Pediatric Postmarketing Pharmacovigilance and Drug Utilization Review

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Product Name(s): Lunesta (eszopiclone)

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Applicant/Sponsor: Sunovion Pharmaceuticals, Inc.

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EXECUTIVE SUMMARY

In accordance with the FDAAA Best Pharmaceuticals for Children Act (BPCA) and Pediatric Research Equity Act (PREA), the Office of Surveillance and Epidemiology (OSE) evaluated postmarketing reports of adverse events and drug utilization data for eszopiclone (Lunesta) in pediatric patients. The focus of this review is pediatric death and pediatric reports of serious events associated with eszopiclone.

Eszopiclone was approved in the US on December 15, 2004, and is indicated for the treatment of insomnia. In controlled outpatient and sleep laboratory studies, eszopiclone administered at bedtime decreased sleep latency and improved sleep maintenance. Eszopiclone is currently not approved for use in the pediatric population.

The Division of Pharmacovigilance I (DPV I) searched the FDA Adverse Event Reporting System (FAERS) database for pediatric reports (<17 years of age) with eszopiclone from December 15, 2004 through July 31, 2014.

We identified five serious pediatric cases. There was one fatal case of an unintentional, multi-drug overdose in a 4-year old male and four non-fatal cases describing convulsions with insufficient information (1), an accidental exposure (1), intentional overdose (1), and psychiatric events confounded by concomitant medications or underlying disease (1). The contribution of eszopiclone to these events could not be determined. The most frequently (n=2) reported PTs included insomnia and vomiting. No other adverse events were reported more than once. Labeled events were consistent with the known risk in the labeling and no increased severity was observed in these cases.

A review of the FAERS data did not identify any new or unexpected events associated with eszopiclone in pediatric patients. The cases were either confounded or the events cannot be attributed solely to eszopiclone use.

Off-label use in the pediatric population (age 0-16 years) accounted for < 1% of total patients who received a eszopiclone prescription dispensed from outpatient retail pharmacies between December 1, 2004 to July 31, 2014. “Sleep Disturbances” (ICD-9 Code 780.5) was the most common diagnosis associated with the pediatric use of eszopiclone during the review period based on office-based physician survey data. However, the number of drug use mentions of eszopiclone among the pediatric population was below the acceptable count allowable to provide a reliable estimate of national use and should therefore be interpreted with caution.

DPV-I will continue monitoring of all adverse events associated with eszopiclone in pediatric patients.
1 INTRODUCTION

1.1 PEDIATRIC REGULATORY HISTORY

Eszopiclone is not approved for use in the pediatric population.

- On April 10, 2012, Sunovion submitted a Supplemental application (S-026) containing final study reports in fulfillment of the Pediatric Written Request of April 13, 2010. PMR 1206-2 was a pediatric study in insomnia associated Attention-Deficit/Hyperactivity (ADHD) in children aged 6-17 years. Lunesta failed to demonstrate efficacy in controlled clinical studies of pediatric patients with ADHD associated insomnia. In a 12-week controlled study, 483 pediatric patients (aged 6-17 years) with insomnia associated with ADHD (with 65% of the patients using concomitant ADHD treatments) were treated with oral tablets of Lunesta (1 or 2 or 3 mg tablets, n=323), or placebo (n=160). Lunesta did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 12 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse reactions observed with Lunesta versus placebo. The adverse reactions included dysgeusia (9% vs. 1%), dizziness (6% vs. 2%), hallucinations (2% vs. 0%) and suicidal ideation (0.3% vs. 0%). Nine patients on LUNESTA (3%) discontinued treatment due to an adverse reaction compared to 3 patients on placebo (2%).

- On August 8, 2011, FDA sent Information Requests (IR) to the sponsors of the hypnotic drugs (including zolpidem, eszopiclone, ramelteon, and zaleplon)\(^1\) notifying them of FDA’s concern that morning drug levels of hypnotic drugs may remain high enough in some individuals or in some identifiable patient subgroups to impair driving to a degree that presents an unacceptable risk both to individuals and the public. To evaluate this issue, FDA requested that all sponsors of hypnotic drugs assess what is currently known about the pharmacokinetic and pharmacodynamic properties of their products, including differences that might arise due to demographic factors such as gender, age, and ethnicity.

FDA made a determination that zolpidem and eszopiclone increase the risk of next-morning impairment. On April 19, 2013, FDA approved labeling to decrease the zolpidem (Ambien) recommended dose for adults from 10 mg once daily to 5 mg for women and either 5 or 10 mg for men (max 10 mg) and to decrease the Ambien CR recommended dose for adults from 12.5 mg once daily to 6.25 mg for women and either 6.25 or 12.5 mg for men (max 12.5 mg), taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. Similarly, on May 15, 2014, FDA approved labeling to decrease the eszopiclone in non-elderly from 2 mg once daily to 1 mg once daily immediately before bedtime (max 3 mg).

\(^1\) Temazepam (NDA 018163), Ambien CR (NDA 021774), Sonata (NDA 020859), Edluar (NDA 021997), Silenor (NDA 022036), Zolpimist (NDA 022196), Halcion (NDA 017892), Ambien (NDA 019908), Butisol (NDA 000793), Doral (NDA 018708), Rozerem (NDA 021782), Dalmane (NDA 016721). Information Request. August 8, 2011.
1.2 **SUMMARY OF RELEVANT PREVIOUS DPV SAFETY REVIEWS**

There are no recently completed DPV reviews that included pediatric cases and are currently pending regulatory action.

1.3 **HIGHLIGHTS OF LABELED SAFETY ISSUES**

**WARNINGS AND PRECAUTIONS**

- CNS depressant effects: Impaired alertness and motor coordination, including risk of morning impairment. Risk increases with dose. Caution patients taking 3 mg dose against driving and against activities requiring complete mental alertness during the morning after use. (5.1)
- Evaluate for Co-Morbid Diagnoses: Reevaluate if insomnia persists after 7 to 10 days of use (5.2)
- Severe Anaphylactic/Anaphylactoid Reactions (angioedema and anaphylaxis have been reported): Do not rechallenge if such reactions occur (5.3)
- Abnormal Thinking, Behavioral Changes (e.g., hallucinations), Complex Behaviors (e.g., “sleep-driving”): Immediately evaluate if occurs (5.4)
- Worsening of Depression or Suicidal Thinking may occur: Prescribe the least number of tablets feasible to avoid intentional overdose (5.4, 5.7)
- Withdrawal Effects: symptoms may occur with rapid dose reduction or discontinuation (5.5, 9.3)
- Elderly Patients: Use lower dose due to impaired motor, cognitive performance and increased sensitivity (2.2, 5.7)
- Patients with hepatic impairment, impaired respiratory function, impaired drug metabolism or hemodynamic responses:

**ADVERSE REACTIONS**

Most commonly observed adverse reactions (incidence ≥2%) were unpleasant taste, headache, somnolence, respiratory infection, dizziness, dry mouth, rash, anxiety, hallucinations, and viral infections (6.1)

**USE IN SPECIFIC POPULATIONS**

**Pediatric Use**

Safety and effectiveness of LUNESTA have not been established in pediatric patients. LUNESTA failed to demonstrate efficacy in controlled clinical studies of pediatric patients with ADHD associated insomnia. In a 12-week controlled study, 483 pediatric patients (aged 6-17 years) with insomnia associated with ADHD (with 65% of the patients using concomitant ADHD treatments) were treated with oral tablets of LUNESTA (1 or 2 or 3 mg tablets, n=323), or placebo (n=160). LUNESTA did not significantly decrease latency to persistent sleep, compared to placebo, as measured by polysomnography after 12 weeks of treatment. Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse reactions

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observed with LUNESTA versus placebo and included dysgeusia (9\% vs. 1\%), dizziness (6\% vs. 2\%), hallucinations (2\% vs. 0\%) and suicidal ideation (0.3\% vs. 0\%). Nine patients on LUNESTA (3\%) discontinued treatment due to an adverse reaction compared to 3 patients on placebo (2\%). In studies in which eszopiclone (2 to 300 mg/kg/day) was orally administered to young rats from weaning through sexual maturity, neurobehavioral impairment (altered auditory startle response) and reproductive toxicity (adverse effects on male reproductive organ weights and histopathology) were observed at doses ≥ 5 mg/kg/day. Delayed sexual maturation was noted in males and females at ≥10 mg/kg/day. The no-effect dose (2 mg/kg) was associated with plasma exposures (AUC) for eszopiclone and metabolite (S)-desmethylzopiclone [(S)-DMZ] approximately 2 times plasma exposures in humans at the maximum recommended dose (MRHD) in adults (3 mg/day). When eszopiclone (doses from 1 to 50 mg/kg/day) was orally administered to young dogs from weaning through sexual maturity, neurotoxicity (convulsions) was observed at doses ≥ 5 mg/kg/day. Hepatotoxicity (elevated liver enzymes and hepatocellular vacuolation and degeneration) and reproductive toxicity (adverse effects on male reproductive organ weights and histopathology) were noted at dose ≥10 mg/kg/day. The no-effect dose (1 mg/kg) was associated with plasma exposures (AUC) to eszopiclone and (S)-DMZ pproximately 3 and 2 times, respectively, plasma exposures in humans at the MRHD in adults.

2 DRUG UTILIZATION DATA

2.1 METHODS AND MATERIALS

2.1.1 Determining Settings of Care
IMS Health, IMS National Sales Perspectives™ database was used to determine the various retail and non-retail channels of distribution for eszopiclone bottles. Sales data for the 12-month period ending in July 2014 indicated that approximately 82\% of eszopiclone bottles were distributed to outpatient retail pharmacy settings, 9\% to mail-order/specialty pharmacies, and 9\% to non-retail pharmacies. As a result, outpatient retail pharmacy utilization patterns were examined. Non-federal hospital, mail-order/specialty pharmacy, and clinic data were not included in this analysis.

2.1.2 Data Sources Used
Database descriptions and limitations of these databases are located in Appendix B.

IMS Health, Vector One®: Total Patient Tracker database was used to provide the national estimates of unique patients who received a dispensed prescription for eszopiclone from U.S. outpatient retail pharmacies, stratified by patient age (0-5 years, 6-16 years, and 17+ years) from December 1, 2004 through July 31, 2014.

IMS Health, National Prescription Audit (NPA™) database was used to obtain the national estimates of dispensed eszopiclone prescriptions by top prescribing specialty from U.S.

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outpatient retail pharmacies from August 1, 2009 through July 31, 2014, cumulative. The time
period examined was based on data availability at the time of the review.
Encuity Research, LLC, TreatmentAnswers™, an U.S. office-based physician survey database
was used to obtain diagnoses associated with the use of eszopiclone, stratified by patient age (0-5
years, 6-16 years, and 17+ years), from December 1, 2004 to July 31, 2014, cumulative.

2.2 RESULTS

2.2.1 Patient Demographics

Table 2.2.1 in Appendix A shows the nationally estimated number of patients who received a
dispensed prescription for eszopiclone, from U.S. outpatient retail pharmacies, stratified by
patient age, from December 1, 2004 through July 31, 2014. In the 12-month period ending in
July 2014, approximately 818,668 patients received a dispensed prescription for eszopiclone.
Pediatric patients aged 0-16 years accounted for <1% (1,586 patients) of total patients and adult
patients aged 17 years and older accounted for 99.8% of total patients. Among pediatric patients,
the largest proportion of use were for patients aged 6-16 years old accounting for approximately
95% (1,503 patients) of pediatric patients, followed by patients aged 0-5 years old with 5% (86
patients) of pediatric patients.

The total number of pediatric patients who received a dispensed prescription for eszopiclone
decreased by 86% from 11,168 patients in the 12-month period ending in July 2006 to 1,586
patients in the 12-month period ending in July 2014 (Figure 2.2.1). Similarly, in the overall
patient population, there was a decrease in use by 61% from approximately 2.1 million patients
in the 12-month period ending in July 2006 to 818,000 total patients in the 12-month period
ending in July 2014.

Figure 2.2.1
2.2.2 Prescriber Specialty

Table 2.2.2 shows the top prescribing specialties for eszopiclone by number of prescriptions dispensed from U.S. outpatient retail pharmacies, August 2009 through July 2014, cumulative. During the time period examined, approximately 18.1 million prescriptions were dispensed for eszopiclone. Approximately 24% of dispensed prescriptions for eszopiclone were prescribed by Family Practice, followed by Internal Medicine at 22% of dispensed prescriptions. Pediatricians accounted for < 1% of dispensed prescriptions (data not shown).

Table 2.2.2
Nationally estimated number of dispensed prescriptions by top prescribing specialties for eszopiclone from the U.S. outpatient retail pharmacies, August 2009 through July 2014, cumulative

<table>
<thead>
<tr>
<th>Specialty</th>
<th>TRx</th>
<th>Share</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESZOPICLONE</td>
<td>18,109,123</td>
<td>100.0%</td>
</tr>
<tr>
<td>FAMILY PRACTICE</td>
<td>4,381,647</td>
<td>24.2%</td>
</tr>
<tr>
<td>INTERNAL MEDICINE</td>
<td>3,890,264</td>
<td>21.5%</td>
</tr>
<tr>
<td>PSYCHIATRY</td>
<td>2,703,275</td>
<td>14.9%</td>
</tr>
<tr>
<td>OSTEOPATHIC MEDICINE</td>
<td>1,766,738</td>
<td>9.8%</td>
</tr>
<tr>
<td>NURSE PRACTITIONER</td>
<td>1,176,911</td>
<td>6.5%</td>
</tr>
<tr>
<td>PHYSICIAN ASSISTANT</td>
<td>636,037</td>
<td>3.5%</td>
</tr>
<tr>
<td>NEUROLOGY</td>
<td>436,022</td>
<td>2.4%</td>
</tr>
<tr>
<td>OBSTETRICS/GYNECOLOGY</td>
<td>358,403</td>
<td>2.0%</td>
</tr>
<tr>
<td>ANESTHESIOLOGY</td>
<td>299,858</td>
<td>1.7%</td>
</tr>
<tr>
<td>RHEUMATOLOGY</td>
<td>230,694</td>
<td>1.3%</td>
</tr>
<tr>
<td>PHYSICAL MEDICINE &amp; REHAB</td>
<td>224,373</td>
<td>1.2%</td>
</tr>
<tr>
<td>PULMONARY DISEASES</td>
<td>217,253</td>
<td>1.2%</td>
</tr>
<tr>
<td>SPECIALTY UNSPECIFIED</td>
<td>194,786</td>
<td>1.1%</td>
</tr>
<tr>
<td>ALL OTHERS (&lt;1% RESPECTIVELY)</td>
<td>1,592,862</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

File NPA 2014-1558 Lunesta by MD 12-8-14

2.2.3 Diagnoses Associated with Use

Table 2.2.3 shows diagnoses associated with the use of eszopiclone by number of drug use mentions4 as reported by U.S. office-based physician surveys, stratified by patient age from December 2004 through July 2014, cumulative. Drug use mentions were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were applied

4 "Drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.
to the estimates. Among the pediatric population (age 0-16 years), sleep disturbances (ICD-9 Code 780.5) was the most common diagnosis associated with the use of eszopiclone during the examined period. However, the number of drug use mentions of eszopiclone among the pediatric population was below the acceptable count allowable to provide a reliable estimate of national use, therefore the results should be interpreted with caution. “Sleep disturbances” was also the top diagnosis associated with eszopiclone use in adult patients aged 17 years and older.

Table 2.2.3
Diagnoses associated with the use* of eszopiclone as reported by U.S. office-based physician survey data, December 2004 - July 2014

<table>
<thead>
<tr>
<th></th>
<th>12/2004-07/2014</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Uses</td>
</tr>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Eszopiclone</td>
<td>10,836</td>
</tr>
<tr>
<td>Age 0-5 years</td>
<td>13</td>
</tr>
<tr>
<td>7805 SLEEP DISTURBANCES</td>
<td>8</td>
</tr>
<tr>
<td>3074 NONORGANIC SLEEP DISORD</td>
<td>4</td>
</tr>
<tr>
<td>Age 6-16 years</td>
<td>32</td>
</tr>
<tr>
<td>7805 SLEEP DISTURBANCES</td>
<td>26</td>
</tr>
<tr>
<td>3110 DEPRESSIVE DISORDER NEC</td>
<td>6</td>
</tr>
<tr>
<td>17+ years</td>
<td>10,458</td>
</tr>
<tr>
<td>7805 SLEEP DISTURBANCES</td>
<td>6,742</td>
</tr>
<tr>
<td>3110 DEPRESSIVE DISORDER NEC</td>
<td>484</td>
</tr>
<tr>
<td>3000 ANXIETY STATES</td>
<td>400</td>
</tr>
<tr>
<td>2962 DEPR PSYCH, SINGL EPISOD</td>
<td>364</td>
</tr>
<tr>
<td>2963 DEPR PSYCH, RECUR EPISOD</td>
<td>288</td>
</tr>
<tr>
<td>3004 NEUROTIC DEPRESSION</td>
<td>166</td>
</tr>
<tr>
<td>2967 BIPOLAR AFFECTIVE NOS</td>
<td>150</td>
</tr>
<tr>
<td>3098 OTHER ADJUST REACTION</td>
<td>134</td>
</tr>
<tr>
<td>3074 NONORGANIC SLEEP DISORD</td>
<td>130</td>
</tr>
<tr>
<td>2968 MANIC-DEPRESSIVE NEC/NOS</td>
<td>119</td>
</tr>
<tr>
<td>7291 MYALGIA AND MYOSITIS NOS</td>
<td>104</td>
</tr>
<tr>
<td>ALL OTHERS (&lt;1% RESPECTIVELY)</td>
<td>1,373</td>
</tr>
<tr>
<td>UNKNOWN AGE</td>
<td>334</td>
</tr>
</tbody>
</table>

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* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.
NOS - Not Otherwise Specified  NEC - Not Elsewhere Classified

3 POSTMARKET ADVERSE EVENT REPORTS

3.1 METHODS AND MATERIALS

3.1.1 FDA Adverse Event Reporting System (FAERS) Search Strategy
The FAERS database was searched with the strategy described in Table 3.1.1. See Appendix C for a description of the FAERS database.
Table 3.1.1 FAERS Search Strategy

<table>
<thead>
<tr>
<th>Date of search</th>
<th>September 7, 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time period of search</td>
<td>December 14, 2004* - July 31, 2014</td>
</tr>
<tr>
<td>Product Name(s)</td>
<td>Lunesta (eszopiclone)</td>
</tr>
<tr>
<td>Search Parameters</td>
<td>All ages, all outcomes, worldwide</td>
</tr>
</tbody>
</table>

*US Approval

3.2 RESULTS

3.2.1 Total number of FAERS cases by Age

Table 3.2.1 Total Adult and pediatric FAERS cases* (December 15, 2004 – July 31, 2014) with eszopiclone

<table>
<thead>
<tr>
<th></th>
<th>All reports (US)</th>
<th>Serious† (US)</th>
<th>Death (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 years)</td>
<td>7533 (7490)</td>
<td>573 (546)</td>
<td>254 (248)</td>
</tr>
<tr>
<td>Pediatrics (0 - &lt;17 years)</td>
<td>20 (20)</td>
<td>10 *(10)</td>
<td>1 ‡ (1)</td>
</tr>
</tbody>
</table>

* May include duplicates and transplacental exposures, and have not been assessed for causality
† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.
‡ See Figure 3.2.2
§ No additional cases of pediatric deaths were identified among cases not reporting an age.

3.2.2 Figure 3.2.2 Selection of Serious Pediatric Cases in FAERS

We identified 10 pediatric reports with a serious outcome (See Table 3.2.1). Figure 3.2.2 below summarizes the specific selection of cases to be summarized in Sections 3.3 and 3.4.

- Pediatric reports with a serious outcome (n=10)
  - Pediatric reports with the outcome of death (n=1)

- Duplicate Reports (n=2) (Including 0 deaths)
- Unduplicated Reports (n=8) (Including 1 death)

- Excluded Reports (n=3) (Including 0 deaths)
  - Incorrect Age (n=1)
  - Congenital Exposure (n=2)

- Pediatric Case Series (5) (Including 1 death)
  See Table 3.2.3
3.2.3 Characteristics of Pediatric Case Series

Appendix D lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control Numbers for the Pediatric Case Series.

<table>
<thead>
<tr>
<th>Table 3.2.3 Characteristics of Pediatric Case Series with Eszopiclone (N=5)</th>
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<tbody>
<tr>
<td><strong>Age (n=5)</strong></td>
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<td><strong>Sex</strong></td>
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<tr>
<td><strong>Country of reporter</strong></td>
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<td></td>
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<tr>
<td><strong>Reported Indication</strong></td>
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<td></td>
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<tr>
<td><strong>Serious Outcome</strong>*</td>
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*Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. A report may have one or more outcome.

3.3 SUMMARY OF SERIOUS ADVERSE EVENT REPORTS (N=5)

We identified five reports with a serious outcome including one death. The remaining 4 non-fatal cases reported: convulsions (1), accidental exposure (1), and psychiatric events (2).

**Unintentional multi-drug overdose - Death (n=1)**

Case#7053024, US 2009

A police detective reported that a mother gave her 4-year old son with autism an eszopiclone tablet because he could not sleep for two nights. She was not sure that her son had consumed the tablet. The next evening, she gave him one eszopiclone tablet (unknown dose) and ibuprofen (unknown dose). Approximately 15 minutes later, she found him with many open bottles of unspecified prescription medications. She had not seen him take the medications and put him to bed. The next day, he was found dead by his father. An autopsy with toxicology findings

Reference ID: 3685419
showed he had taken eszopiclone, oxycodone, oxymorphine hydrochloride, and ibuprofen. The levels of oxycodone and oxymorphone were reported to be lethal.

Reviewer comment: The case describes a lethal exposure to oxycodone and oxymorphone. It is unclear if the eszopiclone was the mother’s or son’s prescription.

**Convulsions (n=1)**

Case#6141751, US 2006
A consumer reported her 16-year old daughter with a history of chronic sleep problems, hypoglycemia, headaches, and depression started taking eszopiclone 3 mg at approximately 10:30 pm. Forty-five minutes later, an ambulance was called. She reported that her daughter’s whole body was shaking and it took five paramedics to restrain her. She then had four hours of convulsions and stayed at the hospital until 5:00 am where she had low blood pressure, was non-coherent, low heart rate (36 bpm), and was vomiting. She was treated with lorazepam and diphenhydramine IV. Her CT scan was normal. On the same day she had two “spells,” where she stared and was unresponsive. The events of non-coherence, low heart rate, vomiting, and low blood pressure resolved. Eszopiclone was discontinued and the discharge report read “possible drug reaction to Lunesta.” Concomitant medications included escitalopram, modafinil, metformin, tiagabine, and norgestrel/ethinyl estradiol.

Reviewer comment: The unlabeled events (convulsions, heart rate decreased, incoherent, loss of consciousness) are related to the convulsions. There is insufficient information to determine whether she had pre-existing seizures because tiagabine was listed as a concomitant medication. It is possible that her history of hypoglycemia may have contributed to the convulsions. The label, Section 8.4 Pediatric Use, states: when eszopiclone (doses from 1 to 50 mg/kg/day) was orally administered to young dogs from weaning through sexual maturity, neurotoxicity (convulsions) was observed at doses ≥ 5 mg/kg/day. Of note, there is no contact information to obtain further follow-up.

**Accidental exposure (n=1)**

Case#7446647, US 2010
A pharmacist reported that a 7-year old male patient with a history of traumatic brain injury and possible autism spectrum disorder started treatment with eszopiclone (unknown indication, strength). He was brought into the Emergency Room and diagnosed as lethargic. His urine was positive for methamphetamines and benzodiazepines. It was discovered that he accidentally took his mother’s alprazolam. Concomitant medication included methylphenidate. At the time of the report, he was recovering from the lethargy and it is unknown if eszopiclone was continued.

Reviewer comment: The case describes lethargy most likely attributable to an unintentional exposure to alprazolam.

**Intentional Overdose (n=1)**

Case#7053024, US 2009
A consumer reported a 15-year old female with a history of mononucleosis, sleep cycle problems, and mild depression was given samples of eszopiclone. She took one tablet of eszopiclone (dose unknown), became irritable, and was unable to fall asleep for 45 minutes. She woke up after an hour and slept “on and off” for the rest of the night. She took another eszopiclone dose (dose unknown) the next night around 11 pm. Within an hour, she was “loopy, goofy, and giggly,” and had exaggerated movements like she was “drunk.” She awoke an hour later, felt depressed, and took 35 acetaminophen tablets. Two hours later she was vomiting and crying. Five hours later, she was vomiting and told her mother. She was taken to the emergency room, treated, recovered, and discharged.

Reviewer comment: The patient was depressed before eszopiclone was started and the contribution of eszopiclone to the events cannot be determined. No other concomitant medications were reported. Additionally, there is no contact information to obtain further follow-up.

Psychiatric events (n=1)

Case#9552072, US 2013
A case report published in the literature describes a 14-year old girl who experienced worsening of sleep and psychiatric disorders while receiving hormones, hypnosedatives, estrogen receptor agonist therapy, unspecified growth hormone, and desmopressin. She experienced nightmares and insomnia. She received melatonin with zopiclone (dose unknown) and melatonin with eszopiclone (dose unknown), to treat her sleep symptoms. These combinations produced worsening of sleep and anxiety with intensified night terrors, vivid dreams and increase distress. She was admitted to the pediatric unit for a one month history of fear of the dark, falling asleep, and exacerbation of rapid-onset obesity, hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD). She also developed nighttime auditory hallucinations, behavioral regression, and cognitive “sun-downing.” She started receiving olanzapine 2.5 mg and citalopram for anxiety and hallucinations with an increase to 5 mg two days later. Her anxiety and sleep improved and hallucinations resolved. She had gained six pounds in one month and olanzapine was discontinued and citalopram was increased. Lorazepam was started and her insomnia, hallucinations, and anxiety remained well-controlled at the last follow-up.

Reviewer comment: The reported events are labeled. She received multiple concomitant medications and has underlying disease (ROHHAD). The contribution of eszopiclone to the events cannot be determined.

4 DISCUSSION

We identified 20 cases reported in association with eszopiclone from approval through July 31, 2014 in pediatric patients. Ten cases reported a serious outcome, of which five were excluded from further review due to duplication, incorrect age, or in-utero exposure. Of the remaining five cases, there was one fatal case of an unintentional overdose in a 4-year old male and four non-fatal cases describing convulsions with insufficient information (1), an accidental exposure (1), intentional overdose (1), and psychiatric events confounded by concomitant medications or underlying disease (1). The contribution of eszopiclone to these events could not be determined. The most frequently (n=2) reported PTs included insomnia and vomiting. No other adverse
events were reported more than once. Labeled events were consistent with the known risk in the labeling and no increased severity was observed in these cases.

There were ten non-serious reports, of which three were excluded from further review because of incorrect age (2), and a duplicate report (1). The remaining seven cases reported grogginess or somnolence (2), drug ineffective (2), accidental exposure (1), paradoxical reaction (1), or hallucinations (1). The hallucinations case did not contain sufficient details for assessment. Except for paradoxical reaction and accidental exposure, these events are expected reactions in association with eszopiclone.

Adverse events of concern in adults from pre-approval studies included neoplasms, infection, accidental injury, and orthostatic hypotension. DPV I did not identify any cases with those events.

Adverse events reported from a pediatric trial in patients with insomnia associated ADHD included dysguesia, dizziness, hallucinations, and suicidal ideation. While there were no reports of dysguesia or dizziness, there was one report each of hallucination and intentional overdose (patient took 35 acetaminophen tablets). Both events are labeled.

No new safety signals were identified, including no increased severity or frequency of any labeled adverse events or deaths directly associated with eszopiclone.

In order to provide context for the adverse event reports submitted to the FAERS database, drug utilization patterns for eszopiclone were assessed. Off-label use of eszopiclone in the pediatric population (aged 0-16 years) accounted for <1% of total patients who received a dispensed eszopiclone prescription from outpatient retail pharmacies between December 1, 2004 to July 31, 2014. Approximately, 1,600 patients aged 0-16 years received a prescription for eszopiclone in the most recent 12-month period ending in July 2014. The national estimated number of pediatric patients decreased by 86% from approximately 11,000 patients in the 12-month period ending in July 2006 to approximately 1,600 patients in the 12-month period ending in July 2014. According to U.S. office-based physician survey data, “Sleep Disturbances” (ICD-9 code 780.5) was the top diagnosis associated with the use of eszopiclone in the pediatric population.

5 CONCLUSION

A review of the FAERS and drug utilization data did not identify any new or unexpected trends or events associated with eszopiclone in pediatric patients. The FAERS cases were either confounded or the events cannot be attributed solely to eszopiclone use.

6 RECOMMENDATIONS

DPV-I will continue monitoring of all adverse events associated with eszopiclone in pediatric patients.
7 REFERENCES


Reference ID: 3685419
# APPENDIX A. DRUG UTILIZATION DATA TABLE

## Table 2.2.1

Nationally estimated number of patients with a dispensed prescription for eszopiclone, stratified by patient age (0-5, 6-16, 17+ years), U.S. outpatient retail pharmacies, December 1, 2004 - July 31, 2014

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patient Count</td>
<td>Share</td>
<td>Patient Count</td>
<td>Share</td>
<td>Patient Count</td>
<td>Share</td>
<td>Patient Count</td>
<td>Share</td>
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<td>Share</td>
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<tr>
<td>Eszopiclone</td>
<td>586,393</td>
<td>100.0%</td>
<td>2,074,981</td>
<td>100.0%</td>
<td>2,125,713</td>
<td>100.0%</td>
<td>1,712,299</td>
<td>100.0%</td>
<td>1,456,772</td>
<td>100.0%</td>
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<tr>
<td>0 - 16 years</td>
<td>2,443</td>
<td>0.4%</td>
<td>11,168</td>
<td>0.5%</td>
<td>11,165</td>
<td>0.5%</td>
<td>7,335</td>
<td>0.4%</td>
<td>4,998</td>
<td>0.3%</td>
</tr>
<tr>
<td>0 - 5 years</td>
<td>156</td>
<td>6.4%</td>
<td>569</td>
<td>5.1%</td>
<td>428</td>
<td>3.8%</td>
<td>294</td>
<td>4.0%</td>
<td>240</td>
<td>4.8%</td>
</tr>
<tr>
<td>6 - 16 years</td>
<td>2,287</td>
<td>92.6%</td>
<td>10,624</td>
<td>95.1%</td>
<td>10,750</td>
<td>96.3%</td>
<td>7,046</td>
<td>96.1%</td>
<td>4,763</td>
<td>95.3%</td>
</tr>
<tr>
<td>17+ years</td>
<td>583,984</td>
<td>99.6%</td>
<td>2,064,450</td>
<td>99.5%</td>
<td>2,115,163</td>
<td>99.5%</td>
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<td>Unknown Age</td>
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<td>0.0%</td>
<td>90</td>
<td>0.0%</td>
<td>101</td>
<td>0.0%</td>
<td>9</td>
<td>0.0%</td>
<td>109</td>
<td>0.0%</td>
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Reference ID: 3685419
APPENDIX B. DRUG UTILIZATION DATABASE DESCRIPTIONS/LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail
The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that eszopiclone was distributed primarily to the outpatient retail pharmacy setting based on the IMS Health, IMS National Sales Perspectives™. The sales data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. Mail-order/specialty pharmacies and non-retail settings data were not included in patient analysis of eszopiclone which may underrepresent use in other settings of care for patients.

IMS Vector One®: Total Patient Tracker (TPT)
Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

The estimates provided are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate and may be due to random error.

IMS, National Prescription Audit
The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of
independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Of note, the time period examined in this review was based on data availability, data are available on-line for 72- rolling months with a lag of 1 month.

**Encuity Research, LLC., TreatmentAnswers™**

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.
APPENDIX C. 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).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

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.
## APPENDIX D. FAERS CASE NUMBERS, FAERS VERSION NUMBERS AND MANUFACTURER CONTROL NUMBERS

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</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LOPA R THAMBI
01/12/2015

PATTY A GREENE
01/13/2015
drug use data cleared 1/7/15 by data vendor

MOHAMED A MOHAMOUD
01/13/2015

MONICA MUNOZ
01/14/2015

GRACE CHAI
01/14/2015

ROBERT L LEVIN
01/14/2015

Reference ID: 3685419