

MEMORANDUM

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

DATE: July 18, 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 Adverse Event Analysis I

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

SUBJECT: Postmarketing Adverse Event Review: Death Cases and Seizure Cases
Drug: Zolpidem (Ambien; NDA 19-908)

RCM#: 2007-255

BACKGROUND

The Office of Pediatric Therapeutics requested a review of all pediatric death cases and all pediatric death cases reporting seizure in patients taking zolpidem (in addition to those reviewed previously¹).

CASES REPORTING DEATH

An AERS search was performed on June 16, 2008 for all cases reporting pediatric (0 to 17 years) use of zolpidem with an outcome of death. Fifteen cases were identified. There were 2 duplicates. Three cases were previously reviewed¹. Reasons for exclusion from the case series are presented in Table 1.

¹ Southworth MR, BPCA review: Zolpidem, OSE, May 28, 2008, RCM #2007-255.

Table 1. Reasons for exclusion from death case series (n=6)

Reason for Exclusion	Number of Cases
Case reported hearsay	1
Accidental ingestion/Maternal Dosing [†]	3
Overdose (chronic use of zolpidem indeterminate)	2

[†]1 case of accidental ingestion; 2 cases mother gave child zolpidem that was not prescribed for the child

The remaining 4 cases are presented below:

ISR 3178837 France: A 2 day old female neonate (GA, weight unreported) died of mesenteric infarction. Her mother had taken heptaminol, zolpidem, tianeptine, bromazepam, timebutine, amoxicillin, oxomemazine, guaifenesine, benzoate sodium, and paracetamol sometime (trimester exposure unreported) during her pregnancy. No further information is available.

ISR 4330741 France: A 3 week old male baby (GA 39 weeks 5 days, weight unreported) experienced cardiac failure and died. He had been diagnosed with cardiac abnormalities at a 22 week ultrasound; Mongolism was diagnosed at birth. The mother was diagnosed with HIV infection at 4 months of pregnancy. She received treatment with zidovudine, lamivudine, lopinavir, ritonavir, zolpidem, bromazepam, and buprenorphine during her pregnancy (dates of exposure unreported).

ISR 169613 United States: A 16 year old female died (circumstances of death unreported). The medical examiner's report stated that the cause of death was cardiac arrhythmia due to ventricular cardiomyopathy. The cardiomyopathy was not previously diagnosed; it was reported that she had a normal EKG 5 years prior to death and "normal blood pressure and pulse". She had received sertraline 50 mg QHS for the treatment of major depressive disorder for approximately one year prior to her death; she had received zolpidem 5 to 10 mg QHS PRN for approximately 6 months prior to her death. Medical history included Asperger's syndrome, major depression, learning disability, and a sleep disorder. No zolpidem was found in the heart blood sample at autopsy.

ISR 3969231 United States: A 15 year old male committed suicide by hanging. He had an 8 month history of depression which included hospitalizations for depression and suicide attempt (he may have been receiving zolpidem at this time, report is unclear). Concomitant medications included paroxetine 20 mg QD (started approximately 20 days prior to his death, dose escalating until time of death), zolpidem 10 mg HS (started 13 days prior), diphenhydramine (started 9 days prior), risperidone 1 mg QD (started approximately 5 days prior).

CASES REPORTING SEIZURE

An AERS search was performed on June 16, 2008 using the HLGTT “Seizures” in pediatric patients (0 to 17 years) taking zolpidem. Nine cases were identified; two were previously reviewed¹. There was one duplicate. Reasons for exclusion from the case series are presented in Table 2.

Table 2. Reasons for exclusion from seizure case series (n=5)

Reason for exclusion	Number of cases
Seizure related to zolpidem overdose/misuse	2
Seizure related to cerebral congenital abnormality/chromosomal abnormality	1
Seizure related to neonatal withdrawal [†]	2

[†]Zolpidem is labeled for with withdrawal symptoms in neonates born to mothers taking zolpidem, including seizures

The remaining case is presented below:

ISR 3928788 United States: A 16 year old experienced hallucinations, not falling asleep, weak muscles, seizures, “becoming catatonic”, and fearful about 3 weeks after starting zolpidem 10 mg (schedule unreported). Concomitant medication includes valproic acid, bupropion, and ziprasidone. At the time of reporting the zolpidem therapy and adverse events continue.

CONCLUSION

This review did not identify any serious unexpected events associated with zolpidem use in pediatric patients with regard to death cases or cases reporting seizures. We will continue to monitor reports of adverse events associated with zolpidem in the pediatric population.

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/s/

Mary Southworth
7/24/2008 12:54:27 PM
DRUG SAFETY OFFICE REVIEWER

Cindy Kortepeter
7/24/2008 01:06:55 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
7/24/2008 05:06:57 PM
DRUG SAFETY OFFICE REVIEWER