

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 28, 2005

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THROUGH: Mark Avigan, M.D., C.M., Director
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TO: Solomon Iyasu, M.D., M.P.H., Team Leader
Division of Pediatric Drug Development, HFD-960
Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
(PID#: D040140)
Sumatriptan Nasal Spray (Imitrex®), NDA 20-626
Pediatric Exclusivity Approval Date: February 18, 2004

Executive Summary

The AERS database was searched for reports of adverse events occurring with the use of sumatriptan (Imitrex®) nasal spray in pediatric patients. Overall, AERS contains 8480 reports (raw count) for all sumatriptan dosage forms (nasal spray, oral tablet and injection), including both adult and pediatric reports. Pediatric reports (ages 0-16 years) account for 177 of the total reports for all sumatriptan dosage forms and 15 reports for the nasal spray dosage form. We focused on the 1-year period following granting pediatric exclusivity, February 18, 2004 to March 18, 2005. A total of 1038 reports (raw count) were received during this period, including both adult and pediatric cases, for all sumatriptan dosage forms. Twenty-two of the 1038 reports received for all sumatriptan dosage forms during the pediatric exclusivity period of interest involved pediatric patients. Only 6 reports received during the pediatric exclusivity period involved pediatric patients treated with sumatriptan nasal spray.

Among the 6 unique pediatric cases captured during the period of exclusivity for the nasal spray, there were no fatalities. All 6 cases were from domestic sources. There were 3 cases of the drug reported to be ineffective. One case of a hypersensitivity reaction reported a positive dechallenge. One case reported an exacerbation of headache; however, in this case it is difficult to attribute the adverse event solely to sumatriptan nasal spray, because this case also reported the use of other concomitant medications and there is no evidence to suggest a greater contribution of one agent over another. The final case involved a patient who experienced hematemesis after one dose of sumatriptan nasal spray. The outcome of this adverse event is unknown.

This review did not identify any remarkable or unexpected safety concerns with the use of sumatriptan nasal spray in this population of pediatric patients. We will continue to routinely monitor reports of adverse events with the use of sumatriptan nasal spray in pediatric patients.

Imitrex (sumatriptan) nasal spray (NDA 20-626) was approved on August 26, 1997 for the acute treatment of migraine attacks with or without aura in adults; Imitrex injection (NDA 20-080) was approved on December 28, 1992 and Imitrex tablets (NDA 20-132) were approved on June 1, 1995). Safety and effectiveness of Imitrex nasal spray in pediatric patients under 18 years of age have not been established; therefore, current labeling states that Imitrex nasal spray is not recommended for use in patients under 18 years of age.

AERS search results for all dosage forms of sumatriptan is described in the Appendix of this review.

AERS Search Results: sumatriptan nasal spray (Imitrex Nasal Spray)

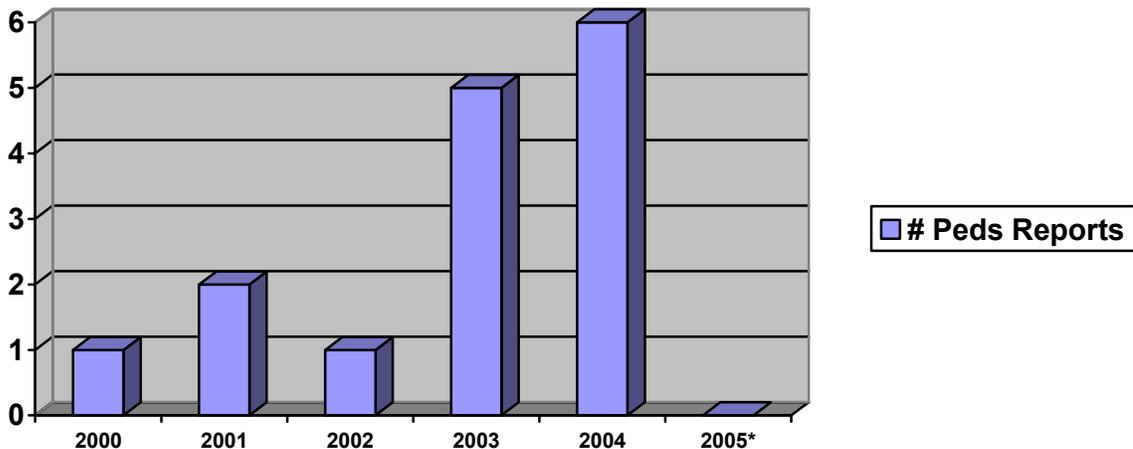
AERS Search includes all sources – U.S. & foreign

A. From marketing approval date (August 26, 1997) through AERS cut-off date (March 18, 2005).

1. Raw counts of reports: Table 1 (parentheses denotes U.S. origin report counts)

	All reports (U.S.)	Serious (U.S.)	Death (U.S.)
All ages	263 (240)	92 (69)	8 (7)
Adults (≥17)	188 (168)	83 (63)	8 (7)
Peds (0-16)	15 (14)	4 (3)	0 (0)

Figure 1: Reporting trend for pediatric reports from approval date (August 26, 1997) through AERS cut-off date (March 18, 2005)



* includes 1st quarter only for 2005

** no reports from approval date (8/26/97 – 1999)

**2. Top reported adverse event PT's and labeling status of these events
(underlined denotes unlabeled events):**

All ages (263 reports):

Drug ineffective (119), pharmaceutical product complaint (33), nausea (30), dysgeusia (26), headache (24), vomiting (22), migraine (12), convulsion (11), chest pain (10), dizziness (9), dyspnea (9), myocardial infarction (8), chest discomfort (7), pain (7), urticaria (7), burning sensation (6), overdose (6), road traffic accident (6)

Adults (188 reports):

Drug ineffective (77), pharmaceutical product complaint (23), nausea (20), dysgeusia (19), vomiting (17), headache (16), chest pain (10), convulsion (9), dyspnea (9), migraine (9), myocardial infarction (8), dizziness (7), chest discomfort (6), pain (6), road traffic accident (6), urticaria (6), angina pectoris (5), asthenia (5), burning sensation (5), colitis ischemic (5), pyrexia (5)

Pediatrics (15 reports):

Drug ineffective (4), headache (2), nausea (2), vomiting (2), *all remaining PTs have a count of (1)*

**B. From Pediatric Exclusivity approval date, February 18, 2004 to
March 18, 2005: (Imitrex Nasal Spray)**

1. Table 2. Raw counts of reports: (parentheses denotes U.S. origin report counts)

	All reports (U.S.)	Serious (U.S.)	Death (U.S.)
All ages	89 (81)	21 (13)	2 (2)
Adults (≥17)	51 (43)	20 (12)	2 (2)
Peds (0-16)	6 (6)	0 (0)	0 (0)

**2. Top reported adverse event PT's and labeling status of these events
(underlined denotes unlabeled events):**

All ages (89 reports):

Drug ineffective (49), pharmaceutical product complaint (15), vomiting (11), nausea (8), dysgeusia (7), headache (6), migraine (4), myocardial infarction (4), dizziness (3), *all remaining PTs have counts of (1) or (2)*

Adults (51 reports):

Drug ineffective (22), vomiting (8), pharmaceutical product complaint (7), dysgeusia (5), nausea (5), myocardial infarction (4), headache (3), migraine (3), aphasia (2), arthralgia (2), asthenia (2), burning sensation (2), cerebrovascular accident (2), chest pain (2), condition aggravated (2), convulsion (2), dizziness (2), dyspnea (2), hypertension (2), ischemic stroke (2), malaise (2), pyrexia (2)

Pediatrics (6 reports):

Drug ineffective (3), chest discomfort (1), erythema (1), hematemesis (1), headache (1), swelling face (1), throat tightness (1)

Postmarketing hands-on review of all pediatric adverse event reports received during the one-year period after pediatric exclusivity was granted (February 18, 2004 to March 18, 2005)

A. Descriptive statistics of 6 pediatric cases regarding gender, age, indications, doses, and outcomes.

Table 3: Characteristics of pediatric cases (reports during the 1-year period after receiving pediatric market exclusivity)

Gender	Female - 2 Male - 4
Age (standard AERS age breakdown)	0 - <1 mo. = 0 1 mo. - < 2 yrs = 0 2 - 5 yrs = 0 6 - 11 yrs = 1 12 - 17 yrs = 5
Age statistics	Mean = 12.8 yrs Median = 13 yrs Range = 9 yrs - 15 yrs
Dose	6 cases reported nasal spray formulation used. 1 case reported 5 mg nasal spray used. 5 cases unspecified the dosage of the nasal spray.
Duration of therapy	Single dose - 3 Unknown - 3
Outcome	Life-threatening - 0 Hospitalized - 0 Congenital anomaly - 0 Other - 0 Unspecified - 6
Indication	Migraine - 6 Unknown - 0

B. Comments regarding labeling status of the top 20 pediatric adverse events and in comparison with the adult adverse event profile (underlined denotes unlabeled events):

A hands-on review revealed that one PT for the pediatric cases had a count of greater than one. The term is drug ineffective. Similarly, the top PT for the adult population during this time frame is also drug ineffective.

The pediatric labeling for this product under **Precautions: Pediatric Use** section states the following:

“Safety and effectiveness of Imitrex nasal spray in pediatric patients under 18 years of age have not been established; therefore, Imitrex nasal spray is not recommended for use in patients under 18 years of age.

Two controlled clinical trials evaluating sumatriptan nasal spray (5 to 20 mg) in pediatric patients aged 12 to 17 years enrolled a total of 1,248 adolescent migraineurs who treated a single attack. The studies did not establish the efficacy of sumatriptan nasal spray compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. Five controlled clinical trials (2 single attack studies, 3 multiple attack studies) evaluating oral sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents. Postmarketing experience documents that serious adverse events have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include events similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse events in pediatric patients who might receive injectable, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients aged younger than 18 years is not recommended.”

C. Summary of non-fatal pediatric cases during the 1-year period after granting of pediatric exclusivity

There were 6 non-fatal cases involving the sumatriptan nasal spray formulation. All 6 cases involved patients receiving sumatriptan nasal spray for treatment of migraine. All of the cases were from domestic sources. One case involved a positive dechallenge.

The cases are briefly described in table 4 below.

Table 4: Summary of non-fatal pediatric cases during the 1-year period after granting of pediatric exclusivity

ISR#	Source	Age (yrs)	Sex	Indication	Dosage and Duration	ADR	Comments
4465507		15	F	migraine	Unknown dosage. One dose given.	chest discomfort, throat tightness, lip swelling, facial erythema	Positive dechallenge. Patient uses sumatriptan 25 mg tablets without any AEs.
4465511		13	M	migraine	Unknown dose and duration	drug ineffective	
4403020		13	M	Migraine	Unknown dose and duration	drug ineffective	Conc. Med: Topamax, Zofran, Tylenol #3
4465513		14	M	migraine	5 mg/dose–one dose given	hematemesis	Outcome of event is unknown.
4465525		13	F	migraine	Unknown dose and duration	headache	Conc. Meds: Inderal, Vioxx, Diflunisal, butalbital, Imitrex tabs. Outcome of event is unknown.
4465551		9	M	migraine	Unknown dosage. One dose given.	drug ineffective	No conc. meds. Pt was not instructed on use of spray

Summary

The AERS database was searched for adverse events occurring with the use of sumatriptan in pediatric patients with an emphasis on the nasal spray formulation and the 1-year period following granting of pediatric exclusivity, February 18, 2004 to March 18, 2005. Of the 22 pediatric reports captured for all sumatriptan dosage forms during this time period, 6 were associated with the nasal spray. A hands-on review revealed that one PT for the pediatric cases had a count of greater than one. The term is drug ineffective. Similarly, the top PT for the adult population during this time frame is also drug ineffective. Among the 6 unique pediatric cases captured during the period of exclusivity for the nasal spray, there were no fatalities. All 6 cases were from domestic sources. There were 3 cases that patients reported the drug to be ineffective. In one of these cases the mother of the patient stated that part of the dose dripped out of the nose of her child because they were not adequately instructed on the proper use of the nasal spray. One hypersensitivity case reported a positive dechallenge. In this case the patient started on sumatriptan nasal spray and 5 minutes after her first dose the patient experienced chest discomfort, throat tightness, lip swelling, and facial erythema. Treatment with sumatriptan nasal spray was discontinued, and the event resolved. The dosage of the sumatriptan nasal spray was unspecified. The patient uses sumatriptan 25 mg tablets without any adverse events. Another case reported an exacerbation of headache; however, in this case it is difficult to attribute the adverse event solely to sumatriptan nasal spray, because this case also reported the use of other concomitant medications and there is no evidence to suggest a greater contribution of one agent over another. The final case involved a patient who experienced hematemesis after one dose of sumatriptan nasal spray. The outcome of this adverse event is unknown.

Sixteen additional pediatric cases associated with sumatriptan were captured during the 1-year period following granting of pediatric exclusivity. However, 9 of these cases were reported with sumatriptan tablets, 3 cases were reported with sumatriptan injection, and 4 cases were reported with an unspecified dosage form.

This review did not identify any remarkable or unexpected safety concerns with the use of sumatriptan nasal spray in this population of pediatric patients. We will continue to routinely monitor reports of adverse events with the use of sumatriptan nasal spray in pediatric patients.

Limitations of the Adverse Event Reporting System (AERS)

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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Concur:

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APPENDIX: AERS Search Results: sumatriptan (All Dosage Forms)

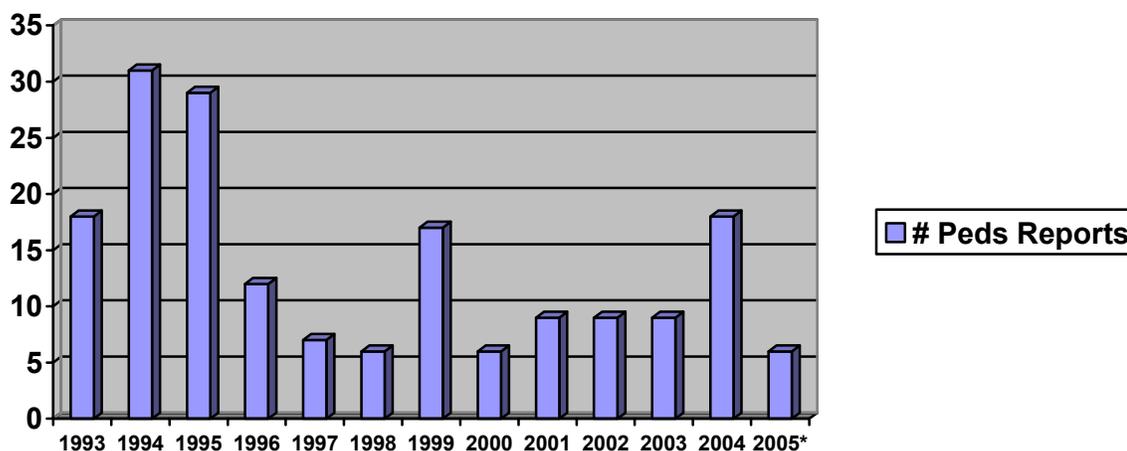
AERS Search includes all sources – U.S. & foreign

D. From marketing approval date (December 28, 1992) through AERS cut-off date (March 18, 2005).

1. Raw counts of reports: Table 1 (parentheses denotes U.S. origin report counts)

	All reports (U.S.)	Serious (U.S.)	Death (U.S.)
All ages	8480 (7608)	2647 (1839)	264 (174)
Adults (≥17)	5495 (4782)	2117 (1455)	212 (138)
Peds (0-16)	177 (159)	71 (54)	7 (6)

Figure 1: Reporting trend for pediatric reports from approval date (December 28, 1992)



* includes 1st quarter only for 2005

3. Top reported adverse event PT's and labeling status of these events (underlined denotes unlabeled events):

All ages (8480 reports):

Drug ineffective (1660), chest pain (997), headache (800), condition aggravated (497), dyspnea (494), paresthesia (485), nausea (469), migraine (423), injection site pain (400), vomiting (394), vasodilation (343), pain (327), hypertension (316), dizziness (307), injection site reaction (289), asthenia (274), myocardial infarction (240), urticaria (205), laryngospasm (204), dermatitis (199)

Adults (5495 reports):

Drug ineffective (1064), chest pain (767), headache (545), dyspnea (403), paresthesia (371), condition aggravated (333), nausea (329), migraine (304), vomiting (289), injection site pain (285), dizziness (240), hypertension (237), vasodilation (229), pain (223), asthenia (219),

myocardial infarction (204), injection site reaction (203), laryngospasm (151), urticaria (150), hypoesthesia (137)

Pediatrics (177 reports):

Headache (22), vomiting (21), drug ineffective (17), chest pain (13), dyspnea (12), dizziness (10), paresthesia (10), apnea (9), condition aggravated (9), convulsion (9), nausea (9), asthenia (8), vasodilation (8), hypertonia (7), hypoesthesia (7), hypertension (6), laryngospasm (6), pain (6)

E. From Pediatric Exclusivity approval date, February 18, 2004 to March 18, 2005: (All Dosage Forms)

1. **Raw counts of reports:** Table 2 (parentheses denotes U.S. origin report counts)

	All reports (U.S.)	Serious (U.S.)	Death (U.S.)
All ages	1038 (904)	237 (163)	17 (14)
Adults (≥17)	572 (464)	222 (114)	15 (12)
Peds (0-16)	22 (16)	9 (3)	0 (0)

2. **Top reported adverse event PT's and labeling status of these events (underlined denotes unlabeled events):**

All ages (1038 reports):

Drug ineffective (364), pharmaceutical product complaint (85), headache (82), nausea (80), vomiting (52), chest pain (45), chest discomfort (32), dyspnea (30), migraine (29), myocardial infarction (28), injection site pain (27), medication error (27), dizziness (25), drug exposure during pregnancy (22), somnolence (22), paresthesia (21), dysgeusia (20), palpitations (20), feeling abnormal (19), therapeutic response decreased (19)

Adults (572 reports):

Drug ineffective (187), pharmaceutical product complaint (54), nausea (53), headache (48), chest pain (41), vomiting (36), dyspnea (26), myocardial infarction (26), migraine (21), chest discomfort (20), dizziness (20), injection site pain (17), burning sensation (15), flushing (14), hyperhidrosis (14), hypoesthesia (14), palpitations (14), paresthesia (14), asthenia (13), hypertension (12)

Pediatrics (22 reports):

Drug ineffective (4), breech presentation (3), casarean section (3), drug exposure during pregnancy (3), facial dysmorphism (3), hypertelorism of orbit (3), paresis (3), vomiting (3), cleft lip and palate (2), headache (2), somnolence (2), toe deformity (2)

Postmarketing hands-on review of all pediatric adverse event reports received during the one-year period after pediatric exclusivity was granted (February 18, 2004 to March 18, 2005)

B. Descriptive statistics of 22 pediatric cases regarding gender, age, indications, doses, and outcomes.

Table 3: Characteristics of pediatric cases (reports during the 1-year period after receiving pediatric market exclusivity)

Gender	Female - 13 Male - 9
Age (standard AERS age breakdown)	0 - <1 mo. = 1 1 mo. - < 2 yrs = 2 2 - 5 yrs = 1 6 - 11 yrs = 2 12 - 17 yrs = 16
Age statistics	Mean = 11.5 yrs Median = 13 yrs Range = 1 day - 17 yrs
Dose	6 cases reported nasal spray formulation used. 1 case reported 5 mg nasal spray used. 5 cases unspecified the dosage of the nasal spray. 9 cases reported oral tablet formulation used. 3 cases reported 100 mg single oral dose. 1 case reported 50 mg single oral dose. 5 cases unspecified the dosage of the oral tablets. 3 cases reported subcutaneous injection used. 4 cases unspecified dosage form and dose.
Duration of therapy	1 day - 9 26 mos. - 1 30 mos. - 1 not specified - 11
Outcome	Life-threatening - 1 Hospitalized - 1 Congenital anomaly - 3 Other - 4 Unspecified - 13
Indication	Migraine - 14 Unknown - 8

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/s/

Sonny Saini
4/28/05 10:27:07 AM
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