytryptamine) (5-HT) agonists by binding to various serotonin receptors, causing vasoconstriction and neuronal inhibition to alleviate migraines. There are 7 types of triptans currently available on the U.S. market: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan. The objective of this study was to examine the use and effects of triptans in pregnancy. Although three of the triptans have pregnancy registries maintained by the manufacturer, triptan use in pregnancy has not been extensively studied. Information on the use of sumatriptan during pregnancy is relatively more abundant, because it has been on the market longer than the other triptans and may also have a higher percentage of the market share. There are no data to suggest teratogenicity for any of the triptans, although preterm birth rates appear to be elevated.

Keywords

serotonin uptake agonists; serotonin receptor; 5-HT; adverse drug events; pharmacology; migraine disorder/drug therapy/physiopathology; gestation

INTRODUCTION

Migraine headaches affect about 16% to 21% of the general population.¹ Whereas the incidence of migraine is about 2.5 times higher among women than men, cases are even more frequent in menstruating women.² In pregnancy, the frequency of migraines tends to decrease throughout gestation, especially during the second and third trimesters.³ This improvement has been reported to occur in 55% to 90% of women during pregnancy² and remains unchanged in 25% of pregnant patients.³

Triptans (as well as drugs such as aspirin and paracetamol/acetaminophen) are considered relatively safe for the treatment of migraines during pregnancy, in comparison with drugs such as ergotamine tartrate and dihydroergotamine, which are typically contraindicated.² Yet, to date, there have been no specific clinical investigations of triptan use during human pregnancy. Furthermore, animal studies conducted on each of the triptans suggest that such

drugs could be used during pregnancy, if the benefits outweigh the risks (product prescribing information).

Currently, 7 triptans are marketed in the United States (Table 1): sumatriptan (Imitrex, Imigran), rizatriptan (Maxalt), naratriptan (Amerge, Naramig), zolmitriptan (Zomig), eletriptan (Relpax), almotriptan (Axert, Almogran), and frovatriptan (Frova, Migard). Sumatriptan, the first triptan to be approved by the U.S. Food and Drug Administration (FDA), was introduced in 1992 and probably has the largest share of the triptan market today. As a result, more post-marketing data are available for sumatriptan than for the other triptans.⁴

THE MECHANISM OF ACTION OF TRIPTANS

Triptans are derivatives of tryptamine and thus share a common structure. They act as serotonin (5-hydroxytryptamine, or 5-HT) agonists by binding to its various receptors. The triptan types differ by their capability to bind to specific 5-HT receptor subtypes.⁵ Because of the varying binding affinities of the different triptans (Table 2), they provoke varying physiological and pharmacological effects. Several mechanisms of action have been proposed for the efficacy of triptans in treating migraines.⁶⁻⁹ The most likely is the activation of the 5-HT receptors, which subsequently decreases the amplified blood flow causing the migraine.⁷ Moreover, triptans may alleviate pain but do not provide cure or prevention.¹⁰

THE METABOLISM OF TRIPTANS DURING PREGNANCY

Triptans are oxidized via phase I metabolic reactions by cytochrome P450 (CYP) enzymes CYP3A4, CYP1A2, and CYP2D6, and monoamine oxidase-A (MAO-A).¹¹ The specific enzymes involved in the metabolism of each of the triptans are summarized in Table 3. The metabolism of triptans is affected by competing drugs that utilize, inhibit, or induce metabolic enzymes, such as MAO or CYP450 isozymes.¹¹ CYP3A4, CYP1A2, and CYP2D6 are the major metabolizing enzymes for eletriptan, frovatriptan, naratriptan, and zolmitriptan. During pregnancy, the activity of CYP3A4 and CYP2D6 increases; therefore, the activity and efficacy of these triptans may be altered accordingly (Table 3). This increase or decrease should be taken into consideration if triptan use is to be continued during gestation.

The monoamine oxidases are the major enzymes involved in the metabolism of almotriptan, rizatriptan, and sumatriptan (Table 3). Although some study reports claim that pregnancy and estrogen-progesterone oral contraceptives do not affect MAO activity, subsequent studies contradict this finding and maintain that MAO activity decreases in pregnancy.¹² Platelet MAO activity decreases during pregnancy in humans.¹³ Furthermore, in animal studies, the pregnancy-related increase in estrogen levels decreased MAO-A activity.^{14,15} On the basis of activities of the primary metabolic enzymes, one would expect a decrease in metabolism for every triptan except eletriptan (and possibly naratriptan) during pregnancy. This in turn could result in more pronounced toxicity/side effects of triptans.

STUDIES OF TRIPTANS IN PREGNANCY

The data on prenatal adverse effects and teratogenicity of triptans in humans are limited, and the reports are somewhat conflicting. As previously mentioned, the data for sumatriptan use is the most significant, as summarized in Table 4. The reported adverse effects of sumatriptan depend on whether the drug is administered orally, nasally, or parenterally. In animal studies, subcutaneous administration of the drug caused a decrease in pup survival at

a relatively low dose, although the bioavailability of the drug is 15% whether administered orally or subcutaneously (sumatriptan prescribing information, Glaxo-SmithKline, 2007).

Adverse effects resulting from maternal or fetal exposure in utero include low birth weight, preterm delivery, and minor fetal anomalies.^{1,3,16} Of the 500 subjects reported in the pregnancy registry for sumatriptan, 4 infants (0.8%) were born with ventricular septal defect (VSD).¹⁷ However, this is not a significant finding, because it is estimated that in the United States up to 4.36% of babies are born with this condition.¹⁸

Animal studies have shown that sumatriptan crosses the placenta in rabbits,⁴ whereas human studies show that approximately 15% of the sumatriptan dose ($t_{1/2} = 2.5$ hours) crosses the placenta over 4 hours.¹⁹ Because fetal 5-HT_{1B/1D} receptors develop through the third trimester, it is not clear whether the triptans could affect fetal development.²⁰

Table 4 summarizes data obtained from animal studies, reported by the individual triptan pharmaceutical manufacturers (individual triptan product information). Among the seven triptans reported, naratriptan ($t_{1/2} = 6$ hours) induced developmental toxicity in pregnant rats and rabbits at oral doses producing maternal plasma drug levels at 2.5 times the maximum recommended daily dose (MRDD). The MRDD for pharmaceuticals is empirically derived from human clinical trials and is an estimated upper dose limit beyond which a drug's efficacy is not increased and/or undesirable adverse effects begin to outweigh beneficial effects. Intravenous administration of sumatriptan to rabbits, at one-tenth of the maximum recommended daily human oral dose, caused embryoletality as well as maternal toxicity in rats (sumatriptan product information, Glaxo-SmithKline, 2007). Because of the very low margin described for this formulation, caution should be practiced when using the injected form. Other triptans have distinct no-effect doses depending on the different conditions and dosage forms.

Studies based on pregnancy registries for sumatriptan and rizatriptan are summarized in Table 5. The most common adverse events reported with the use of triptans during pregnancy are spontaneous abortion, preterm delivery (defined medically as birth occurring earlier than 37 completed weeks of gestation), and low birth weight (<2.5 kg or <5 lb 8 oz). However, one must consider that reporting to these pregnancy registries is voluntary and therefore not comprehensive or systematic. Furthermore, it is more likely that adverse events would be reported and therefore there is a reporting bias.

Several different databases are located in the United States and Europe (eg, U.S. pregnancy registries; Danish birth registry; Swedish birth registry). Of the two studies that measured the incidence of preterm birth following intrapartum sumatriptan use, a statistically significant increase was reported in only one, whereas a slight but nonsignificant increase in preterm births was reported in the other.^{1,16} Preterm birth appears to be the most common adverse event reported due to the use of triptans during pregnancy. Maternal use of sumatriptan during the third trimester increased the sensitivity of 5-HT_{1B/1D} receptors, leading to umbilical cord artery contraction in normal pregnancies.²⁰

Low concentrations of most triptans are detected in breast milk (Table 5). Moreover, sumatriptan and eletriptan levels measured in human breast milk were much lower than levels in maternal serum.²¹ Therefore, it is likely that these levels may not adversely affect the nursing baby.

Pregnancy registries were created to track adverse events due to drug exposure during gestation.²² The registries record the trimester of exposure, average dose, maternal health, and neonatal outcome. However, retrospective enrollment is often biased and tends to

include more birth defects.⁴ The only companies currently providing registries are Glaxo-SmithKline and Merck.

Table 6 describes the available registry data for all three triptan manufacturers currently providing this service. As of October 2006, the naratriptan registry had enrolled 55 women, of whom 52 were prospectively enrolled, even though naratriptan has been on the U.S. market since 1998 (Sumatriptan and Naratriptan Pregnancy Registry, 2007).²³ Sumatriptan, the first of its kind to be marketed in 1992, has a large portion of market share. The pregnancy registry for sumatriptan was created in 1996 and includes 500 pregnancies prospectively enrolled through October 2006 (Sumatriptan and Naratriptan Pregnancy Registry, 2007).²³

DISCUSSION

Women suffering from migraine headache whose onsets were at menarche and those with episodes of perimenstrual migraine headache are more likely to go into remission during pregnancy. Furthermore, several retrospective studies have shown a tendency for migraine headache to improve with pregnancy; between 60% and 70% of women with migraine report significant improvement mainly during the second and third trimesters. However, for the remainder, it is of concern that treatment of their migraine symptoms may lead to pregnancy complications, thus making it imperative that the benefits of drug treatment be weighed against the risks. One study has shown that the occurrence of migraines during gestation did not increase the risk for pregnancy complications such as birth defects or miscarriage.²⁴ However, data analysis of migraine treatment during pregnancy is challenging because of the difficulty of distinguishing whether the reported complications are secondary to drug exposure alone or whether the disease severity plays a confounding effect. The current literature does not provide evidence for adverse effects of triptan on pregnancy outcome. The information provided in Table 5 indicates that the only significant finding, out of the Danish registry, is an elevated risk of preterm delivery reported with sumatriptan in comparison with controls—patients with migraine and no treatment¹ [odds ratio (OR), 6.3; 95% confidence interval (CI), 1.2–32.0], while the odds of healthy women having preterm delivery were (OR, 3.3; 95% CI, 1.3–8.5). The same study showed an association between triptan exposure during pregnancy and an increased risk for having a low-birth-weight newborn for all migraine patients who delivered at term (OR, 3.0; 95% CI, 1.3–7.0).

Because of their voluntary nature of reporting, pregnancy registries are subject to recall bias and may overreport possible adverse outcomes. Furthermore, of the seven triptans, only naratriptan, rizatriptan, and sumatriptan have pregnancy registries (Table 6). Therefore, important pregnancy-related information may be lacking for the remaining four triptans (almotriptan, eletriptan, frovatriptan, and zolmitriptan).

The pharmacokinetics of triptans vary widely between individuals and could be explained by the effect of P-glycoprotein efflux transporters, triptan-metabolizing enzymes (CYP450 and MAO), and/or drug bioavailability. Data on the effects of triptans during pregnancy are scarce, and for ethical reasons there are no controlled studies. The available literature indicates that perinatal and pregnancy outcome does not differ for patients exposed to triptans after conception, although preterm birth rates may be slightly elevated. However, the current available information is not adequate for ruling out a mild increase in the risk for teratogenic effects of treatment during pregnancy. Although it is recommended that drugs in general be avoided during pregnancy, particularly when the data are limited, migraine relief is necessary, and therefore risk-benefit decisions should guide triptan use. Even though there may be differences in the safety among the various types of triptans, the data currently

available do not provide sufficient information for any significant conclusion on their relative safety.

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References

- Olesen C, Steffensen FH, Sorensen HT, et al. Pregnancy outcome following prescription for sumatriptan. *Headache*. 2000; 40:20–24. [PubMed: 10759898]
- Pfaffenrath V, Rehm M. Migraine in pregnancy: what are the safest treatment options? *Drug Safety*. 1998; 19:383–388. [PubMed: 9825951]
- Hilaire ML, Cross LB, Eichner SF. Treatment of migraine headaches with sumatriptan in pregnancy. *Ann Pharmacother*. 2004; 38:1726–1730. [PubMed: 15316107]
- Loder E. Safety of sumatriptan in pregnancy: a review of the data so far. *CNS Drugs*. 2003; 17:1–7. [PubMed: 12467489]
- Nelson DL. 5-HT₅ receptors. *Curr Drug Targets CNS Neurol Disord*. 2004; 3:53–58. [PubMed: 14965244]
- Humphrey PPA, Feniuk W. Mode of action of the anti-migraine drug sumatriptan. *Trends Pharmacol Sci*. 1991; 12:444–446. [PubMed: 1665260]
- Nappi G, Sandrini G, Sances G. Tolerability of the triptans: clinical implications. *Drug Saf*. 2003; 26:93–107. [PubMed: 12534326]
- Moskowitz MA. Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. *Trends Pharmacol Sci*. 1992; 13:307–311. [PubMed: 1329294]
- Hoskin KL, Kaube H, Goadsby PJ. Sumatriptan can inhibit trigeminal afferents by an exclusively neural mechanism. *Brain Res*. 1996; 119:1419–1428.
- Graves BW. Management of migraine headaches. *J Midwifery Women's Health*. 2006; 51:174–184. [PubMed: 16647669]
- Armstrong SC, Cozza KL. Triptans. *Psychosomatics*. 2002; 43:502–504. [PubMed: 12444236]
- Feldman JM, Roche J. Effect of oral contraceptives on platelet monoamine oxidase, monoamine excretion, and adrenocortical function. *Clin Pharmacol Ther*. 1976; 20:670–675. [PubMed: 991538]
- Wahlund LO, Saaf J, Eneroth-Grimfors E, et al. Reduced platelet MAO activity during pregnancy. *Acta Physiol Scand*. 1986; 126:135–138. [PubMed: 3953300]
- Parvez S, Parvez SH, Youdim MB. Variation in activity of monoamine metabolizing enzymes in rat liver during pregnancy. *Br J Pharmacol*. 1975; 53:241–246. [PubMed: 1170911]
- Zhang Z, Chen K, Shih JC, et al. Estrogen-related receptors: stimulated monoamine oxidase B promoter activity is down-regulated by estrogen receptors. *Mol Endocrinol*. 2006; 20:1547–1561. [PubMed: 16484337]
- Fox AW, Chambers CD, Anderson PO, et al. Evidence-based assessment of pregnancy outcome after sumatriptan exposure. *Headache*. 2002; 42:8–15. [PubMed: 12005279]
- Briggs G. *Drugs in Pregnancy and Lactation*. Philadelphia: Lippincott Williams & Wilkins; 2005.
- Sands AJ, Casey FA, Craig BG, et al. Incidence and risk factors for ventricular septal defect in “low risk” neonates. *Arch Dis Child Fetal Neonatal Ed*. 1999; 81:F61–63. [PubMed: 10375365]
- Schenker S, Yang Y, Perez A, et al. Sumatriptan (Imitrex) transport by the human placenta. *Proc Soc Exp Biol Med*. 1995; 210:213–220. [PubMed: 8539258]

20. Gupta S, Hanff LM, Visser W, et al. Functional reactivity of 5-HT receptors in human umbilical cord and maternal subcutaneous fat arteries after normotensive or pre-eclamptic pregnancy. *J Hypertens.* 2006; 24:1345–1353. [PubMed: 16794484]
21. Evans RW, Diamond ML. Is sumatriptan use safe during pregnancy? *Headache.* 2000; 40:856–857. [PubMed: 11135034]
22. Reiff-Eldridge R, Heffner CR, Ephross SA, et al. Monitoring pregnancy outcomes after prenatal drug exposure through prospective pregnancy registries: a pharmaceutical company commitment. *Am J Obstet Gynecol.* 2000; 182(1 Pt 1):159–163. [PubMed: 10649172]
23. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk.* 7. Philadelphia: Lippincott Williams & Wilkins; 2005.
24. Aube M. Migraine in pregnancy. *Neurology.* 1999; 53(4 Suppl 1):S26–S28. [PubMed: 10487510]
25. Gras J, Llenas J, Jansat JM, et al. Almotriptan, a new anti-migraine agent: a review. *CNS Drug Rev.* 2002; 8:217–234. [PubMed: 12353056]
26. Deleu D, Hanssens Y. Current and emerging second-generation triptans in acute migraine therapy: a comparative review. *J Clin Pharmacol.* 2000; 40:687–700. [PubMed: 10883409]
27. Johnson DE, Rollema H, Schmidt AW, et al. Serotonergic effects and extracellular brain levels of eletriptan, zolmitriptan and sumatriptan in rat brain. *Eur J Pharmacol.* 2001; 425:203–210. [PubMed: 11513839]
28. Tepper SJ, Rapoport AM, Sheftell FD. Mechanisms of action of the 5-HT_{1B/1D} receptor agonists. *Arch Neurol.* 2002; 59:1084–1088. [PubMed: 12117355]
29. Villalon CM, Centurion D, Valdivia LF, et al. Migraine: pathophysiology, pharmacology, treatment and future trends. *Curr Vasc Pharmacol.* 2003; 1:71–84. [PubMed: 15320857]
30. Jahnichen S, Glusa E, Pertz HH. Evidence for 5-HT_{2B} and 5-HT₇ receptor-mediated relaxation in pulmonary arteries of weaned pigs. *Naunyn Schmiedebergs Arch Pharmacol.* 2005; 371:89–98. [PubMed: 15726452]
31. Pauwels PJ, Palmier C, Dupuis DS, et al. Interaction of 5-HT_{1B/D} ligands with recombinant h 5-HT_{1A} receptors: intrinsic activity and modulation by G-protein activation state. *Naunyn Schmiedebergs Arch Pharmacol.* 1998; 357:490–499. [PubMed: 9650800]
32. Razzaque Z, Pickard JD, Ma QP, et al. 5-HT_{1B}-receptors and vascular reactivity in human isolated blood vessels: assessment of the potential craniovascular selectivity of sumatriptan. *Br J Clin Pharmacol.* 2002; 53:266–274. [PubMed: 11874390]
33. Silva SA, Marques FB, Fontes Ribeiro CA. Characterization of the human basilar artery contractile response to 5-HT and triptans. *Fundam Clin Pharmacol.* 2007; 21:265–272. [PubMed: 17521295]
34. Boess FG, Monsma FJ Jr, Sleight AJ. Identification of residues in transmembrane regions III and VI that contribute to the ligand binding site of the serotonin 5-HT₆ receptor. *J Neurochem.* 1998; 71:2169–2177. [PubMed: 9798944]
35. Bai F, Yin T, Johnstone EM, et al. Molecular cloning and pharmacological characterization of the guinea pig 5-HT_{1E} receptor. *Eur J Pharmacol.* 2004; 484:127–139. [PubMed: 14744596]
36. Thomas DR. 5-HT_{5A} receptors as a therapeutic target. *Pharmacol Ther.* 2006; 111:707–714. [PubMed: 16516972]
37. O'Quinn S, Davis RL, Gutterman DL, et al. Prospective large-scale study of the tolerability of subcutaneous sumatriptan injection for acute treatment of migraine. *Cephalalgia.* 1999; 19:223–231. discussion, 200. [PubMed: 10376167]
38. Fiore M, Shields KE, Santanello N, et al. Exposure to rizatriptan during pregnancy: post-marketing experience up to 30 June 2004. *Cephalalgia.* 2005; 25:685–688. [PubMed: 16109049]
39. 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. [PubMed: 11318881]
40. Shuhaiber S, Pastuszak A, Schick B, et al. Pregnancy outcome following first trimester exposure to sumatriptan. *Neurology.* 1998; 51:581–583. [PubMed: 9710039]

TABLE 1**Triptans: Trade Names and Manufacturers**

Generic Name	Trade Name	Year FDA Approved	Manufacturer
Almotriptan	Axert	2001	Ortho-McNeil
Eletriptan	Relpax	2002	Pfizer
Frovatriptan	Frova	2001	Endo
Naratriptan	Amerge	1998	Glaxo-SmithKline
Rizatriptan	Maxalt	1998	Merck
	Maxalt Disintegrating		
Sumatriptan	Imitrex Injectable	1992	Glaxo-SmithKline
	Imitrex Tabs	1995	
	Imitrex Nasal	1997	
Zolmitriptan	Zomig	1997	AstraZeneca
	Zomig	2001	
	Disintegrating	2003	
	Zomig Nasal		

TABLE 2

Individual Triptan Classes and Subtypes of Serotonin Receptors and Metabolic Pathways^{11,25–36}

Generic Name	High-Affinity Receptor Binding	Weak-Affinity Receptor Binding	Modest-Affinity Receptor Binding	Reference
Almotriptan	5-HT _{1D}	5-HT _{1A}		11,25
	5-HT _{1B}	5-HT ₇		
	5-HT _{1F}			
Eletriptan	5-HT _{1B}		5-HT _{1A}	11,26–29
	5-HT _{1D}		5-HT _{1E}	
	5-HT _{1F}		5-HT ₇ [*]	
Frovatriptan	5-HT _{1B}			11, 26, 28–30
	5-HT _{1D}			
	5-HT _{1F}			
Naratriptan	5-HT _{1D}		5-HT _{1A}	11,31–33
	5-HT _{1B}			
	5-HT _{1F}			
Rizatriptan	5-HT _{1B}	5-HT _{1A}		11,26,28, 29,31
	5-HT _{1D}	5-HT _{1E}		
		5-HT _{1F}		
Sumatriptan	5-HT _{1D}	5-HT _{1A}	5-HT _{1E}	11,29,31, 32,34–36
	5-HT _{1B}	5-HT _{5A}		
	5-HT _{1F}	5-HT ₆		
		5-HT ₇		
Zolmitriptan	5-HT _{1D}	5-HT _{1A}		11,31–33
	5-HT _{1B}			
	5-HT _{1F}			

* Although no peer-reviewed literature was found to document 5-HT_{2B} agonism, the Relpax product label states that there is modest-affinity receptor binding to 5-HT_{2B} (Relpax prescribing information, Pfizer, 2007).

TABLE 3**Triptan Drug Metabolism in Pregnancy**

Drug	Metabolic Enzymes*	Activity in Pregnancy
Almotriptan	MAO-A	?
	CYP3A4	↑
	CYP2D6	↑
Eletriptan	CYP3A4	↑
Frovatriptan	CYP1A2	↓
Naratriptan	CYP450 [†]	?
	MAO-A	?
Rizatriptan	MAO-A	?
Sumatriptan	MAO-A	?
Zolmitriptan	CYP1A2	↓
	MAO-A	?

* Enzymes with most significant activity are listed first.

[†] Specific enzymes not yet known.

Animal Studies of Triptans

TABLE 4

Generic Name	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan
Trade Name	Axert	Relpax	Frova	Amerge	Maxalt	Imitrex	Zomig
Dosage Form	Tablets	Tablets	Tablets	Tablets	Tablets	Tablets	Tablets
Embryolethality in animals	At extremely high doses—50 × MRDD	N/A	Yes; no-effect dose not established	Yes, at 2.5 × MRDD	N/A	Yes, at 9 × MRDD	Yes, at extremely high doses
Offspring weight decrease in animals	At high doses—40 × MRDD	At 6–12 × MRDD	Yes; no-effect dose not established	Yes, at 2.5 × MRDD	Yes, at 15 × MRDD	N/A	N/A
In human milk?	Unknown	Yes	In rats	In rats	In rats	Unknown	Unknown
Developmental variations in animals	Fetal skeletal variations at 80 × MRDD	Vertebral and sternal variations at 4 × MRDD	Renal effects at extremely high doses; no-effect dose not established	Skeletal, at 2.5 × MRDD; no-effect dose not established; behavioral at 11 × MRDD	Learning capacity decrease at 7.5 × MRDD	Blood vessel effects at 6 × MRDD; skeletal at 3 × MRDD	At extremely high doses
Maternally toxic in rats	N/A	Yes, at 12 × MRDD	N/A	Yes, at high doses; no-effect dose not established	None apparent	Yes, at 9 × MRDD	Yes, at 11 × MRDD
Postnatal death of offspring in animals	N/A	N/A	N/A	N/A	Decrease in survival at 7.5 × MRDD	Decrease in survival at 10 × MRDD	Not noted
Pregnancy category	C	C	C	C	C	C	C
Pregnancy registry	No	No	No	Yes	Yes	Yes	No

Source: Product prescribing information.

MRDD, maximum recommended daily dose; N/A, not available.

TABLE 5
Summary of Human Studies in Relation to Three Most Common Reported Adverse Events

Reference	Drug Company	Source	Triptan Studied	Spontaneous Abortion	Preterm Delivery [*]	Low Birth Weight [†]
1	No	Danish Birth Registry	Sumatriptan	N/A	Significantly elevated with sumatriptan	Elevated in migraine patients, not with sumatriptan
37	Yes	Open-label study	Sumatriptan (injection)	Not statistically higher	N/A	N/A
38	Yes	Company registry	Rizatriptan	Found, but not enough data to conclude	Found, but not enough data to conclude	N/A
39	Yes	Swedish Medical Birth Registry	Sumatriptan	N/A	Slightly more often, but not statistically significant	Slightly higher, but not statistically significant
40	No	Company registry	Sumatriptan	Slightly higher, but not statistically significant	N/A	Did not differ
22	Yes	Company registry	Sumatriptan	Found in first trimester exposure, not statistically significant	N/A	N/A

N/A, not available.
^{*} Preterm delivery, <37 weeks;
[†] Low birth weight, <2.5 kg.

TABLE 6

US Pregnancy Registries, Through 31 October 2006

Triptan	Date Established	Number Enrolled Prospectively	Number Enrolled Retrospectively	Contact Phone Number
Naratriptan	January 1, 1996	52	3	800-670-6126
Rizatriptan	June 29, 1998	67	7	800-986-8999
Sumatriptan	January 1, 1996	500	26	800-336-2176

Sources: The Sumatriptan and Naratriptan Pregnancy Registry Interim Report: 1 January 1996 through 31 October 2006 (Glaxo-SmithKline); Annual Report from the Merck Pregnancy Registry for Maxalt (rizatriptan benzoate), covering the period from approval (June 1998) through October 31, 2006; product information.