

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

DATE: March 14, 2005

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Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
(PID#: D030717)
Zolmitriptan tablets (Zomig®), NDA 20-768
Pediatric Exclusivity Approval Date: December 18, 2003

Executive Summary

As requested by the Office of Counter-Terrorism and Pediatrics, we reviewed the pediatric adverse events in association with the use of zolmitriptan (Zomig® tablets) in children aged 16 years and younger. The time period of interest was the one-year period following FDA Pediatric Exclusivity approval, December 18, 2003 through January 18, 2005. The date of January 18, 2005 was selected as the data termination date to allow for one-month lag time for report entry into AERS. Overall, AERS contained 727 reports (raw count) for all zolmitriptan products, including both adult and pediatric reports. For the 13-month period following granting of pediatric exclusivity, 12/18/03 - 1/18/05, a total of 67 reports were entered into AERS for zolmitriptan, of which, 2 reports involved pediatric patients.

The first case was reported in a 2.5 year old child (sex is unknown) and involved an accidental overdose of one dose of Zomig 2.5 mg. The patient was hospitalized for observation for two days and was discharged without sequelae.

The second case was reported in a 14 year old male. This case involves a different formulation of zolmitriptan (Zomig-ZMT® orally disintegrating tablets; NDA 21-231). The patient was taking Zomig-ZMT for headaches for 10 months and states that the product has not been effective in relieving his headaches. He doubled his dose of Zomig-ZMT to 5 mg, experienced a partial seizure and was hospitalized for three days. This is an unlabeled adverse event. The patient has a history of benign astrocytoma that was surgically removed. However, the surgery

resulted in the patient experiencing seizures. He was not taking anticonvulsants at the time the seizures occurred.

This review did not identify any remarkable safety concerns with the tablet formulation or the orally disintegrating tablet formulation of zolmitriptan. We will continue routine monitoring of pediatric adverse events with zolmitriptan.

Zomig (NDA 20-768) was approved on November 25, 1997 and Zomig-ZMT orally disintegrating tablets (NDA 21-231) was approved on February 13, 2001 for the acute treatment of migraine with or without aura in adults. Safety and effectiveness of Zomig and Zomig-ZMT has not been established, therefore, Zomig and Zomig-ZMT are not recommended for use in patients under 18 years of age.

AERS Search Results: zolmitriptan (all dosage forms)

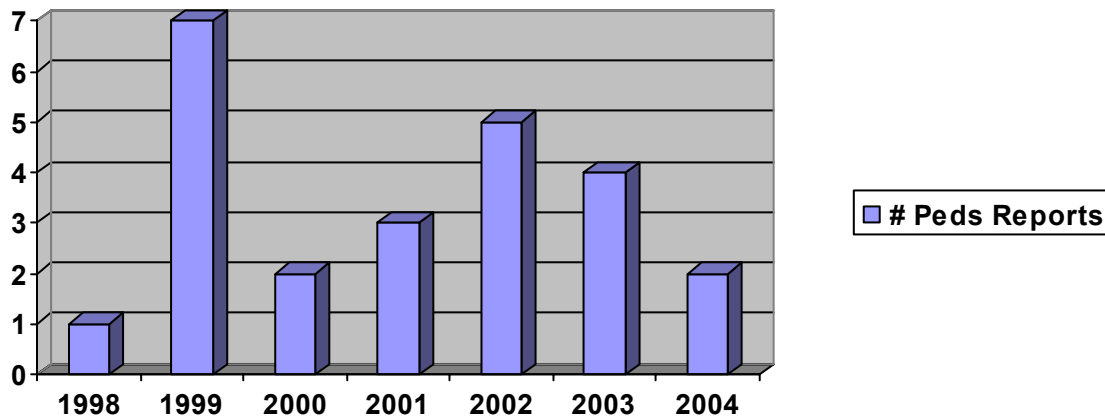
AERS Search includes all sources – U.S. & foreign

A. From marketing approval date (November 25, 1997) through AERS cut-off date (January 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	727 (448)	438 (224)	31 (15)
Adults (≥17)	591 (343)	367 (170)	26 (11)
Peds (0-16)	24 (19)	14 (10)	2 (2)

Figure 1: Reporting trend for pediatric reports from approval date (November 25, 1997):



2. Top 20 reported adverse event PT's and labeling status of these events (underlined)

denotes unlabeled events):

All ages (727 reports):

Headache (107), chest pain (76), nausea (48), dyspnea (47), dizziness (43), vomiting (41), paraesthesia (39), arthralgia (34), drug interaction (33), chest discomfort (32), drug ineffective (32), migraine (30), myocardial infarction (25), hyperhidrosis (24), throat tightness (22), pain (21), palpitations (20), flushing (19), neck pain (19), cerebrovascular accident (18)

Adults (591 reports):

Headache (96), chest pain (69), nausea (45), dizziness (39), dyspnea (39), paraesthesia (36), vomiting (36), arthralgia (31), migraine (27), chest discomfort (26), drug ineffective (24), drug interaction (23), myocardial infarction (22), hyperhidrosis (20), neck pain (19), palpitations (19), fatigue (18), asthenia (17), burning sensations (17), condition aggravated (17)

Pediatrics (24 reports):

Dizziness (3), dyspnea (3), throat tightness (3), vomiting (3), apnea (2), brain edema (2), cardiac arrest (2), complications of maternal exposure to therapeutic drugs (2), drug ineffective (2), headache (2), lethargy (2), nausea (2), pharyngeal edema (2), pupil fixed (2), respiratory disorder (2), urticaria (2), accidental exposure (1), accidental overdose (1), amnesia (1), arthralgia (1)

B. From Pediatric Exclusivity approval date, December 18, 2003 to January 18, 2005:

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	67 (22)	54 (16)	1 (0)
Adults (≥17)	56 (16)	46 (12)	0 (0)
Peds (0-16)	2 (1)	2 (1)	0 (0)

2. **Top 20 reported adverse event PT's and labeling status of these events (underlined denotes unlabeled events):**

All ages (67 reports):

Headache (8), abortion induced (7), fetal movements decreased (5), oligohydramnios (5), renal failure (5), chest pain (4), complications of maternal exposure to therapeutic drugs (4), condition aggravated (4), drug exposure during pregnancy (4), hypertension (4), nausea (4), vomiting (4), abdominal pain (3), arthralgia (3), carotid artery dissection (3), carotid artery occlusion (3), cerebral infarction (3), cerebrovascular accident (3), dizziness (3), drug interaction (3)

Adults(56 reports):

Headache (7), abortion induced (5), renal failure (5), hypertension (4), nausea (4), oligohydramnios (4), vomiting (4), abdominal pain (3), arthralgia (3), carotid artery dissection (3), carotid artery occlusion (3), cerebral infarction (3), chest pain (3), complications of maternal exposure to therapeutic drugs (3), condition aggravated (3), dizziness (3), drug exposure during pregnancy (3), drug interaction (3), fall (3), fetal movements decreased (3)

Pediatrics (2 reports):

Accidental exposure (1), accidental overdose (1), condition aggravated (1), drug effect decreased (1), headache (1), medication error (1), simple partial seizures (1)

Postmarketing Review of All Peds Adverse Event Reports from December 18, 2003 to January 18, 2005

Two cases of hospitalization were identified in this time period. One hospitalization case (ISR# 4322209-8)¹ was reported in a 2.5 year old child (sex is unknown). This case was reported by the mother as an accidental overdose of one dose of Zomig 2.5 mg. This case had no mention of signs/symptoms associated with the overdose of Zomig by the child. The patient was hospitalized for observation for two days. This case resolved without sequelae. There was no relevant past medical history and no report of concomitant medication usage.

The second hospitalization case (ISR# 4446139-6)² was reported in a 14 year old male. This case is regarding a different formulation of zolmitriptan (Zomig-ZMT® orally disintegrating tablets; NDA# 21-231). The patient was taking Zomig-ZMT for headaches for 10 months and states that the product has not been effective in relieving his headaches. He doubled his dose of Zomig-ZMT to 5 mg and experienced a partial seizure. He was hospitalized for three days and was treated with Depakote® (divalproex sodium) for the seizure. This is an unlabeled adverse event. The patient has a history of benign astrocytoma that was surgically removed. However, the surgery resulted in the patient experiencing seizures. The patient was not taking anticonvulsants at the time the seizures occurred. The patient has a history of tetracycline allergy, phenytoin allergy, and carbamazepine allergy. Concomitant medication included folic acid.

Conclusion

We identified two unlabeled adverse events for zolmitriptan for the 12-month time period after pediatric exclusivity was granted. One adverse event case associated with zolmitriptan (Zomig tablets) was an accidental overdose that resolved without sequelae. The second adverse event case was associated with zolmitriptan (Zomig-ZMT orally disintegrating tablets) and resulted in the patient experiencing a partial seizure.

We will continue monitoring pediatric adverse events with zolmitriptan.

¹ Foreign case

² Domestic case

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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