Pediatric Focused Safety Review: Lunesta (eszopiclone)
Pediatric Advisory Committee Meeting
March 24, 2015

Erica D. Radden, MD
Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Outline

• Background Information
• Pediatric Studies
• Pediatric Labeling Changes
• Drug Use Trends
• Adverse Events
• Summary
Background Drug Information: Lunesta (eszopiclone)

- **Therapeutic Category:** nonbenzodiazepine hypnotic agent
- **Sponsor:** Sunovion Pharmaceuticals, Inc.
- **Indication:** Treatment of insomnia
- **Formulation:** 1 mg, 2 mg, and 3 mg tablets
- **Dosage and Administration (Adults only):**
  
  1 mg, immediately before bedtime, with at least 7-8 hours remaining before the planned time of awakening. (Maximum: 3 mg)
Background Drug Information:
Lunesta (eszopiclone)

• **Original Market approval:** December 15, 2004
• **Pediatric labeling changes:** October 10, 2012
  – 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 Attention Deficit/Hyperactivity (ADHD) associated insomnia in patients 6-17 years of age.
  – PREA studies waived for ages 0 to 5 years.
Background Drug Information: Lunesta (eszopiclone)

- **August 8, 2011**: FDA notified sponsors of the hypnotic drugs (including zolpidem, eszopiclone, ramelteon, and zaleplon) of a safety concern related to persistent elevation of hypnotic drug levels that may impair driving to a degree that presents an unacceptable risk both to individuals and the public.
  - FDA requested assessment of known pharmacokinetic/pharmacodynamic properties of their products, including differences that might arise due to demographic factors such as gender, age, and ethnicity.
  - FDA determined that zolpidem and eszopiclone increase the risk of next-morning impairment.
- **May 15, 2014**: FDA approved labeling to decrease zolpidem and eszopiclone doses.
  - eszopiclone dose in non-elderly decreased from 2 mg once daily to 1 mg once daily immediately before bedtime (maximum: 3 mg).
Pediatric Efficacy and Safety Study: Lunesta (eszopiclone)

- 12-week controlled study in pediatric patients aged 6-17 years with insomnia associated with ADHD (n=483).
  - 65% of the patients using concomitant ADHD treatments.
- Treated with oral tablets of Lunesta (1, 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.
- Most frequent treatment emergent adverse reactions with Lunesta versus placebo:
  - dysgeusia (9% vs. 1%)
  - hallucinations (2% vs. 0%)
  - dizziness (6% vs. 2%)
  - suicidal ideation (0.3% vs. 0%).
Pediatric Labeling Changes: Lunesta (eszopiclone)

8.4 Use in Specific Populations, Pediatric Use

– Safety and effectiveness have not been established in pediatric patients.
– Negative clinical study described.
– Psychiatric and nervous system disorders comprised the most frequent treatment emergent adverse reactions with Lunesta versus placebo.
– Information on juvenile animal studies (rats and dogs) also included.
Pediatric Patient Utilization: eszopiclone

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

*Dec 04 - Jul 05 is a partial year

Drug Utilization: eszopiclone

Nationally estimated number of patients who received a prescription for eszopiclone, stratified by patient age, dispensed through U.S. outpatient retail pharmacies, August 2013 - July 2014

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Patients (N)</th>
<th>Share (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Patients</td>
<td>818,668</td>
<td>100.0%</td>
</tr>
<tr>
<td>0-16 years</td>
<td>1,586</td>
<td>0.2%</td>
</tr>
<tr>
<td>0-5 years</td>
<td>86</td>
<td>5.4%</td>
</tr>
<tr>
<td>6-16 years</td>
<td>1,503</td>
<td>94.8%</td>
</tr>
<tr>
<td>17+ years</td>
<td>817,051</td>
<td>99.8%</td>
</tr>
<tr>
<td>Unknown Age</td>
<td>1,209</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Drug Utilization: eszopiclone

Prescribing Specialty\(^1\) and Diagnosis\(^2\)

- **Top prescribing specialties**
  - (% of total outpatient retail prescriptions dispensed)
    - Family Practice (24% of prescriptions)
    - Internal Medicine (22% of prescriptions)
    - Pediatric specialists accounted for 1% of total prescriptions

- **Top Diagnosis**
  - Sleep Disturbances (ICD-9 code 780.5) was the top diagnosis captured in pediatric patients across all age groups based on U.S. office-based physician surveys.

## Total Number* of Lunesta Adverse Event Reports Since Approval
(December 14, 2004- July 31, 2014)

<table>
<thead>
<tr>
<th></th>
<th>All reports</th>
<th>Serious**</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (≥ 17 yrs.)</td>
<td>7533 (7490)</td>
<td>573 (546)</td>
<td>254 (248)</td>
</tr>
<tr>
<td>Pediatrics (0-&lt;17 yrs.)</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 events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

†No additional cases of pediatric deaths were identified among cases not reporting an age.
Selection of Serious Pediatric FAERS Cases

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

Duplicate reports (n=2)
(INCLUDING 0 DEATHS)
Pediatric “unknown age” reports (n=0)

Unduplicated reports (n=8)
(INCLUDING 1 DEATH)

Excluded Reports (n=3)
(INCLUDING 0 DEATHS)
• Incorrect Age (n=1)
• Transplacental Exposure (n=2)

Pediatric serious cases (n=5)
(INCLUDING 1 DEATH)
Summary of Serious Adverse Events: Lunesta (eszopiclone) (n=5)

- Unlabeled/potentially unrelated to eszopiclone (n=3)
  - Death due to unintentional multi-drug overdose
  - Accidental exposure
  - Convulsions

- Labeled (n=2)
  - Intentional overdose
  - Psychiatric events (insomnia, nightmares, vivid dreams, distress, anxiety, auditory hallucinations, behavioral regression, “sun-downing”)
Lunesta (eszopiclone): Fatal Adverse Event (n=1)

Unintentional multi-drug overdose (n=1)

• 4-year-old male with autism given eszopiclone (unknown dose) and ibuprofen (unknown dose) for insomnia, and subsequently found with many open bottles of unspecified prescription medications.

• Parent put him to bed and found him dead the next day.

• Toxicology findings showed he had taken eszopiclone, oxycodone, oxymorphone hydrochloride, and ibuprofen, and confirmed lethal levels of oxycodone and oxymorphone.

Comment: Autopsy reports exposure to oxycodone and oxymorphone (reportedly lethal levels), ibuprofen and eszopiclone. Unclear if the eszopiclone was the mother’s or son’s prescription. Overdosage section in Lunesta labeling states “fatalities related to Lunesta overdoses were reported only in combination with other CNS drugs or alcohol.”

*Unlabeled events are underlined.
Serious Non-Fatal Unlabeled Adverse Events: Lunesta (eszopiclone)

Accidental exposure (n=1)

- 7-year old male patient with a history of traumatic brain injury and possible autism spectrum disorder on methylphenidate and started eszopiclone (unknown indication, strength) brought into the Emergency Room for lethargy.
- Medication in household: alprazolam
- Urine was positive for methamphetamines and benzodiazepines.
- No further information

Comment: Although Lunesta labeling includes psychomotor impairment, the patient's lethargy is most likely attributable to an unintentional exposure to alprazolam.

*Unlabeled events are underlined.*
Serious Non-Fatal Unlabeled Adverse Events: Lunesta (eszopiclone)

Convulsions (n=1)

- 16-year-old female with chronic sleep problems, hypoglycemia, headaches, and depression took eszopiclone 3 mg and developed persistent convulsions requiring hospitalization. She also developed hypotension, bradycardia (36 bpm), vomiting and was incoherent with subsequent non-responsiveness.
- Treatment: lorazepam, diphenhydramine. Normal CT and symptoms resolved.
- Eszopiclone discontinued due to “possible drug reaction to Lunesta.”
- Concomitant medications: escitalopram, modafinil, metformin, tiagabine, and norgestrel/ethinyl estradiol.

Comment: Hypotension, bradycardia, incoherence, and loss of consciousness could be related to the convulsions, and are described in the Overdosage section of Lunesta labeling. Escitalopram labeling describes seizures. Use of the anticonvulsant, tiagabine, suggests pre-existing seizures. History of hypoglycemia is a potential contributing factor. Convulsions are noted in juvenile dog study in Pediatric Use subsection of Lunesta labeling.

*Unlabeled events are underlined.
Serious Non-Fatal Labeled Adverse Events: Lunesta (eszopiclone)

Events occurred only once unless otherwise specified

5 Warnings and Precautions

Intentional overdose*

CNS depressant effects

Psychiatric events
  [(insomnia*(n=2), nightmares, vivid dreams*, distress*, anxiety*, auditory hallucinations*, behavioral regression, “sun-downing”)]

8.4 Pediatric Use

Suicidal ideation

Hallucinations

*Also classified as an Adverse Reaction

Note: multiple labeled events may have been reported in a single case
Summary Pediatric Focused Safety Review: Lunesta (eszopiclone)

• This concludes the pediatric focused safety review.

• Labeling describes lack of efficacy of Lunesta for insomnia associated with ADHD.

• All events were single cases, and had confounding factors or limited information from which to draw causality.

• The safety review identified no new safety signals.

• FDA recommends continuing ongoing surveillance.

• Does the Committee concur?
ACKNOWLEDGEMENTS

Division of Neurology Products
Billy Dunn, MD
Eric Bastings, MD
Ronald Farkas, MD, PhD
Alice Hughes, MD
Veneeta Tandon, PhD
Cathleen Michaloski, BSN, MPH

Division of Psychiatry Products
Kavneet Kohli-Chhabra, MD
Brendan Muoio, PharmD

Division of Pediatrics and Maternal Health
Lynne Yao, MD
Hari Cheryl Sachs, MD
Denise Pica-Branco, PhD

Office of Pediatric Therapeutics
Dianne Murphy, MD
Robert ‘Skip’ Nelson, MD, PhD
Judith Cope, MD, MPH
Amy Odegaard, MPH
Pam Weinel, MS, MBA, RN

Office of Surveillance and Epidemiology
Robert L. Levin, MD
Grace Chai, PharmD
Monica Munoz, PharmD, MS, BCPS
Mohamed A. Mohamoud, PharmD, MPH, BCPS
Lopa Thambi, Pharm D
Patty Greene, PharmD