

One Year Post Exclusivity Adverse Event Review: Ambien® (zolpidem)

**Pediatric Advisory Committee Meeting
November 18, 2008**

**Elizabeth L. Durmowicz, MD, FAAP; Medical Officer
Pediatric and Maternal Health Staff
Office of New Drugs
Food and Drug Administration**



1

Outline

- **Background Drug Information**
- **Drug Use Trends**
- **Pediatric Exclusivity Studies**
- **Pediatric Exclusivity Labeling Changes**
- **Additional Relevant Safety Labeling**
- **Adverse Events**
 - Since approval
 - One-year post exclusivity
- **Summary**

2

Background Drug Information

- **Drug:** Ambien® (zolpidem)
- **Therapeutic Category:** sedative hypnotic (imidazopyridine class)
- **Sponsor:** Sanofi Aventis US
- **Original Market Approval:** December 16, 1992
- **Pediatric Exclusivity Granted:** November 20, 2006
- **Pediatric Labeling Changes:** March 28, 2007
- **Indication:**
 - Adult only: short-term treatment of insomnia characterized by difficulties with sleep initiation

3

Drug Use Trends

December 1, 2004 – November 30, 2007

Ambien® (zolpidem)

- Overall use increasing in adults (~15% since exclusivity)
- Overall use in pediatrics decreasing (~5% since exclusivity)
- Patients 0-16 accounted for < 1% (~ 51, 000) of total dispensed prescriptions¹ and < 1% (~25,000) total projected patients who filled a Rx for Ambien®²
- General Practice/Family Practice/Doctors of Osteopathy was the top prescribing specialty for Ambien®¹
- Top diagnosis codes³:
 - Patients 6 to 11 years: “Sleep Disturbances”
 - Patients 12 to 16 years, “Sleep Disturbances” and “Depressive Disorder, NEC”

¹SDI LLC: Vector One®, National (VONA) Dec 2004 to Nov 2007, Data extracted May 2008

²SDI LLC: Vector One®, Total Patient Tracker Dec 2004 to Nov 2007, Data extracted June 2008

³SDI Physician Drug and Diagnosis Audit, Dec 2004 to Nov 2007, Data extracted June 2008

4

Pediatric Exclusivity Studies:

Ambien[®] (zolpidem)

ADHD-Associated Insomnia in Children 6-17 years

- A pharmacokinetic study in 64 patients 2-18 years of age was conducted to inform the clinical trial (0.25 mg/kg/day to max. 10 mg/day).
- Phase III double-blind, randomized, placebo-controlled, parallel group study comparing the efficacy and safety of zolpidem to placebo in 201 pediatric patients with ADHD-associated insomnia for 8 weeks.
- Zolpidem did not significantly decrease latency to persistent sleep compared to placebo.

5

Pediatric Exclusivity Studies

Safety

Ambien[®] (zolpidem)

- Deaths: None
- Treatment Emergent Adverse Events: Psychiatric and Nervous System Disorders > 5% (treatment vs. placebo)
 - *dizziness (23.5% vs. 1.5%)
 - headache (12.5% vs. 9.2%)
 - *hallucinations (7.4% vs. 0%)

*In the adult trials, the incidence of hallucinations was < 1% and dizziness was 1%-5%

6

Pediatric Exclusivity Studies Labeling Changes (March 2007)

Ambien® (zolpidem)

- To reflect that zolpidem did not decrease sleep latency
- To describe psychiatric and CNS adverse events
- To indicate that safety and effectiveness in pediatric patients have not been established

Highlights

- Warnings and Precautions
- Use in Specific Populations (Pediatric Use)

Full Prescribing Information

- 5 Warnings and Precautions
- 8 Use In Specific Populations: Pediatric Use
- 17 Patient Counseling Information

7

Pediatric Exclusivity Studies Current Labeling Ambien® (zolpidem)

Highlights:

USE IN SPECIFIC POPULATIONS

Pediatric use: Safety and effectiveness not established. Hallucinations (incidence rate 7.4%) and other psychiatric and/or nervous system adverse reactions were observed frequently in a study of pediatric patients with Attention- Deficit/Hyperactivity Disorder (5.6, 8.4).

Full Prescribing Information:

5 WARNINGS AND PRECAUTIONS (5.3 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 [*See Use in Specific Populations (8.4)*].

8

Pediatric Exclusivity Studies

Current Labeling

Ambien[®] (zolpidem)

Full Prescribing Information (Cont):

5 WARNINGS AND PRECAUTIONS (5.6 Special Populations: Use in 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 [*See Use in Specific Populations (8.4)*].

9

Pediatric Exclusivity Studies

Current Labeling

Ambien[®] (zolpidem)

8.4 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 (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 reactions 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%) [see Warnings and Precautions(5.6)]. Ten patients on zolpidem (7.4%) discontinued treatment due to an adverse reaction.

17.4 Medication Guide

AMBIEN is not for children.

10

Additional Relevant Safety Labeling

Ambien® (zolpidem)

- **Warnings & Precautions:**
 - Need to evaluate for co-morbid diagnoses
 - Severe anaphylactic and anaphylactoid reactions (anaphylaxis and angioedema).
 - Abnormal thinking and behavioral changes
 - Withdrawal effects
 - CNS depressant effects
 - Worsening of depression or suicidal thinking
 - Special populations (elderly/debilitated patients and patients with hepatic impairment)
- **Pregnancy: Category C**
- **Important AEs:**
 - Listed in Warnings and Precautions

11

Adverse Event Reports since Market Approval (December 16, 1992)

Ambien® (zolpidem)

Crude counts*	All reports (US)	Serious** (US)	Death (US)
All ages	6816 (5040)	4823 (3172)	810 (688)
Adults (≥ 17)	4872 (3270)	3831 (2346)	697 (591)
Pediatrics (0-16)	134 (77)	107 (57)	15 (11)
Unknown Age	1810 (1693)	885 (769)	98 (86)

*includes duplicates and unknown ages

**Serious AEs per regulatory definition (CFR 314.80) include death, life-threatening, hospitalization (initial or prolonged), disability & congenital anomaly

12

Adverse Event Reports of Death Since Market Approval (December 16, 1992)

Ambien® (zolpidem)

- n=13 (15 cases identified, 2 duplicates)
See Integrated Death Summary Table
- 6 cases excluded (hearsay, accidental ingestion, inappropriate maternal dosing, overdose)
- Of the remaining 7 reports
 - Suicide n=2. 15 y/o and 17 y/o with a history of suicide attempt and/or mental health disorder
 - Cardiomyopathy n=1
 - Congenital Abnormalities/Neonatal Complications n=4.
All included exposure to multiple medications in utero.

13

Adverse Event Reports during One- Year Post Exclusivity Period

Ambien® (zolpidem)

Crude counts	All reports (US)	Serious (US)	Death (US)
All ages	1394 (980)	1268 (860)	149 (89)
Adults (≥ 17)	977 (637)	886 (551)	119 (71)
Pediatrics (0-16)	20 (8)	18 (7)	4 (1)
Unknown Age	397 (335)	364 (301)	26 (17)

14

Fatal Adverse Events

1-year after Pediatric Exclusivity

Ambien® (zolpidem)

Crude counts n=4 (2 cases excluded) → Unique cases n=2

Additional case n=1 (17 y/o)

- 17 y/o male apparent suicide; PMHx: anxiety and insomnia, psychiatric treatment; diary revealed suicidal thoughts and gender identity disorder. Although reported to take zolpidem on a regular basis, drug screen positive for caffeine only. (US)
- Pregnancy termination at approximately 23 weeks of gestation secondary to multiple anomalies and malformations. Preliminary autopsy results suggested a neurological cause for the deformities. Multiple maternal medications. (Switzerland)
- A newborn male born at home presented to the ED ~ 1 hour after birth in respiratory arrest. Resuscitation was unsuccessful. The mother was reportedly a chronic substance abuser who used multiple medications. (US)

15

Adverse Events

1-year after Pediatric Exclusivity

Ambien® (zolpidem)

Serious Adverse Events (Patients 0-17 years)

n=13, unduplicated

includes death reports (n=3)

- Neurologic or Psychologic events (n=6)
- Congenital Abnormalities/Neonatal Complications (n=5)
- Hypersensitivity (n=1)
- Generic complaint (n=1)

No new serious unexpected events identified

16

Neurological/Psychological Serious Adverse Events

1-year after Pediatric Exclusivity
Ambien® (zolpidem)

All reports in adolescents (n=6):

- *Suicide (death previously described, slide 15)*
- Seizures, tetany, extrapyramidal effects and dystonia
- Seizure, also on weight control medication
- “Felt drunk”
- Delirium
- Dizziness, palpitations and hallucinations

Further analysis of seizures in patients 0-17 years
unrevealing

17

Serious Adverse Events 1-year after Pediatric Exclusivity Ambien® (zolpidem)

Congenital Abnormalities/Fetal Malformation/Neonatal
Complications

- *Neonatal death (death previously described, slide 15)*
 - *Therapeutic abortion* (death previously described, slide 15)*
 - Term neonate experienced respiratory failure at the time of birth. Mother on multiple medications.
 - Term neonate with talipes*. Mom on multiple medications
 - Neonate with glandular hypospadias*. Mom on multiple medications
- * No pattern of malformation or teratogenicity noted*

Other

- Hypersensitivity Reaction**: Adolescent with rash after first dose; rash, vomiting and throat swelling shut after second dose.
***Anaphylaxis is a labeled event*
- Generic: Adolescent with reported lack of effect when switched to generic form.

18

Summary: Ambien® (zolpidem)

- Due to the Pediatric Exclusivity Studies, labeling has been changed to reflect that compared to placebo:
 - Zolpidem treatment did not significantly improve sleep onset and was associated with increased risk of neurologic and psychiatric adverse reactions, particularly hallucinations, in pediatric patients with ADHD.
 - No unexpected adverse events were identified during the one-year pediatric exclusivity review.
- FDA recommends returning to routine/standard safety monitoring for all patients.
- Does the Advisory Committee concur?

19

Acknowledgements

OND

DNP
Carole Davis, DO, MPH
Devanand Jilapalli, MD
Russell Katz, MD
Elizabeth McNeil, MD
Sally Usdin Yasuda, MS, PharmD
PMHS
Lisa L. Mathis, USPHS, MD
Denise Pica-Branco, PhD
Hari Cheryl Sachs, MD

OPT

Debbie Avant, RPh
Judith Cope, MD, MPH
Suzanne Malli, BA, BSN
Dianne Murphy, MD

OSE

Daniel Brounstein, MPH

DEPI

Laura Governale, Pharm D, MBA
Hina Mehta, Pharm D

DPV I

Mark Avigan, MD, CM
Charlene Flowers, RPh
Cindy Kortepeter, Pharm D
Ann McMahon, MD
Mary Ross Southworth, Pharm D

20