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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Postmarketing Pharmacovigilance

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Product Name(s): Zolmitriptan	Zomig Nasal Spray	Zomig Oral tablet	Zomig-ZMT Oral disintegrating tablet
NDA#	21-450	20-768	21-231
Applicant/Sponsor:	AstraZeneca	AstraZeneca	AstraZeneca

Pediatric Labeling Approval Date: June 12, 2015

OSE RCM #: 2018-339

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EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for zolmitriptan in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA) prompted by the 6/12/2015 pediatric labeling change for zolmitriptan (Zomig) nasal spray. This review focuses on all adverse events associated with zolmitriptan, all formulations, in pediatric patients aged 17 years and younger.

FDA approved zolmitriptan nasal spray, a 5-hydroxytryptamine (5-HT) 1B/1D receptor agonist, or triptan, for the acute treatment of migraine with or without aura in adults on 9/30/2003. FDA extended the indication for zolmitriptan nasal spray to include pediatric patients aged 12 to 17 years on 6/12/2015. FDA approved zolmitriptan oral tablets in 1997, and zolmitriptan oral disintegrating tablets (Zomig-ZMT) in 2001. FDA's initial approval of all zolmitriptan formulations was for the acute treatment of migraine in adults only.

We identified four pediatric FAERS cases with zolmitriptan covering the period 5/22/2014 – 3/31/2018. We did not identify any cases reporting the nasal spray formulation, reporting death as an outcome, or any new or unexpected safety concerns. These four cases reported serious outcomes after zolmitriptan oral administration, including hospitalization (3) and other serious important medical event (1). The four cases lack sufficient information for the determination of a potential cause of the accidental exposure (1) or for adequate assessment of a drug-event causal association (3).

We recommend routine pharmacovigilance monitoring of zolmitriptan for all formulations in adults and pediatric populations.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports for zolmitriptan in pediatric patients through age 17 years. The Division of Pharmacovigilance (DPV-I) conducted this review in accordance with the Food and Drug Administration Amendments Act (FDAAA) Pediatric Research Equity Act (PREA). This review focuses on all adverse events associated with zolmitriptan, all formulations, in pediatric patients ages ≤ 17 years.

1.1 PEDIATRIC REGULATORY HISTORY

FDA initially approved zolmitriptan (Zomig) oral tablets, a 5-hydroxytryptamine (5-HT) and 1B/1D receptor agonist, or triptan, on 11/25/1997 for the treatment of migraine headaches in adults. FDA subsequently approved zolmitriptan orally disintegrating tablets (Zomig-ZMT) on 2/13/2001 and the zolmitriptan nasal spray (Zomig Nasal Spray) on 9/30/2003 for the treatment of acute migraines in adults. The dosage strengths approved for use in adults are 2.5 mg and 5 mg. The maximum daily dose should not exceed 10 mg in any 24-hour period.

DPV performed two previous evaluations of postmarketing adverse event reports for zolmitriptan in pediatric patients.

1. DPV's evaluation dated 3/14/2005 was prompted by the pediatric labeling change for zolmitriptan tablets on 12/18/2003 which concluded that the safety and effectiveness of zolmitriptan tablets had not been established in pediatric patients (ages 12 to 17 years). Reported adverse events in pediatric patients were similar in nature and incidence to adverse events reported in adults. FDA presented DPV's evaluation to the Pediatric Advisory Committee (PAC) on 6/03/2005. DPV's evaluation did not identify any new safety concerns, and recommended return to routine monitoring for adverse events with zolmitriptan tablets.

2. DPV's evaluation dated 7/22/2011 was prompted by the pediatric labeling change for zolmitriptan nasal spray on 10/14/2008, which concluded that the safety and effectiveness had not been established in pediatric patients less than 18 years of age. A single, multi-center, double-blind randomized placebo-controlled study failed to demonstrate efficacy in pediatric patients ages 12 -17 years for the acute treatment of migraine headaches. In this single study, reported adverse events in pediatrics were similar to those reported in adults. FDA presented DPV's evaluation to the PAC on 9/22/2011. DPV's evaluation did not identify any new safety concerns, and recommended return to routine monitoring for adverse events with all zolmitriptan formulations.

This DPV evaluation is prompted by the pediatric labeling change for zolmitriptan nasal spray on 06/12/2015, which concluded that the safety and effectiveness was established in

pediatric patients aged 12 to 17 years. The effectiveness of zolmitriptan nasal spray in the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in a placebo-controlled study with 81 pediatric patients receiving zolmitriptan 2.5 mg and 229 pediatric patients receiving zolmitriptan 5 mg. The safety of zolmitriptan nasal spray in pediatric patients 12 to 17 years of age was established in two placebo-controlled studies in 81 pediatric patients receiving zolmitriptan 2.5 mg and 431 pediatric patients receiving zolmitriptan 5 mg. The adverse events reported in pediatric patients were similar to those reported in adults. The safety and effectiveness of zolmitriptan has not been established in pediatric patients under 12 years.

1.2 RELEVANT LABELED SAFETY INFORMATION (EXCERPT)

The recommended starting dose for zolmitriptan nasal spray in adult and pediatric patients 12 years of age and older is 2.5 mg. As the individual response to zolmitriptan nasal spray may vary, the dose should be adjusted on an individual basis. The maximum recommended single dose of ZOMIG is 5 mg. The maximum daily dose should not exceed 10 mg in any 24-hour period.[1]

----------CONTRAINDICATIONS----------

- History of ischemic heart disease or coronary artery vasospasm
- Symptomatic Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine
- Peripheral vascular disease
- Ischemic bowel disease
- Uncontrolled hypertension
- Recent (within 24 hours) use of another 5-HT 1 agonist (e.g., another triptan) or of an ergot-type medication
- MAO‑A inhibitor used in past 2 weeks
- Hypersensitivity to Zomig

----------WARNINGS AND PRECAUTIONS----------

- Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors
- Arrhythmias: Discontinue dosing if occurs
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue dosing if occurs
- Gastrointestinal ischemic events, peripheral vasospastic reactions: Discontinue dosing if occurs
- Medication Overuse Headache: Detoxification may be necessary

- Serotonin syndrome: Discontinue dosing if occurs
- Increase in blood pressure: very rarely associated with significant events

----------**ADVERSE REACTIONS**----------

6.1 Clinical Trials Experience

Pediatric Patients 12 to 17 Years of Age

The safety of ZOMIG nasal spray in the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in two studies [see Pediatric Use (8.4) and Clinical Studies (14.2)].

The most common adverse reactions (incidence of ≥ 2% of pediatric patients receiving 2.5 mg and 5 mg ZOMIG nasal spray and numerically greater than placebo) after a single dose are summarized in Table 2. Dysgeusia (unusual taste) was the most common adverse reaction, with a numerically greater incidence for patients receiving ZOMIG compared to placebo (10% vs. 2%). Other common adverse reactions were nasal discomfort, dizziness, oropharyngeal pain, and nausea.

----------**USE IN SPECIFIC POPULATIONS**----------

8.4 Pediatric Use

Safety and effectiveness of ZOMIG in pediatric patients under 12 years of age have not been established.

The efficacy of ZOMIG nasal spray in the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in a placebo-controlled study with a total of 81 pediatric patients receiving ZOMIG 2.5 mg and 229 pediatric patients receiving ZOMIG 5 mg [see Clinical Studies (14.2)]. In an earlier study with a different design, ZOMIG 5 mg nasal spray was evaluated in the acute treatment of migraine headache in 171 pediatric patients 12 to 17 years of age. In that study, the efficacy of ZOMIG nasal spray was not established.

The safety of ZOMIG nasal spray in the acute treatment of migraine in pediatric patients 12 to 17 years of age was established in two placebo-controlled studies with a total of 81 pediatric patients receiving ZOMIG 2.5 mg and 431 pediatric patients receiving ZOMIG 5 mg [see Adverse Reactions (6.1)].

The safety profile of ZOMIG nasal spray in pediatric patients 12 to 17 years of age is similar to the profile observed in adults [see Adverse Reactions (6.1)].

In the postmarketing experience with triptans, including ZOMIG, there is a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events; those that were reported are similar in nature to those reported rarely in adults.

2 METHODS AND MATERIALS

2.1 FDA ADVERSE EVENT REPORTING SYSTEM SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1. See Appendix A for a description of the FAERS database.

Table 1. FAERS Search Strategy	
Date of search	04/10/2018
Time period of search	5/22/2014* - 3/31/2018
Search type	FBIS – Profile Report (product manufacturer reporting summary) query and Quick Query
Product name(s)	Product names: Zomig and Zomig ZMT Active ingredient: zolmitriptan
Search parameters	All ages, all outcomes, worldwide
* A year prior to a comprehensive OND review, including zolmitriptan safety information from FAERS spontaneous data.	

The available zolmitriptan formulations are oral and disintegrating tablets, and nasal spray. Studies showed the systemic exposures between zolmitriptan oral and nasal spray in adults and pediatrics (ages 12 – 17 years) were similar.[2] We reviewed all FAERS reports reporting use of zolmitriptan oral and intranasal formulations in pediatric patients ≤ 17 years of age because of similar systemic exposure.

3 RESULTS

3.1 TOTAL NUMBER OF FAERS REPORTS BY AGE

Table 2 presents the number of adult and pediatric FAERS reports from 5/22/2014 to 3/31/2018 with zolmitriptan.

Table 2. Total Adult and Pediatric FAERS Reports* Received by FDA from 5/22/2014 to 3/31/2018 with Zolmitriptan			
	All reports (U.S.)	**Serious† (U.S.)**	**Death (U.S.)**
Adults (≥ 17 years)	208 (117)	130 (39)	3 (0)
Pediatrics (0 - ≤17 years)	9 (1)	9 (1)	0 (0)
* May include duplicates and transplacental exposures, and have not been assessed for causality † For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.			

3.2 *SELECTION OF PEDIATRIC CASES IN FAERS*

We retrieved nine pediatric reports with zolmitriptan. After accounting for duplicate reports (n=4) and transplacental exposure reports (n=1), we identified four pediatric cases for further discussion.

Appendix B lists the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for our pediatric case series (n=4).

Table 3 summarizes the four FAERS cases in pediatric patients with zolmitriptan reporting a serious outcome received by FDA from 5/22/2014 to 3/31/2018.

Table 3. Characteristics of Pediatric Cases with Zolmitriptan, Received by FDA from 5/22/2014 to 3/31/2018 (N=4).		
Age	2- < 6 years	1
	12- ≤ 17 years	3
Sex	Female	2
	Male	2
Report year	2014 (1), 2016 (1), 2017 (2)	
Reported reason for use	Migraine	2
	Accidental ingestion	1
	Off label use	1
Serious outcome*	Hospitalized	2
	Other serious	1

* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events.

3.3 SUMMARY OF FATAL PEDIATRIC ADVERSE EVENT CASES (N=0)

We did not identify any fatal pediatric adverse event reports.

3.4 SUMMARY OF NON-FATAL PEDIATRIC ADVERSE EVENT CASES (N=4)

We identified four FAERS cases reporting serious outcomes with zolmitriptan for oral administration in pediatric patients ≤ 17 years of age. We did not identify any FAERS pediatric cases reporting intranasal zolmitriptan administration.

The four pediatric FAERS cases are described below.

- **FAERS #10362315-V1, MCN: IT-ASTRAZENECA-2014SE55518A, ITA, 2014:** a 2.7-year-old male accidentally took 5 mg oral zolmitriptan and experienced vomiting. He was hospitalized for medical observation. His blood pressure and heart rate were reported within limits for his age. The Anti-poison center suggested monitoring of vital sign and the administration of active carbon, but it was unknown if the patient received active carbon therapy. He recovered and was discharged the next day.

- **FAERS #13916257-V1, MCN: JP-ASTRAZENECA-2017SE86995A, JPN, 2017:** a 14-year-old male took zolmitriptan (dose not reported) for an "off label use" and experienced aggravated renal function and was hospitalized. No additional information was provided.
- **FAERS #13680921-V1, MCN: GB-ASTRAZENECA-2017SE64545, GBR, 2017:** a 15-year-old male took zolmitriptan 2.5 mg for migraines and experienced disorientation and confusion. He reported an inability to tell where objects and people were in relation to himself and that symptoms resolved and he did not seek medical help. No additional information was provided.
- **FAERS #12154179-V1, MCN:US-GLENMARK GENERICS (EUROPE) LTD-2015GMK020934, U.S., 2016: 2015GMK020934/(US):** a community pharmacist reported a 17-year-old female took oral Zomig (zolmitriptan) for migraines and developed "serotonin syndrome" when she switched to Glenmark zolmitriptan 2.5 mg tablet once daily. She had no issues taking brand Zomig (zolmitriptan). The only current condition reported was migraine and she was on no concomitant medications. On the same day, after taking the first Glenmark tablet, she developed "severe ultra serotonin reaction" with the symptoms of elevated heart rate, confusion, and sweating. She was hospitalized and zolmitriptan was discontinued. She recovered and was discharged the next day. Glenmark's analysis of the lot number did not identify any "abnormalities that could lead to the complaint. In addition, the product meets its predetermined, approved quality parameters."

  Reviewer's comment: Zolmitriptan is labeled for serotonin syndrome in the WARNINGS AND PRECAUTIONS section. The development of a potentially life-threatening serotonin syndrome may occur with triptans, including sumatriptan, particularly during combined use with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). In this case, although her signs and symptoms are suggestive of serotonin syndrome, the case did not meet the published Hunter and Sternbach diagnostic criteria for serotonin syndrome.[3]

These four cases lack sufficient information for the determination of a potential cause of the accidental exposure (i.e., medication error) or for adequate assessment of a drug-event causal association (e.g., temporality to zolmitriptan initiation, medical history, concomitant medications, and the details on prior doses and use of Zomig and toxicologic assessment for sympathomimetic drugs in the latter case).

4 CONCLUSION

We did not identify any new or unexpected pediatric safety concerns at this time.

5 RECOMMENDATIONS

We recommend routine pharmacovigilance monitoring of zolmitriptan for all formulations in adult and pediatric populations.

6 REFERENCES

1. Zomig Nasal Spray [package insert]. Hayward, CA 94544: AstraZeneca LLC.; 11/2016.
2. Kasim S. Clinical Review NDA 21450/S-008: Zomig (Zolmitriptan) Nasal Spray, Acute Migraine, Adolescents 12-17 Years old. May 22, 2015.
3. Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM. 2003 Sep;96(9):635-42.

7 APPENDICES

7.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

7.2 Appendix B. FAERS Case Numbers, FAERS Version Numbers And Manufacturer Control Numbers For The Pediatric Case Series With Zolmitriptan (N=4)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age	Sex	Country Derived	Serious Outcome(s)*
1	8/5/2014	10362315	V 1	IT-ASTRAZENECA-2014SE55518	Expedited (15-DAY)	2.7 Years	Male	ITA	HO
2	6/23/2017	13680921	V 1	GB-ASTRAZENECA-2017SE64545	Expedited (15-DAY)	15 Years	Female	GBR	OT
3	8/29/2017	13916257	V 1	JP-ASTRAZENECA-2017SE86995	Expedited (15-DAY)	14 Years	Male	JPN	HO
4	03/07/2016	12154179	V 1	US-GLENMARK GENERICS (EUROPE) LTD-2015GMK020934	Periodic	17 Years	Female	US	HO

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.

Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, CA= Congenital Anomaly, OT= Other serious important medical event

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