

MEMORANDUM

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

DATE: May 28, 2008

TO: Lisa L. Mathis, M.D., Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OC

FROM: Mary Ross Southworth PharmD, Postmarketing Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Cindy Kortepeter, PharmD
Safety Evaluator Team Leader
and
Mark Avigan, MD, CM
Director
Division of Adverse Events Analysis I

SUBJECT: Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Zolpidem (Ambien; NDA 19-908)
Pediatric Exclusivity Approval Date: 11/20/2006

RCM#: 2007-255

Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of zolpidem in pediatric patients. Up to the "data lock" date of December 20, 2007, AERS contained 6816 reports for zolpidem (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports (raw counts) represent approximately 2.0% of the total (134/6816).

DAEAI was asked to focus on the 1-year period following the approval of pediatric exclusivity (November 20, 2006). We used an AERS data lock of December 20, 2007 to allow time for reports received up to November 20, 2007 to be entered into AERS. During the first year after pediatric exclusivity was granted, AERS received a total of 1394 reports (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports (raw counts) represent approximately 1.4% of the total number of cases (20/1394).

There were 13 unique AERS cases involving patients 0 to 17 years old identified during the one-year post exclusivity period (November 20, 2006 through December 20, 2007). The events in these cases were neurologic/psychologic events, hypersensitivity reaction, generic complaint, and congenital abnormality. The majority of these events are labeled (hypersensitivity, some neurologic/psychologic events) or an association could not be made between the event and zolpidem use (congenital anomaly, generic complaint, and some neurologic/psychologic events).

In conclusion, this review did not identify any serious unexpected events associated with zolpidem use in pediatric patients. We will continue to monitor reports of adverse events associated with zolpidem use.

1.0 Background

Zolpidem, a non-benzodiazepine hypnotic (marketed as AMBIEN by Sanofi-Avenis) was approved by the FDA on December 16, 1992. Pediatric exclusivity was granted on November 20, 2006. The Agency approved a supplemental NDA which added information to the label regarding the results of a placebo controlled trial on March 28, 2008. (see section 2.3). The data submitted in the NDA were insufficient to recommend a new indication for pediatric use of zolpidem, as the primary endpoint was not achieved (decreased latency to persistent sleep¹). Adverse reactions noted in the medical review¹ of the supplement included dizziness and headache (occurring more frequently in the zolpidem group vs. placebo). Of particular note, hallucinations were the most common adverse event leading to patient discontinuation (incidence of 7.4% in the zolpidem group vs. 0% in the placebo group). This information is reflected in the labeling (see section 2.3).

Recent OSE safety reviews of post-marketing adverse events associated with zolpidem resulted in the addition of information about serious anaphylaxis/angioedema events² and complex sleep related events³ (i.e., “sleep driving”), to the WARNINGS AND PRECAUTIONS section of labeling. An additional review^{4,5} of suicide with the non-benzodiazepine hypnotics (zolpidem, zaleplon, and eszopiclone) was also completed; this issue remains under review by the Agency.

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of zolpidem in pediatric patients. Up to the "data lock" date of December 20, 2007, AERS contained 6816 reports for zolpidem (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports (raw counts) represent approximately 2.0% of the total (134/6816). All

¹ McNeil, D. Elizabeth, Clinical Review (for submission #022) , February 2, 2007.

² Southworth MR, OSE review: “Anaphylaxis/Angioedema with zolpidem, zaleplon, eszopiclone, and ramelteon”, PID# D060494, September 8, 2006.

³ Southworth MR, OSE review: “Sleep driving with zolpidem, zaleplon, and eszopiclone”, PID# D060196, April 7, 2006

⁴ Southworth MR, OSE review: “Suicide with zolpidem, zaleplon, and eszopiclone”, PID #:D050402, D050403, D050404, August 31, 2006.

⁵ Southworth MR, OSE review: “Suicide with ramelteon”, RCM #2007-1250. July 2007.

serious cases reported during the one-year post pediatric exclusivity period in patients 0 to 17 years old associated with zolpidem use were analyzed.

2. Product, Indications, and Pediatric Labeling

2.1 Ambien Product

Ambien (zolpidem) is sponsored by Sanofi-Aventis. The immediate release tablet was approved in the US on December 16, 1992; the extended release formulation (zolpidem CR) was approved on September 2, 2005. It is formulated in the following:

Tablets: 5 mg, 10 mg, 12.5 mg (extended release tablet), 6.25 mg (extended release tablet)

2.2 Ambien approved indications

Zolpidem is indicated the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem CR is approved for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

2.3 Ambien Pediatric labeling

WARNINGS AND PRECAUTIONS (Abnormal thinking and behavioral changes)

In controlled trials, < 1% of adults with insomnia who received zolpidem reported hallucinations. In a clinical trial, 7.4 % of pediatric patients with insomnia associated with attention-deficit/hyperactivity disorder (ADHD), who received zolpidem reported hallucinations.

WARNINGS AND PRECAUTIONS (Special Populations: Pediatric patients)

Safety and effectiveness of zolpidem have not been established in pediatric patients. In an 8-week study in pediatric patients (aged 6–17 years) with insomnia associated with ADHD, zolpidem did not decrease sleep latency compared to placebo. Hallucinations were reported in 7.4% of the pediatric patients who received zolpidem; none of the pediatric patients who received placebo reported hallucinations.

USE IN SPECIFIC POPULATIONS (Pediatric Use)

Safety and effectiveness of zolpidem have not been established in pediatric patients.

In an 8-week controlled study, 201 pediatric patients (aged 6–17 years) with insomnia associated with attention-deficit/hyperactivity disorder (90% of the patients were using psychoanaleptics), were treated with an oral solution of zolpidem, 0.25 mg/kg/day, up to a maximum of 10 mg/day (n=136), or placebo (n = 65). Zolpidem did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 4 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent (> 5%) treatment emergent adverse events observed with

zolpidem versus placebo and included dizziness (23.5% vs. 1.5%), headache (12.5% vs. 9.2%), and hallucinations (7.4% vs. 0%).... Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse event.

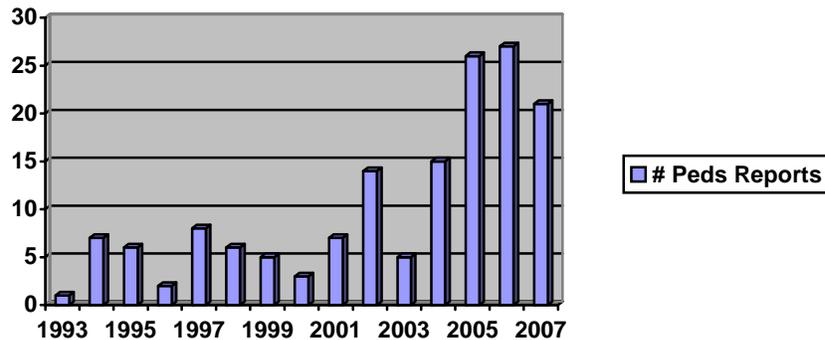
3. AERS Search Results: Zolpidem

3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval date (Table 1)

Table 1: Crude counts¹ of AERS Reports for All Sources from Marketing Approval Date (12/16/1992 – 12/20/207) (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	4872 (3270)	3831 (2346)	697 (591)
Pediatrics (0-16 yrs.)	134 (77)	107 (57)	15 (11)
Age unknown (Null values)	1810 (1693)	885 (769)	98 (86)
Total	6816 (5040)	4823 (3172)	810 (688)

¹ May include duplicates; miscoded cases
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.

Figure 1: Reporting trend for pediatric reports (Age 0 to 17) from approval date (12/16/1992) to 12/20/2007:



3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

Table 2: Crude counts¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (11/20/2006-12/20/07) (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Adults (≥ 17 yrs.)	977 (637)	886 (551)	119 (71)
Pediatrics (0-16 yrs)	20 (8)	18 (7)	4 (1)
Age unknown (Null Values)	397 (335)	364 (301)	26 (17)

Table 2: Crude counts¹ of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (11/20/2006-12/20/07) (US counts in parentheses)			
	All reports (US)	Serious ² (US)	Death (US)
Total	1394 (980)	1268 (860)	149 (89)
¹ May include duplicates; miscoded cases			
² Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.			

4. Postmarketing Review of All Serious Pediatric (0 to 17 years) Adverse Event Reports associated with Zolpidem use 1-year after Pediatric Exclusivity Granted

A search of AERS was performed on March 7, 2008 to identify *all serious cases* during the one year period after Pediatric exclusivity was granted (11/20/2006-12/20/2007) reported in those ≤ 17 years of age in association with zolpidem use; 24 cases were retrieved; there were 3 duplicates. Five cases were excluded because they involved misuse/abuse of zolpidem. Two cases were excluded because they reported accidental ingestion. One case was excluded because the patient was >17 years of age (included in search results due to coding error). The remaining 13 cases are summarized below:

Neurologic/Psychologic Events:

ISR 5236066 Florida: A 17 year old male was found dead from an apparent suicide approximately 5 months after initiating zolpidem 5 mg at bedtime for insomnia. Past medical history included anxiety and insomnia (per psychiatrist and psychologist). On the night prior to the suicide (according to a diary and note found with the body), he experienced losing motor control and judgment, dizziness, restlessness, paranoia and hallucinations (bright lights, waves, shadows). It was unclear if he had taken zolpidem that evening, though it was reported that he “routinely took zolpidem to help him sleep”. The next morning, his father found his body supine in bed with a plastic bag around his head. There was a bottle of what appeared to be antifreeze next to the bottle. A diary kept by the patient revealed thoughts of suicide (onset unreported) and gender identity disorder. An autopsy revealed congested lungs with recent hemorrhage and liver and kidney congestion; a drug screen showed the presence of caffeine only. This case was reported by an attorney.

ISR 5212134 Japan: A 17 year old male experienced delirium after taking one dose of zolpidem 10 mg for sleep phase delay syndrome. He was taken to the hospital where lab test revealed hypocapnea and hypochloremia. The patient recovered one day later with no corrective treatment.

ISR 5281882 West Virginia: A 17 year old male experienced seizures, tetany, extrapyramidal effects and dystonia 1 and ½ weeks after initiating zolpidem CR 12.5 mg. He was treated in the emergency room with benztropine mesylate, lorazepam, and diphenhydramine. No further information is available

ISR 5483995 Colorado: A 17 year old female experienced a seizure while taking zolpidem (dose, duration unreported). She was also taking a weight control medication

that was “obtained illegally”. It was unclear if she took the zolpidem at the time of the seizure.

ISR 5321536 New Jersey: A 14 year old male experienced feeling drunk after taking zolpidem 10 mg (unclear after how many doses). He was receiving concurrent therapy with ramelteon 8 mg at bedtime for insomnia. He discontinued the zolpidem and recovered.

ISR 5219578 Michigan: A 15 year old female experienced dizziness, palpitations, and hallucinations after taking her 3rd dose of zolpidem (1st dose 5 mg, 2nd and 3rd dose 10 mg). She was taken to the ED where she was given fluids and charcoal and was discharged. No further information is available.

Hypersensitivity Reaction

ISR 5494829 South Carolina: A 16 year old female experienced shakiness and rash after her first dose of zolpidem 10 mg. She was treated with diphenhydramine. One day later she took another dose; 2-3 hours later she experienced shakiness, rash, vomiting, headache, vertigo, leg numbness, and throat swelling shut. She was treated in the emergency room and recovered (therapy unreported). She was also receiving citalopram (dose, duration not reported).

Generic Complaint

ISR 5467989 USA: A 17 year old female experienced lack of effect when switched to the generic form of zolpidem 10 mg. No further information is available.

Congenital Abnormalities/Fetal Malformation/Neonatal Complications

ISR 5277106 France: A male neonate (GA ~37 weeks) was born with glandular hypospadias (surgically corrected at ~1 month old). The mother had taken acetylsalicylate DL-lysine, zolmitriptan, paroxetine, ranitidine, domperidone, metopimazine, betaine citrate, and zolpidem during her first trimester; her medical history was significant for headache/migraine, nausea/vomiting, and depression. At approximately the 14th week of pregnancy, she discontinued all medications, except metopimazine⁶ and betaine⁷ (which were discontinued at an unspecified time).

ISR 5427986 Switzerland: A 36 year old female underwent a therapeutic abortion at approximately 23 weeks of gestation. Ultrasound of the fetus revealed multiple anomalies and malformations including: retrognathia, deformation of the thorax and vertebral column, pterygia at elbows and ankles, and lack of mobility. The patient had received citalopram and chlorprothixene during the first and second trimesters and flurazepam during the first trimester only. Preliminary autopsy results suggest a neurological cause

⁶ Dopamine antagonist used for nausea

⁷ Dietary supplement used to aid digestion

for the deformities (probably medullary neuronal depletion). No further information is available.

ISR 5516895 Japan: A male neonate (GA 38 weeks) experienced respiratory failure at the time of birth. The mother (age unreported) had taken the following medications during pregnancy (duration unreported, but at least the evening labor began): milnacipran⁸, bromazepam, quetiapine, triazolam, flunitazepam, chlorpromazine, and zolpidem. She had also taken estazolam at some time during her pregnancy. Upon birth, the neonate had no spontaneous respirations and was hypotonic; he was intubated. He recovered and was extubated 1 day later. Blood tests of the neonate showed detectable levels of bromazepam, zolpidem, and quetiapine. No further information is available.

ISR 5162061 France: A male neonate (GA ~40 weeks) was born with talipes. The 31 year old mother had taken tetrazepam, tramadol, chlorazepate, venlafaxine, and zolpidem during the 1st trimester. No further information is available.

ISR 5472236 USA: A newborn male (GA unreported) was born at home and presented to the ED approximately 1 hour after birth in respiratory arrest; attempts to resuscitate were unsuccessful. The mother was reportedly a chronic substance abuser who took alprazolam throughout her pregnancy. Upon autopsy, the following drugs were detected: alprazolam, diphenhydramine, fluioxetine, norfluoxetine, zolpidem, and caffeine. No further information is available.

5. Discussion

Thirteen unique cases (8 domestic, 5 foreign) reporting serious adverse events in pediatric (≤ 17 years old) patients taking zolpidem were found in AERS.

Six cases reported neurologic or psychiatric effects. Most of these events would be considered labeled (delirium, “feeling drunk”, dizziness/hallucinations, tetany). In the case involving suicide, it is difficult to ascertain zolpidem’s contribution to the event. However, all benzodiazepine (BZD) and non-BZD hypnotics contain the following statement in warning:

“In primarily depressed patients, worsening of depression, including suicidal thinking has been reported in association with the use of sedative/hypnotics.”

In addition, the language in the zolpidem CR label has been modified (based on a review of postmarketing cases by OSE⁴) to state the following:

“In primarily depressed patients, worsening of depression, including suicidal thoughts and actions (including completed suicides), have been reported in association with the use of sedative/hypnotics.”

⁸ Cyclopropanecarboxylic acid derivative antidepressant which acts on serotonin and norepinephrine receptors

The Agency is currently reviewing the other BZDs and non-BZDs used for sleep (zaleplon, eszopiclone, ramelteon, triazolam, lorazepam, estazolam, etc.) to determine whether this language should be applied to the entire class.

Two cases report the occurrence of seizures in patient taking zolpidem. In one case the patient was also taking an un-named illegally obtained weight control medication. In the other (which also reported tetany, extrapyramidal effects, and dystonia), few details were provided regarding concomitant medications and medical conditions. Zolpidem is labeled for tetany, involuntary muscle contractions, abnormal gait, and restlessness which may be characteristics associated with extrapyramidal effects. In addition, seizures are listed as being associated with the withdrawal of zolpidem. However, based on the information reported in these cases, no conclusion regarding zolpidem and extrapyramidal effects or seizures can be made.

Hypersensitivity reaction was reported in one case and is labeled. The case reporting a complaint of loss of efficacy upon switching to generic zolpidem is severely lacking in details.

Five cases of congenital abnormalities or neonatal complications in children born to mothers who had taken zolpidem were identified. There was no commonality in the type of anomaly reported. It is impossible to ascertain from these cases whether zolpidem played a contributory role.

6. Conclusions/Recommendations

This review did not identify any serious unexpected events associated with zolpidem use in pediatric patients. We will continue to monitor reports of adverse events associated with zolpidem and will notify you of any potential safety signals in the pediatric population.

Mary Ross Southworth, PharmD
concur:

Cindy Kortepeter, PharmD
Safety Evaluator Team Leader

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/s/

Mary Southworth
6/3/2008 01:12:26 PM
DRUG SAFETY OFFICE REVIEWER

Cindy Kortepeter
6/3/2008 01:26:43 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
6/3/2008 05:23:07 PM
DRUG SAFETY OFFICE REVIEWER