# CLINICAL REVIEW

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|---|---|
| **Application Type** | **Pediatric Supplement** |
| **Application Number(s)** | **NDA 21476; Supplement 26** |
| **Priority or Standard** | **Standard** |
| **Submit Date(s)** | **April 9 2012** |
| **Received Date(s)** | **April 10 2012** |
| **PDUFA Goal Date** | **October 10, 2012** |
| **Division / Office** | **DNP/OND** |
| **Reviewer Name(s)** | **Ramesh Raman, MD, FACP** |
| **Review Completion Date** | **August 10 2012** |
| **Established Name** | **Eszopiclone** |
| **Trade Name** | **Lunesta** |
| **Therapeutic Class** | **Sedative/hypnotic** |
| **Applicant** | **Sunovion Pharmaceuticals Inc.** |
| **Formulation(s)** | **1mg, 2mg, 3mg Tablets** |
| **Dosing Regimen** | **Immediately before bedtime** |
| **Indication(s)** | **Treatment of (b) (4) Insomnia** |
| **Intended Population(s)** | |

Template Version:  March 6, 2009

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# 1 Recommendations/Risk Benefit Assessment

## 1.1 Recommendation on Regulatory Action

Although the benefit of Lunesta for the treatment of ADHD associated insomnia in the pediatric population was not demonstrated or established and no efficacy claims are being sought, the pediatric drug development program was conducted successfully meeting and fulfilling the PREA post marketing commitment and Written Request requirements set forth by the Agency. Therefore, the application is considered acceptable for approval for fulfilling these pediatric requirements.

## 1.2 Risk Benefit Assessment

The effectiveness of Lunesta for the treatment of ADHD associated insomnia in the pediatric population is not established as the clinical studies did not demonstrate any benefit. Although the safety findings did not identify major safety concerns, the data did suggest that some relevant adverse events such as dizziness and hallucinations occurred frequently and dizziness appeared to be dose dependent. Regardless, risk benefit assessments without established efficacy even in the presence of acceptable risks, albeit small, are irrelevant. However, inclusion of appropriate language in the label that will adequately highlight the failed efficacy results and provide useful information on the noted adverse events reflecting on the safety profile of Lunesta in the exposed pediatric population is recommended.

## 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

## 1.4 Recommendations for Postmarket Requirements and Commitments

None.

# 2 Introduction and Regulatory Background

## 2.1 Product Information

Lunesta (Eszopiclone, (S)-zopiclone,) a non-benzodiazepine cyclopyrrolone, is a sedative hypnotic that was approved on Dec 15, 2004 under NDA 21-476 for treatment

of insomnia in adults as 1 mg, 2 mg, and 3 mg tablets. Lunesta was launched commercially in the US on 04 April 2005.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Not applicable.

## 2.3 Availability of Proposed Active Ingredient in the United States

Not applicable.

## 2.4 Important Safety Issues With Consideration to Related Drugs

None.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Lunesta was approved on Dec 15, 2004 under NDA 21-476 for treatment of insomnia in adults as 1 mg, 2 mg, and 3 mg tablets. Lunesta was launched commercially in the US on 04 April 2005.

Upon approval of the Lunesta NDA, the pediatric study requirement was waived for ages 0 to less than 3 years and deferred for ages 3 to 17 years. This PREA postmarketing commitment for LUNESTA was initially due March 2010. Subsequently, a request to extend this deferral date was submitted November 24, 2008.

A Pediatric Written Request (PWR) was issued August 2, 2006 (and amended 13 April 2010) which requested submission from four types of studies: juvenile animal toxicity studies, human pharmacokinetic, pharmacodynamic and tolerability studies; efficacy and safety study and long term safety study. The clinical studies required the investigation of eszopiclone use for childhood insomnia in children aged 6-17 years of age with attention-deficit hyperactivity (ADHD) disorder. The due date stated in the August 2, 2006 PWR was 15 September 2011. With the April 13, 2010 PWR amendment, the due date for the completion of the studies was May 30, 2012.

In response, the Sponsor (Sunovion Pharmaceuticals Inc. [previously known as Sepracor Inc.] and referred to as Sunovion hereon), on April 9 2012 (under NDA 21-476, Supplement 26 [sequence 0045]) submitted data from 4 completed pediatric clinical studies: two Phase 3 studies (190-246 [pivotal study] and 190-247 [long-term safety study]) and two Phase 1 PK/PD studies (190-201 and 190-202). All 4 studies were conducted in the US. In this submission, data from these 4 studies are presented. A Pre-NDA meeting took place on Jan 12, 2012.

The following were the salient regulatory activities directly related to the two Phase 3 clinical studies (190-246 [pivotal study] and 190-247 [long-term safety study]):

- Partial Clinical hold & Complete Response
  - On Jun 24 2009 the on-going Phase 3 studies were placed on a partial clinical hold (ref TCON of Jun 2009 & letter of Jul 2009) due to specific deficiencies relating to nonclinical findings. Phase 1 studies had been completed by this time. Sponsor suspended studies & discontinued all subjects. Sponsor provided a Complete Response (November 2009 [Serial No. 294]) and clinical hold was lifted (ref December 2009 communication). Study was re-initiated under the original protocol. Both Phase 3 studies resumed screening in early February 2010.

- Adverse Events of Special Interest (AESI)
  - Hallucinations and Dizziness were added as AESI. The potential for eszopiclone to cause hallucinations in pediatric subjects with ADHD, according to the Sponsor, stemmed from the observation that such an increase occurred with administration of zolpidem in the pediatric population. On 21 September 2009, the Agency communicated this emerging concern via TCON and additionally, the Agency requested for better characterization of 'dizziness'. Consequently, Sponsor added hallucinations and dizziness to the clinical protocol as adverse events of special interest (AESI) such that the Investigator captured additional required information (e.g., start and stop time of the adverse event (AE) and type [in cases of hallucination]).

*Reviewer Comments*

It should be noted that efficacy was not established in the pivotal Study 190-246, and therefore, Sunovion is not pursuing a pediatric indication for eszopiclone.

During the review cycle, the Agency's DSI, Office of Compliance, upon the request of the Division conducted inspection of one of the clinical sites from a list that was generated by the Division from the pivotal study 190-246. There were no limitations that were identified during this inspection.

During the review cycle, pediatric exclusivity was granted.

## 2.6 Other Relevant Background Information

None.

# 3 Ethics and Good Clinical Practices

## 3.1 Submission Quality and Integrity

*Reviewer Comments*

These are acceptable.

## 3.2 Compliance with Good Clinical Practices

According to the Sponsor, all studies were conducted in accordance with the Declaration of Helsinki and met local legal, ethical and Good Clinical Practice (GCP) requirements. All studies were performed in accordance with the International Conference on Harmonization (ICH) E6 GCP guideline as well as the ICH E9 statistical guideline. The GCP statements for these studies were provided (Submission Appendix 1, Section 2.5- Clinical Overview).

## 3.3 Financial Disclosures

*Reviewer Comments*

Sponsor's financial disclosure certification (Submission Section 1.3.4) that is based on 21 CFR 54.2(a) as the reference, appears reasonable.

# 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

## 4.1 Chemistry Manufacturing and Controls

Not applicable.

## 4.2 Clinical Microbiology

Not applicable.

## 4.3 Preclinical Pharmacology/Toxicology

*Reviewer Comments*

Reference is made to the original NDA reviews. Reference is also made to the Agency preclinical pharmacology/toxicology review of the submitted non-clinical data (juvenile

animal toxicity studies) related to the pediatric population as specified in the Pediatric Written Request (PWR) of August 2, 2006.

### 4.4 Clinical Pharmacology

*Reviewer Comments*

Reference is made to the original NDA reviews. Reference is also made to the Agency clinical pharmacology toxicology review of the submitted clinical pharmacokinetic and pharmacodynamic data related to the pediatric population as specified in the Pediatric Written Request (PWR) of August 2, 2006. The Agency PK reviewer has found the submission acceptable.

#### 4.4.1 Mechanism of Action

It is postulated that Lunesta most likely interacts with GABA (γ-aminobutyric acid) receptor complexes at binding domains located close to the benzodiazepine receptors with actions similar to those of benzodiazepines.

#### 4.4.2 Pharmacodynamics

*Reviewer Comments*

See Agency PK review.

#### 4.4.3 Pharmacokinetics

See Agency PK review.

## 5 Sources of Clinical Data

Four clinical studies (#190-201, #190-202, #190-246, and #190-247) were conducted and completed by the Sponsor as part of the eszopiclone pediatric development program. Studies 190-201 and 190-202 were Phase 1 ascending dose PK/PD studies in adolescents and children, respectively with ADHD-associated insomnia. These studies were completed prior to the initiation of studies 190-246 and 190-247. Study 190-246 was a 12-week Phase 3 randomized, double-blind, placebo-controlled efficacy and safety trial and study 190-247 was an open-label, long-term, safety trial.

### 5.1 Tables of Studies/Clinical Trials

See Appendix.

## 5.2 Review Strategy

*Reviewer Comments*

Because the pivotal Phase 3 pediatric study 190-246 results failed to demonstrate efficacy and that the Sponsor is not making any pediatric efficacy claims, the focus of this clinical review was generally on the safety findings from the four clinical studies. To make clinically meaningful interpretations of the safety data, while the overall safety information that was provided was reviewed; further emphasis was however placed on the controlled data stemming from the pivotal study 190-246 in which Lunesta was compared to placebo.

## 5.3 Discussion of Individual Studies/Clinical Trials

*Reviewer Comments*

Amongst the two Phase3 clinical pediatric studies that were conducted, the double-blind placebo controlled study 190-246 was considered pivotal. As it was noted in the section 5.2, the focus of the review was on the pivotal Phase 3 study 190-246. Please refer to the agency clinical pharmacology review for discussions involving the Phase 1 PK/PD studies.

For pivotal study 190-246, protocol version 2.0 (Jun 02, 2010) that served as the reference for this review is discussed below.

**Pivotal Phase 3 Study 190-246**

*Title of Study*

A Randomized, Placebo-Controlled, Double-Blind, Fixed-Dose Study of the Efficacy and Safety of Eszopiclone in Children (6 to 11 years) and Adolescents (12 to 17 years) with Attention-Deficit/Hyperactivity Disorder-Associated Insomnia.

This was a multicenter study that involved 63 principal investigators and 63 clinical sites. First subject first visit was 26 April 2009 and the last subject last visit was 19 July 2011.

*Reviewer Comments*

55 (~18%) subjects who completed Study 190-246 were rolled over to the long-term safety study 190-247. 249 (~82%) subjects in study 190-247 were treatment-naïve who had no previous exposure to eszopiclone.

*Study Objectives*

Primary

The primary objective was to determine the hypnotic efficacy and safety of eszopiclone in children (6-11 years of age, inclusive) and adolescents (12-17 years of age, inclusive) with ADHD-associated insomnia.

Secondary

The secondary objective was to evaluate next-day residual effects of eszopiclone use in the pediatric patient population.

*Methodology*

This was a multicenter, randomized, double-blind, placebo-controlled, fixed-dose study of eszopiclone in pediatric subjects 6 through 17 years of age, inclusive, with Attention-Deficit/Hyperactivity Disorder (ADHD)-associated insomnia established by the Mini International Neuropsychiatric Interview for children and adolescents (MINI-Kid) version 6.0.

All subjects received double-blind study medication once daily at bedtime for up to 12 weeks. Following completion of the 12-week double-blind treatment period, all subjects received single-blind placebo once daily at bedtime for up to 2 weeks as a washout period to evaluate treatment rebound effects.

Subjects remained as inpatients overnight for the polysomnography (PSG) Baseline visit (Visit 2) and the Week 12 visit (Visit 7) for PSG testing.

All subjects had scheduled clinic visits at the following time points during the study:

Day -30 to-15 (Screening; Visit 1); Day -14 to -7 (PSG Baseline; Visit 2); Day 0 (Randomization; Visit 3); Week 2 ± 3 days (Visit 4); Week 6 ± 7 days (Visit 5); Week 10 ± 7 days (Visit 6); Week 12 ± 3 days (Visit 7); Week 14 ± 3 days (Visit 8; End of Study/Early Termination).

PSG was conducted as specified in the instruction manual for data acquisition and transmission. A central scoring facility was used. Subjects were to check into the clinic between 5:00 PM and 6:00 PM and remain inpatient overnight to undergo PSG at each of these visits. Bedtime (lights-out time) was defined as any time between 9:00 PM and 1:00 AM, with the exact time determined during the visit based on the subject's typical lights-out time and his/her level of activity and/or tiredness. Subjects were to be connected to the PSG equipment approximately 30 minutes prior to their typical lights-out time and PSG recording was to start at lights out time (0 minutes). At Visit 7, subjects were to be instructed to take the dose of study medication 30 minutes prior to lights-out time. Minimum time in bed was defined as 5 hours (from lights-out time), and maximum time in bed was defined as 9 hours. Subjects were permitted to get out of bed and terminate the PSG recording after 5 hours only if the subject had been awake

for ≥ 30 minutes and had requested to have the PSG recording terminated. Every effort was to be made to encourage the subject to remain in bed for at least 8 hours. If a subject was sleeping more than 9 hours, the study staff was to awaken the subject and terminate the PSG recording.

Actigraphy data were collected via actigraph wrist monitors for a subset of subjects at a subset of clinical sites. Actigraphy wrist monitors were issued to subjects participating in the actigraphy subset at Visits 2, 3, 5, 6, and 7, and were not to be removed by the subject. Actigraphy wrist monitors were programmed to automatically record without any input from the subject.

*Number of subjects (planned and analyzed)*

Planned: 450; Randomized: 486; Analyzed: 483 (Intent-to-Treat [ITT]); 483 (Safety Population); 266 (Actigraphy Population); 371 (Single-Blind Follow-up Population); 429 (Per Protocol); Completed: 371 (Double-Blind) and 366 (Single-Blind Follow-up); Discontinued: 115 (Double-Blind) and 5 (Single-Blind Follow-up)

*Diagnosis and main criteria for inclusion*

ADHD-associated insomnia children (6-11 years of age, inclusive) and adolescents (12-17 years of age, inclusive).

*Reviewer Comments*

Inclusion Criteria

According to the protocol for study 190-246, all subjects must have met the following inclusion criteria amongst others-

- Subjects must have a diagnosis of ADHD, as defined by Diagnostic and Statistical Manual of Mental Disorders IV criteria and confirmed by the MINI-Kid performed at Visit 1.
- Subjects must have documented ADHD-associated insomnia, that was defined as the subject or subject's parent/legal guardian having reported repeated difficulty with sleep initiation (sleep latency >30 minutes) or consolidation (wake time after sleep onset >45 minutes), despite adequate age-appropriate time and opportunity for sleep.
- Subject's Baseline PSG must reveal either >30 minutes latency to persistent sleep (LPS) or >45 minutes wake after sleep onset (WASO).

*Reviewer Comments*

Prior and Concomitant Medications

According to the protocol for study 190-246 (section 9.4.7.1, 190-246 body, p. 35/6496) all medications taken from 30 days prior to subject signing informed consent / assent

through to the end of study were recorded. Medications taken from the period of 30 days prior to the subject signing informed consent / assent to the first day of study drug was considered prior medications. Medications taken after the first dose of study drug, or ongoing at the time of first dose of study drug, was considered concomitant. Medications for ADHD were allowed if the subject was on a stable dose range and regimen for a minimum of 1 month prior to the time of consent. Such subjects were allowed to change ADHD medication formulation(s) while on study.

Across studies, the overall incidence of concomitant medication use was approximately 58% to 100% of eszopiclone-treated subjects. The most commonly-reported medication classes overall were psychoanaleptics (primarily methylphenidate / methylphenidate hydrochloride [trade name Ritalin]), anti-inflammatory and antirheumatic products (primarily ibuprofen), and analgesics (primarily paracetamol, except Study 1909-202 with no analgesic use).

*Test product, dose and mode of administration, batch number*

1 mg (Batch # C1326001, R0295002, and CFFP), 2 mg (Batch # C1352001, CFFS, and C1353001), or 3 mg (Batch # C1353001 and CFFT) eszopiclone tablets contained in film and foil blister cards. Subjects were instructed to take the dose of study medication orally once daily at bedtime. The dose of eszopiclone tablets was 1 or 2 mg (for children ages 6 to 11 years), and 2 or 3 mg (for adolescents ages 12 to 17 years). Subjects were instructed to take the dose of study medication orally once daily at bedtime (double-blind study medication from Visit 3 to Visit 7 and single-blind placebo from Visit 7 to Visit 8).

*Reviewer Comments*

Selection of Doses in the Study

According to the Sponsor, dose selection for this study was based on the results of clinical Studies 190-201 and 190-202 in which single doses of eszopiclone were administered to pediatric subjects aged 12-17 years and 6-11 years, respectively. In addition, results of toxicology studies performed in juvenile rats and dogs (Sepracor Document Nos. 190-890 and 190-891) and the established pharmacokinetic (PK) profile in adults were taken into consideration. The doses (1 or 2 mg in children 6-11 years-old, and 2 or 3 mg in adolescents 12-17 years-old) were expected to result in systemic exposure that, on average, according to the Sponsor was below the no-observed adverse effect level (NOAEL) in juvenile male rats. These doses were also to provide exposures similar to those seen in adults, and that were associated with efficacy.

*Duration of treatment*

The total duration of a subject's participation in the study was approximately 18 weeks (4 weeks screening, 12 weeks of double-blind treatment, and 2 weeks single-blind washout).

*Reference therapy, dose and mode of administration, batch number*

Matching placebo tablet (Batch # C1235001 and CFFN).

*Criteria for evaluation:* ***Efficacy***

The ***primary endpoint*** was the change from baseline to the end of the double-blind treatment period (Week 12) in PSG-defined Latency to Persistent Sleep (LPS), which was defined as the time (minutes) from the time of lights out to the beginning of the first of 20 consecutive epochs (10 minutes) scored as non-wake. Baseline was defined as the value obtained at the last time point prior to the first dose of study medication. The change from baseline was computed by subtracting the baseline LPS value from the Week 12 LPS value, so that a negative change reflected an improvement.

*Key Secondary Efficacy Endpoints* were:

- Change from baseline (Day 0) to each post-baseline study visit in subjective Sleep Latency (SL).
- Change from PSG Baseline to the end of the double-blind treatment period (Week 12) in PSG-defined Wake time After Sleep Onset (WASO).
- Change from baseline (Day 0) to each post-baseline study visit in subjective WASO.
- Change from baseline (Day 0) to each post-baseline study visit in Clinical Global Impression (CGI)-Parent/Caregiver.
- Change from baseline (Day 0) to each post-baseline study visit in CGI–Child.
- Change from baseline (Day 0) to each post-baseline study visit in Conners' ADHD rating scale.

Other secondary endpoints included:

- Change from PSG Baseline to the end of the double-blind treatment (Week 12) period in PSG-defined sleep efficiency.
- Change from PSG Baseline to the end of double-blind treatment period (Week 12) in PSG-defined Number of Awakenings After Sleep Onset (NAASO).
- Change from baseline (Day 0) to each post-baseline study visit in subjective NAASO.
- Change from PSG Baseline to the end of the double-blind treatment period (Week 12) in PSG-defined Total Sleep Time (TST).
- Change from baseline (Day 0) to each post-baseline study visit in subjective TST.
- Change in SL, TST, WASO, and NAASO measured by actigraphy monitoring in the actigraphy subset of subjects from the 7-nights prior to first dose to the 7-night periods beginning after Visits 3 and 5, and the 7-night period prior to Visit 7.

- Change in behavioral variables (as assessed by Pediatric Daytime Sleepiness Scale [PDSS], Child Behavior Checklist [CBCL], and Pediatric Quality-of-Life scale [Short Form-10, SF-10]) from baseline (Day 0) to each post-baseline study visit.
- Change in cognition variables (as assessed by Conners' Continuous Performance Test II [CCPT-II] and Coding Copy Subtest A or B, or Digit Symbol Substitution Test [DSST] scaled score, as appropriate for subject age) from baseline (Day 0) to each post-baseline study visit.
- Change in school tardiness/attendance reports from Day 0 to Visits 5, 7, and 8.

*Criteria for evaluation:* ***Safety***

Safety endpoints included:

- Clinical evaluations (adverse events, vital sign measurements, orthostatic effects, physical examination findings, neurologic examination findings, body weight, and 12-lead Electrocardiogram [ECG]).
- Clinical laboratory tests (serum chemistry, hematology, and urinalysis).
- Change in Columbia-Suicide Severity Rating Scale (C-SSRS) item responses.
- Safety and tolerability including actigraphy-defined rebound effects, discontinuation effects, and morning residual effects based on the PDSS.

*Reviewer Comments*

Study Stopping Rules and the Data and Safety Monitoring Board

The sponsor appointed an independent Data and Safety Monitoring Board (DSMB) to evaluate accumulating safety outcome data in this trial. The DSMB reviewed safety outcomes such as serious adverse events and other safety data summaries periodically throughout the study.

*Statistical Methods*

*Reviewer Comments*

Based on the discussions with the Agency statistician, it is the understanding of this reviewer that the statistical methods that were implemented in the efficacy analyses that were reviewed by the Agency statistician were found to be acceptable. In the context of failed efficacy results (both primary and secondary), further comments is not warranted.

# 6 Review of Efficacy

## ***Efficacy Summary***

*Reviewer Comments*

In the context of failed efficacy results (both primary and secondary), further comments is not warranted.

## 6.1 Indication

### 6.1.1 Methods

*Reviewer Comments*

See section 5.3. Based on the discussions with the Agency statistician, it is the understanding of this reviewer that the statistical methods that were implemented in the efficacy analyses that were reviewed by the Agency statistician were found to be acceptable.

### 6.1.2 Demographics

See section 7 of the review.

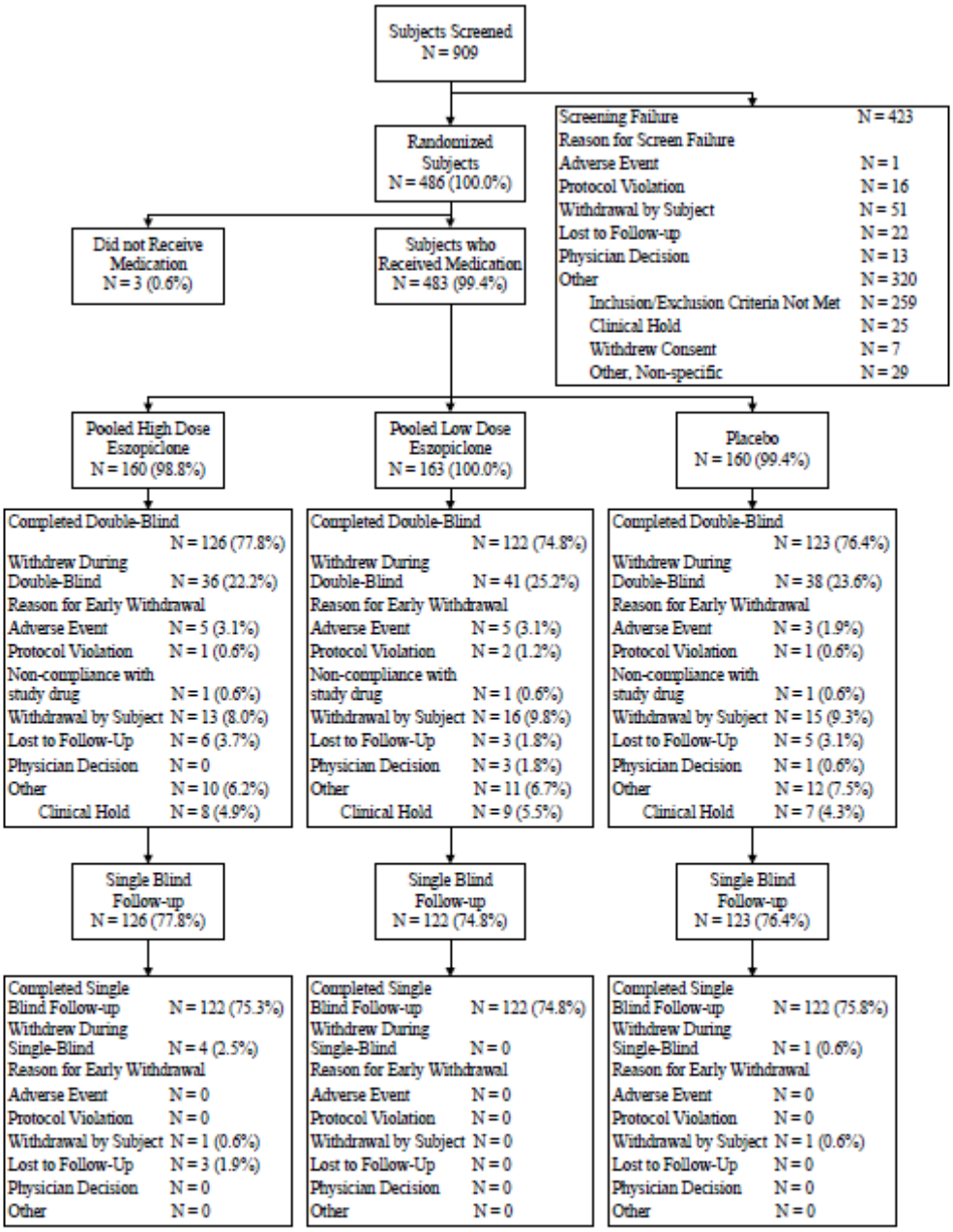
### 6.1.3 Subject Disposition

**Table 6.1.3 A**

| **Table*** **Subject Disposition** **Phase 3 Studies Combined (190-246 & 190-247)*** | |
|---|---|
| **Category** | Eszopiclone Overall (1 mg, 2 mg, and 3 mg) (N=589) |
| Enrolled/randomized | 593 |
| Enrolled/randomized and dosed (ITT | 589 |
| Completed the study | 329 (55.9) |
| Discontinued from the study | 260 (44.1) |
| Withdrawal by subject | 96 (16.3) |
| Other | 50 (8.5) |
| Adverse event | 45[b] (7.6) |
| Lost to follow-up | 41 (7.0) |
| Protocol violation | 18 (3.1) |
| Physician decision | 7 (1.2) |
| Noncompliance with study drug | 3 (0.5) |

* Ref: Copied Sponsor's Table 8; Section 2.7.4; p 28/71. Modified for format only.
Abbreviations: ISS = integrated summary of safety; ITT = intent-to-treat; PD = pharmacodynamic; PK = pharmacokinetic.
[a] The ITT population consisted of all subjects who had taken any dose of eszopiclone.
[b] One subject (190-246-0045-S002) had an AE during the screening period that resulted in study discontinuation (ie, not treatment emergent) (ISS Listing 6.0). The remaining 44 subjects with TEAEs resulting in study discontinuation are included in Table 13.
Note: Percentages were calculated based on the number of unique ITT subjects. Subjects were summarized according to the eszopiclone dose actually received.
Note: Subjects who completed Study 190-246 and rolled-over into Study 190-247 were included only once using the status from the latter study (190-247). Subjects who received placebo in Study 190-246 and did not roll-over into Study 190-247 were not included.
Reference: ISS Table 2.2

The subject disposition for pivotal study 190-246 is shown schematically (image of schema copied from Sponsor's submission) below-




Note: The reasons for screen failure, percentages are calculated based on the number of screen failures. For all other categories, percentages are calculated based on the number of randomized subjects in each dose group. The per-protocol population includes subjects in the ITT population who did not have any important protocol deviations as determined by a blinded data review.

Note: The 3 subjects who were randomized but not dosed are included in the "Withdrew During Double-Blind" totals.

Source: Table 14.1.1.1

## 6.1.4 Analysis of Primary Endpoint(s)

Efficacy of eszopiclone was not demonstrated when administered to children and adolescents with ADHD-associated insomnia. There was no statistically significant difference from placebo for either the high-dose (2 or 3 mg) eszopiclone (*P* = 0.3749) or

the low-dose (1 or 2 mg) eszopiclone (*P* > 0.9999) groups in the primary efficacy endpoint of change from baseline to Week 12 in PSG-defined LPS.

*Reviewer Comments*

According to the Sponsor, because the primary efficacy endpoint for both the pooled low-dose and pooled high-dose eszopiclone comparison versus placebo were not significant using the Bonferroni adjusted gatekeeping approach, the sequence of statistical testing was stopped after the primary efficacy endpoint (but exploratory unadjusted *P*-values were provided for each endpoint).

According to the Sponsor, interactions between treatment effect and age, gender, or race were not observed for the primary endpoint (PSG-defined LPS). The type of concomitant ADHD medication did not appear to influence PSG derived LPS results either. Most eszopiclone subjects were male (61.8% and 63.5% in the Phase 3 studies combined and Phase 1 studies combined, respectively). According to the Agency statistician's analyses, the predominant male population did not influence or drive the efficacy results- an important factor that allows for the acceptance of the deviation from what was stated in the PWR (pediatric written request). Specifically, the following was what was stated in the PWR- "Pediatric patients must be approximately evenly distributed between sexes".

Given the negative efficacy results (for primary and secondary end points) and that the Sponsor is not making any efficacy claims, further comments on efficacy are not made.

**Table 6.1.4 A**

**Table***
**Summary of the Least Square Mean Results of the Primary and Key Secondary Endpoints Study 190-246 (Intent-to-Treat Population)**

| Parameter | Statistic | Pooled High-Dose Eszopiclone (N=160) | Pooled Low-Dose Eszopiclone (N=163) | Placebo (N=160) |
|---|---|---|---|---|
| **Primary Endpoint** | | | | |
| Change from Baseline in Objective LPS at Week 12 (minutes) | LS-Mean (SE) | -18.33 (3.91) | -23.45 (3.91) | -25.66 (3.92) |
| | Unadjusted *P*-value (Treatment Difference) | 0.1875 | 0.6893 | - |
| | Adjusted *P*-value Treatment Difference) | 0.3749 | > 0.9999 | - |
| **Key Secondary Endpoints** | | | | |
| Change from | LS-Mean (SE) | -23.35 (3.40) | -16.75 (3.41) | -17.30 (3.43) |

| | | | | |
|---|---|---|---|---|
| | Unadjusted *P*-value (Treatment Difference) | 0.2118 | 0.9092 | - |
| | Adjusted *P*-value (Treatment Difference) | a NA | a NA | - |
| CGI Parent/Caregiver at Week 12 | LS-Mean (SE) | 2.3 (0.1) | 2.6 (0.1) | 2.7 (0.1) |
| | Unadjusted *P*-value (Treatment Difference) | 0.0090 | 0.2386 | - |
| | Adjusted *P*-value (Treatment Difference) | a NA | a NA | - |
| CGI Child at Week 12 | LS-Mean (SE) | 2.3 (0.1) | 2.5 (0.1) | 2.7 (0.1) |
| | Unadjusted *P*-value (Treatment Difference) | 0.0026 | 0.1285 | - |
| | Adjusted *P*-value (Treatment Difference) | a NA | a NA | - |
| Change from Baseline in Conners' ADHD (Inattention) | LS-Mean (SE) | -8.8 (1.0) | -5.8 (1.0) | -7.1 (1.0) |
| | Unadjusted *P*-value (Treatment Difference) | 0.2382 | 0.3518 | - |
| | Adjusted *P*-value (Treatment Difference) | a NA | a NA | - |

* Ref: Copied Sponsor's Table 2; Clinical Overview; p 13; Modified for format only.
Abbreviations: CGI = Clinical Global Impression; ITT = Intent-to-Treat; LPS = Latency to Persistent Sleep; SE = standard error; WASO = wake after sleep onset.
[a] Because the primary efficacy endpoint was not significant using the Bonferroni adjusted gatekeeping approach, the sequence of statistical testing was stopped after the primary efficacy endpoint, therefore this key secondary efficacy variable is considered not statistically significant.
Reference: CSR 190-246, Table 14.2.1.1

### 6.1.5 Analysis of Secondary Endpoints(s)

*Reviewer Comments*

See 6.1.4.

### 6.1.6 Other Endpoints

Not applicable.

### 6.1.7 Subpopulations

Not applicable.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

### 6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

# 7 Review of Safety

***Safety Summary***

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

4 pediatric clinical trials of eszopiclone by phase of development in which safety was assessed were:

Phase 3:

- Pediatric efficacy and safety (Study 190-246): 12-week, double-blind, placebo-controlled study in children (6 to 11 years of age; 1 mg or 2 mg eszopiclone or placebo) and adolescents (12 to 17 years of age; 2 mg or 3 mg eszopiclone or placebo) with ADHD-associated insomnia.
- Pediatric long-term safety (Study 190-247): 1-year, open-label study in children (6 to 11 years of age; 2 mg eszopiclone) and adolescents (12 to 17 years of age; 3 mg eszopiclone) with ADHD-associated insomnia.

Phase 1:

- Pediatric safety, tolerability, and PK/PD (190-201): single-dose, open-label, dose-escalation study in adolescents (12 to 17 years of age) with ADHD-associated insomnia; 1 mg, 2 mg, or 3 mg eszopiclone.
- Pediatric safety, tolerability, and PK/PD (190-202): single-dose, open-label, dose-escalation study in children (6 to 11 years of age) with ADHD-associated insomnia; 0.6 mg, 1 mg, 2 mg, or 3 mg eszopiclone.

*Reviewer Comments*

See Appendix Tables 1 and Table 2. All studies were conducted in the US and employed once-daily dosing at bedtime. In Study 190-247, 55 (~18%) subjects were roll over subjects who previously completed Study 190-246 prior to the close of Study 190-247 enrollment in October 2010). 249 (~82%) subjects were treatment-naïve subjects (not previously exposed to eszopiclone).

The safety assessments that were evaluated are shown in the table below.

**Table 7.1.1 A**

**Table***
**Safety Assessments**

| Source of Data | Pooled Analyses | | | Individual Phase 3 | | Individual Phase 1 | |
|---|---|---|---|---|---|---|---|
| | All 4 Studies (190-201, 190-202, 190-246, and 190-247) Combined | Phase 3 Studies (190-246 and 190-247) Combined | Phase 1 Studies (190-201 and 190-202) Combined | Study 190-246[a] | Study 190-247[a] | Study 190-201[a] | Study 190-202[a] |
| **Safety Assessment** | | | | | | | |
| Enumeration of subjects | X | | | | | | |
| Extent of exposure | X | X | | | | | |
| Disposition | | X | X | X | | | |
| Demography and baseline characteristics | | X | X | | | | |
| Medical history | | | | X | X | X | X |
| Concomitant meds | | | | X | X | X | X |
| Adverse events (including AESI and additional events of interest) | | X | X | X[b] | X[b] | | |
| Discontinuation/ withdrawal effects[c] | | | | X | | | |
| Rebound effects[d] | | | | X | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Next-day performance effects[e] | | | | X | X | | |
| Clinical lab parameters | | | | X | X | X | X |
| Vital signs | | | | X | X | X | X |
| Orthostatic effects | | | | X | X | X | X |
| ECGs | | | | X | X | X | X |
| Physical examinations | | | | X | X | X | X |
| Neuro examinations | | | | X | X | X | X |
| C-SSRS | | | | X | X | | |

*Ref: Copied Sponsor's Table 1, Section 2.7.4, p. 10; Summary of Clinical Safety; Modified for format only
Abbreviations: AESI = adverse events of special interest (skin reactions, dizziness, hallucinations, and suicidality); CSR = clinical study report; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; TEAE = treatment-emergent adverse event.

[a] Safety results were not pooled, but were presented individually in the SCS (referenced from the individual study CSRs in 5.3 Clinical Study Reports and Related Information).

[b] TEAEs by demographic subgroup were not pooled analyses, but were presented individually in the SCS (referenced from the individual study CSRs in 5.3 Clinical Study Reports and Related Information).

[c] Included adverse events and actigraphy parameters (sleep latency [SL], total sleep time [TST], wake after sleep onset [WASO], and number of awakenings after sleep onset [NAASO]).

[d] Included actigraphy parameters (SL, TST, WASO, and NAASO).

[e] Included objective assessments (Conners' Continuous Performance Test II [CCPT-II], Coding Copy Subtest/Digit Symbol Substitution Test [DSST]) and subjective assessments (Pediatric Daytime Sleepiness Scale [PDSS], parent-/subject-completed sleep questionnaire [daytime alertness, ability to concentrate, physical well-being, ability to function], Child Behavior Checklist [CBCL], Pediatric Quality-of-Life Scale [SF-10], and somnolence TEAEs).

### 7.1.2 Categorization of Adverse Events

*Reviewer Comments*

Adverse events included spontaneously-reported and elicited events, as well as clinically significant (CS) abnormal objective findings (e.g., clinical laboratory values, ECG values, or physical examination observations). Adverse events were collected from the time the informed consent was signed to the end of the study. Serious adverse events were collected and reported on the SAE form from the time of informed consent/assent to 30 days post last dose and were followed until resolution or until the subject was lost to follow-up.

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 12.0 or higher. Treatment-emergent adverse events (TEAEs) were defined as:

- AEs that occurred or worsened (increased in severity and/or frequency) on or after the date of the first dose of study medication, or
- AEs with a missing start date on or after the date of the first dose of study medication, or
- AEs with a missing start date and a stop date on or after the date of the first dose of dose of study medication, or

- AEs with a missing start date and a stop date on or after the date of the first dose of study medication
- AEs with both a missing start date and a missing stop date.

The definitions for reporting adverse events based on the different categories were:

- *Severity* (mild or moderate or severe)
- *Relationship* (not related or unlikely or possible or probable or definite)
- *Frequency* (once or intermittent or continuous)
- *Action taken regarding study drug* (none or interrupted or modified or discontinued or other).

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

*Reviewer Comments*

The presented safety data included pooled safety data from eszopiclone-treated subjects from each study. However, there was only 1 placebo-controlled study (190-246).

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Across the eszopiclone pediatric program, 710 subjects received eszopiclone and 160 subjects received placebo. A total of 663 unique subjects were exposed to eszopiclone at once-daily bedtime dose levels ranging from 0.6 mg to 3 mg.

**For all 4 studies combined**, the mean number of days of eszopiclone administration was 134 days (range: 1 to 476 days) and the total number of eszopiclone tablets taken, on average, was 126 (range: 1 to 479 tablets). A total of 161 unique subjects had a duration of eszopiclone exposure of at least 6 months and 112 unique subjects had a duration of eszopiclone exposure of at least 12 months.

For the Phase 3 studies combined, the mean number of days of eszopiclone administration was 151 days (range: 1 to 476 days) and the total number of eszopiclone tablets taken, on average, was 145 (range: 1 to 479 tablets). A total of 161 unique subjects had a duration of eszopiclone exposure of at least 6 months and 112 unique subjects had a duration of eszopiclone exposure of at least 12 months.

*Reviewer Comments*

There were 55 roll-over subjects in Study 190-247 who were not compared to Study 190-246 in the assessment of unique subjects; nor were placebo subjects assessed for uniqueness. None of the Study 190-201 subjects participated in Study 190-202 (or vice versa) due to the differing entrance criteria for age. No eszopiclone-treated subject participated twice in the same study and 11 eszopiclone-treated subjects participated in multiple studies (permissible by entry criteria): 10 subjects participated in 2 studies (190-201 and 190-246; 190-202 and 190-246; 190-202 and 190-247) and 1 subject participated in 3 studies (190-202, 190-246, and 190-247).

**Table 7.2.1 A**

**Table***
**Subject Enumeration**
**All Studies (190-201, 190-202, 190-246, 190-247)**

| Category | Placebo n (%) | Eszopiclone 0.6 mg n (%) | Eszopiclone 1 mg n (%) | Eszopiclone 2 mg n (%) | Eszopiclone 3 mg n (%) | Eszopiclone Overall n (%) |
|---|---|---|---|---|---|---|
| Total non-unique subjects (ITT) | 160 | 11 | 111 | 357 | 231 | 710 |
| Total unique subjects[a] | NA | 11 | 111 | 346 | 219 | 663 |
| Unique subjects in Phase 3 studies combined | NA | 0 | 86 | 324 | 195 | 589 |
| 12-week efficacy and safety study | | | | | | |
| **190-246** | **160 (100.0)** | **0** | **86 (77.5)** | **162 (45.4)** | **74 (32.0)** | **322 (45.4)** |
| Long-term safety study | | | | | | |
| 190-247 | 0 | 0 | 0 | 171 (47.9) | 132 (57.1) | 303 (42.7) |
| Unique subjects in Phase 1 studies combined | 0 | 11 | 25 | 24 | 25 | 85 |
| Single-dose PK/PD studies | | | | | | |
| 190-201 | 0 | 0 | 12 (10.8) | 12 (3.4) | 12 (5.2) | 36 (5.1) |
| 190-202 | 0 | 11(100.0) | 13 (11.7) | 12 (3.4) | 13 (5.6) | 49 (6.9) |

* Ref: Copied Sponsor's Table 3; Section 2.7.4; p 21/71. Modified for format only.
Abbreviations: CSR = clinical study report; ISS = integrated summary of safety; ITT = intent-to-treat; NA = not assessed; PD = pharmacodynamic; PK = pharmacokinetic.
[a] Date of birth and gender were used as identifiers in conjunction with a manual comparison of other criteria (eg, subject initials, race, height, weight, etc) to determine whether a subject participated in more than 1 study or participated more than once in the same study. For the total number of unique subjects, subjects who participated in more than 1 study or more than once in the same study were only counted once. Roll-over subjects in Study 190-247 were not compared to Study 190-246 in the assessment of unique subjects.
Note: Percentages were calculated based on the number of nonunique ITT subjects within each treatment column. Subjects were summarized according to the eszopiclone dose actually received.
Reference: ISS Table 1.0 and Study 190-246 CSR Table 14.1.1.1

Demographic and baseline characteristics were similar for the Phase 3 studies combined and Phase 1 studies combined. Most eszopiclone subjects were male (61.8% and 63.5% in the Phase 3 studies combined and Phase 1 studies combined,

respectively), White (77.2% and 72.9%, respectively), and not of Hispanic/Latino ethnicity (83.4% and 78.8%, respectively). A slightly higher proportion of eszopiclone subjects were in the 6 to 11 year-old category (55.3% and 57.6%, respectively) compared with the 12 to 17 year-old category (44.7% and 42.4%, respectively). According to the study designs, Study 190-201 enrolled only 12 to 17 year-olds and Study 190-202 enrolled only 6 to 11 year-olds.

For Study 190-246, there were 257 (53.2%) children and 226 (46.8%) adolescents. There were 85 (53.5%), 86 (52.8%), and 86 (53.4%) children in the high-dose eszopiclone, low-dose eszopiclone, and placebo groups, respectively, and 74 (46.5%), 77 (47.2%), and 75 (46.6%) adolescents in the respective dose groups.

## 7.3 Major Safety Results

For the ***Phase 1 studies combined***, there were no deaths, treatment-emergent SAEs, discontinuations due to TEAEs, or severe TEAEs for eszopiclone-treated subjects. Overall, 16 (18.8%) eszopiclone-treated subjects experienced at least 1 TEAE. There was no increase in the overall incidence of TEAEs across increasing eszopiclone dose levels (3 [27.3%], 7 [28.0%], 3 [12.5%], and 3 [12.0%] subjects in the 0.6 mg, 1 mg, 2 mg, and 3 mg eszopiclone dose groups, respectively) (Ref Sponsor's ISS Tables 5.1, 5.2, and 5.3; ISS Listing 5.0).

For the ***Phase 3 studies combined***, there was 1 (0.2%) death (accidental drowning). 6 subjects (1.0%) experienced treatment-emergent serious adverse events, 44 subjects (7.5%) discontinued due to adverse events, and 13 subjects (2.2%) experienced severe adverse events. Overall, 395 (67.1%) eszopiclone-treated subjects experienced at least one TEAE.

The table below provides the summary of TEAEs for the ***pivotal study 190-246***.

**Table 7.3 A**

**Table***
**Summary of Adverse Events Pivotal Study 190-246***

| | Pooled High Dose N=159 | Pooled Low Dose N=163 | Placebo N=161 |
|---|---|---|---|
| | Subject n (%) | Subject n (%) | Subject n (%) |
| Subjects with any TEAE | 97 (61) | 97 (59.5) | 74 (46) |
| Severe TEAE | 1 (0.6) | 1 (0.6) | 2 (1.2) |
| Serious TEAE | 2 (1.3) | 0 | 0 |
| Fatal TEAE | 0 | 0 | 0 |
| Discontinued study due to TEAE | 5 (3.1) | 4 (2.5) | 3 (1.9) |

*Ref: Derived from Sponsor's Submission (Study 190-246 CSR Tables 14.3.1.1.1, 14.3.1.2.1, 14.3.1.3.1, and 14.3.2.13; Listings 16.2.7.2 and 16.2.7.3).

### 7.3.1 Deaths

1 death (1/663 [0.2%] due to accidental drowning (Subject 190-247-0043-S001; 11 year old WM; No concomitant meds) occurred on day 321- approximately 3 weeks following the last known 2 mg eszopiclone dose in Study 190-247.

*Sponsor's Narrative of Fatal Event- Drowning*

"The subject and 3 other children left the group they were with to go to a nearby creek. They did not have adult supervision. The subject jumped in the water, bobbed up and down a couple of times, then disappeared below the surface. The other children looked for him briefly before calling 911 for help. The subject was found dead about 2 hours later by divers. An autopsy was performed and confirmed the cause of death as drowning. The manner of death was reported as an accident and the description of injury was that the decedent had drowned in freshwater. The subject did not indicate any suicidal ideation or suicidal behavior on the Columbia-Suicide Severity Rating Scale over his lifetime or during the study."

*Reviewer Comments*

In the opinion of this reviewer, Lunesta as a direct cause for death is unlikely.

### 7.3.2 Nonfatal Serious Adverse Events

There were a total of 5 nonfatal serious adverse events reported for 5 Lunesta-treated subjects. These were:

1. Event *Sedation*
   Sedation was reported on Day 2 of 2 mg eszopiclone treatment in Study 190-246 (Subject 190-246-0092-S002; 8 yr; WF; moderate intensity; within one hour after taking study drug).
   *Same subject also experienced dizziness mild intensity- possibly related- see below*
2. Event *Respiratory distress*
   This event was reported on Day 88, which was during the single-blind placebo follow-up period following 2 mg eszopiclone in Study 190-246 (Subject 190-246-0120-S009; 11 yr; AA; Hx of Asthma)
3. Event *Upper limb fracture*
   This event was reported on Day 102 of 3 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0025-S503; 12 yr; WM; fell while skate boarding in park).
4. Event *Viral infection*
   This event was reported on Day 123 of 3 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0025-S510; 16 yr; WF; Hx of psoriatic arthritis; on lisdexamfetamine mesilate; URI with fever and cervical adenopathy, + beta-hemolytic strep).
5. Event *Delirium*

This event was reported on Day 57 of 2 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0065-S508).
*Same subject also experienced peri-oral rash (classified as dermatitis- not related)*

The narrative (s) of patient (s) who experienced non-fatal serious adverse events that was felt to be clinically relevant (by this reviewer) and attributable to Lunesta as the most likely cause were:

*Sponsor's Narrative of Non-fatal Serious Adverse Event- Delirium*

The subject was an 8-year-old White male with ADHD and insomnia, and a medical history significant for asthma, allergic rhinitis, enuresis, and eczema, and with no history of confusion or delirium. Concomitant medications reported at study entry included cetirizine, salbutamol, and methylphenidate hydrochloride. This treatment-naïve subject received open-label 2 mg eszopiclone from 09 September 2010 to 07 November 2010. On 04 Nov 2010 (day 57 into open-label treatment)- the subject remained awake and began speaking nonsense several hours after taking the medication. It was reported that he threw a music player and said that he wished he was dead. The Investigator did not consider this to be suicidal ideation as the subject did not remember the event and denied any suicidal ideation. This delirium serious adverse event resolved the same day (Day 57) without treatment, and was assessed by the Investigator as definitely related to study medication. The subject did not indicate any suicidal ideation or suicidal behavior on the Columbia-Suicide Severity Rating Scale over his lifetime or during the study.

*Reviewer Comments*

Of the 5 reported cases of non-fatal serious adverse events, the event of sedation and delirium can be considered related to Lunesta. Sedation can be considered an extension of the direct pharmacological effect of eszopiclone and therefore not necessarily a serious adverse event as reported. The event of delirium, as described in the aforementioned narrative– "*began speaking nonsense several hours after taking the medication*" clearly suggests an abnormal behavior that perhaps can be attributable to Lunesta, the narrative itself lacks details and specifics that is typically characteristic of delirium. Based on the provided narrative for the case reported as viral infection, although the initial clinical presentation may have resembled a viral syndrome, the subsequent course of events, findings and the management of this patient does not fit such a picture of a viral infection.

### 7.3.3 Dropouts and/or Discontinuations

66 TEAEs resulting in study discontinuation occurred in 44 (44/663 [6.6%]) Lunesta-treated subjects all of which were reported in the combined Phase 3 studies with no reports for the Phase1 studies combined.

In the *pivotal study 190-246*, 3 subjects in the *placebo group* (3/161[1.9%]), 4 subjects in the *pooled low-dose Lunesta group* (4/163 [2.5%]), and 5 subjects in the *pooled high-dose Lunesta group* (5/159 [3.1%]) discontinued from the study (Ref: Sponsor's Table 45, Clinical Study Report 190-246, p 149/6496- see Table below). Events leading to the discontinuation of more than 1 subject included: psychomotor hyperactivity (3 subjects); irritability (2 subjects); and dizziness (2 subjects).

**Table 7.3.3 A**

**Table***
**Treatment Emergent Adverse Events Leading to Discontinuation Study 190-246 By System Organ Class and Preferred Term (Safety Population)**

| System Organ Class Preferred Term | Pooled High Dose Eszopiclone (N=159) | Pooled Low Dose Eszopiclone (N=163) | Placebo (N=161) | Total (N=483) |
|---|---|---|---|---|
| | Subjects n (%) | Subjects n (%) | Subjects n (%) | Subjects n (%) |
| **Overall** | **5 (3.1)** | **4 (2.5)** | **3 (1.9)** | **12 (2.5)** |
| **Gastrointestinal disorders** | **0** | **0** | **1 (0.6)** | **1 (0.2)** |
| Diarrhoea | 0 | 0 | 1 (0.6) | 1 (0.2) |
| **General disorders and administration site conditions** | **0** | **2 (1.2)** | **0** | **2 (0.4)** |
| Irritability | 0 | 2 (1.2) | 0 | 2 (0.4) |
| **Nervous system disorders** | **4 (2.5)** | **1 (0.6)** | **2 (1.2)** | **7 (1.4)** |
| Dizziness | 1 (0.6) | 1 (0.6) | 0 | 2 (0.4) |
| Dysarthria | 1 (0.6) | 0 | 0 | 1 (0.2) |
| Headache | 0 | 0 | 1 (0.6) | 1 (0.2) |
| Psychomotor hyperactivity | 2 (1.3) | | 1 (0.6) | 3 (0.6) |
| **Psychiatric disorders** | **2 (1.3)** | **2 (1.2)** | **0** | **4 (0.8)** |
| Abnormal dreams | 0 | 1 (0.6) | 0 | 1 (0.2) |
| Depression | 0 | 1 (0.6) | 0 | 1 (0.2) |
| Hallucination, visual | 1 (0.6) | 0 | 0 | 1 (0.2) |
| Initial insomnia | 1 (0.6) | 0 | 0 | 1 (0.2) |
| Suicidal ideation | 0 | 1 (0.6) | 0 | 1 (0.2) |
| **Skin and subcutaneous tissue disorders** | **0** | **0** | **1 (0.6)** | **1 (0.2)** |

| | | | | |
|---|---|---|---|---|
| Pruritus | 0 | 0 | 1 (0.6) | 1 (0.2) |

*Ref: Copied Sponsor's Table 45, Clinical Study Report 190-246, p 149/6496- Modified for format only
Notes: Adverse events were coded using MedDRA 12.0. For the subject level calculations, a subject with multiple events in a given System Organ Class (SOC) or Preferred Term (PT) was counted only once per SOC or PT. Percentages were calculated based on the number of subjects in the Safety population in each treatment group. Adverse events were considered treatment emergent if they occurred or increased in severity on or after the date of first dose of study medication.

### 7.3.4 Significant Adverse Events

The following adverse events are discussed under the significant adverse events-

- Protocol-defined Adverse Events of Special Interest (AESI)
- Additional Adverse Events of Interest
- Severe Adverse Events (SAE)

**Protocol-defined Adverse Events of Special Interest**

For studies 190-246 and 190-247, skin reactions, dizziness, hallucinations and suicidality were predefined as adverse events of special interest.

There were a total of 123 treatment-emergent AESIs reported for 93/589 (15.8%) eszopiclone-treated subjects for the Phase 3 studies combined and 1 treatment-emergent AESI reported for 1/85 (1.2%) eszopiclone-treated subject for the Phase 1 studies combined. None of the AESIs in eszopiclone-treated subjects were serious, 1 was severe (dizziness), and 15 resulted in subject discontinuation from the study (6 cases of dizziness, 6 cases of hallucination, and 3 cases of suicidality [suicide attempt and 2 cases of suicidal ideation]).

*Skin Reaction*
There were a total of 34 skin reaction TEAEs (preferred terms of eczema, erythema, dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, drug eruption, excoriation, pityriasis rosea, pruritus, rash, skin irritation, urticaria) reported for 26 (4.4%) eszopiclone-treated subjects for the Phase 3 studies combined and 1 skin reaction TEAE reported for 1 (1.2%) 0.6 mg eszopiclone-treated subject for the Phase 1 studies combined. The incidences of skin reactions in both eszopiclone groups were not higher than incidence in the placebo group in study **190-246** (placebo 9 [5.6%], low-dose eszopiclone 6 [3.7%], and high-dose eszopiclone 7 [4.4%]) (Ref: Study 190-246 CSR Table 14.3.2.1).

There was 1 eszopiclone-treated subject (Subject 190-247-0065-S501) with a drug eruption TEAE, and the reported term indicated that it was a rash secondary to amoxicillin. None of the skin reaction TEAEs for eszopiclone-treated subjects were serious, of severe intensity, or resulted in discontinuation from the study.

*Dizziness*

There were a total of 62 dizziness TEAEs (preferred terms of dizziness, vertigo) reported for 50 (8.5%) eszopiclone-treated subjects for the Phase 3 studies combined and none for the Phase 1 studies combined.

*Dizziness had a dose-response relationship in study **190-246*** (placebo 4 [2.5%], low-dose eszopiclone 6 [3.7%], and high-dose eszopiclone 14 [8.8%]). None of the dizziness TEAEs for eszopiclone-treated subjects were serious, 1 was of severe intensity (Subject 190-247-0043-S508), and 6 resulted in discontinuation from the study from Day 1 to Day 18 of 2 mg eszopiclone treatment (Subject 190-246-0017-S006, Subject 190-246-0102-S007, Subject 190-247-0008-S506, Subject 190-247-0023-S502, Subject 190-247-0025-S529, and Subject 190-247-0043-S508).

*Hallucination*

The overall incidence of hallucination TEAEs (preferred terms of hallucination; hallucination, auditory; hallucination, visual; hypnagogic hallucination) was (16/663 [2.4%] eszopiclone-treated subjects versus 0% of placebo subjects). There were 22 hallucination TEAEs reported for 16 (2.7%) eszopiclone-treated subjects for the Phase 3 studies combined; none were reported for the Phase 1 studies combined.

Hallucinations did not have a dose-response relationship in study **190-246** (placebo 0 [0%], low-dose eszopiclone 4 [2.5%], and high-dose eszopiclone 2 [1.3%]) and were only observed in eszopiclone-treated subjects. None of the hallucination TEAEs for eszopiclone-treated subjects were serious or of severe intensity. Six resulted in discontinuation from the study from Day 1 to Day 43 of 2 mg eszopiclone treatment (Subject 190-246-0017-S006, Subject 190-247-0002-S014, Subject 190-247-0008-S506, Subject 190-247-0037-S507, Subject 190-247-0113-S507, and Subject 190-247-0114-S504).

*Suicidality*

There were a total of 4 suicidality TEAEs (preferred terms of *self-injurious ideation*, *suicidal ideation*, and *suicide attempt*) reported for 4 (0.7%) eszopiclone-treated subjects for the Phase 3 studies combined; none were reported for the Phase 1 studies combined.

Suicidality did not have a dose-response relationship in study **190-246** (placebo 0 [0%], low-dose eszopiclone 1 [0.6%], and high-dose eszopiclone 0 [0%]). None of the suicidality TEAEs for eszopiclone-treated subjects were serious or of severe intensity.

Three resulted in discontinuation from the study on Day 37, Day 321, and Day 52 of 2 mg, 3 mg, and 3 mg eszopiclone treatment, respectively (Subject 190-246-0033-S018 [suicidal ideation], Subject 190-247-0032-S503 [depression with suicidal attempt-aborted attempt- “had knife in hand to stab himself, but did not act because did not want to hurt family”], and Subject 190-247-0126-S501 [suicidal ideation]).

Self-injurious ideation occurred in Subject 190-247-0050-S010 (reported as having thoughts without definite plans or intent of hurting [not killing] when she goes to bed that lasted until she fell asleep).

*Reviewer Comments*

It is the understanding of this reviewer, that the Sponsor chosen word "suicidality" is not an accepted terminology within the Agency when reference is made to events such as suicidal ideation, suicidal attempts, etc. The recommended terminology is suicidal behaviors and suicidal thoughts. In accordance with this understanding, it is recommended that the language in the label be changed to include suicidal behaviors and suicidal thoughts. Further, following internal discussions, it was decided that the term suicidal ideation could be used as an alternate to the term suicidal thought.

**Table 7.3.4 A**

**Table***
**Treatment Emergent Adverse Events of Special Interest (Safety Population)**

| AE of Special Interest | Statistic | Pooled High Dose Eszopiclone (N=159) | Pooled Low Dose Eszopiclone (N=163) | Placebo (N=161) |
|---|---|---|---|---|
| Skin Reactions | n (%) | 7 (4.4) | 6 (3.7) | 9 (5.6) |
| | Treatment Difference | -1.2 | -1.9 | - |
| | 90% Confidence Interval | -10.4, 8.2 | -11.2, 7.3 | - |
| Dizziness | n (%) | 14 (8.8) | 6 (3.7) | 4 (2.5) |
| | Treatment Difference | 6.3 | 1.2 | - |
| | 90% Confidence Interval | -2.9, 15.7 | -8.1, 10.4 | - |
| Hallucinations | n (%) | 2 (1.3) | 4 (2.5) | 0 |
| | Treatment Difference | 1.3 | 2.5 | - |
| | 90% Confidence Interval | -8.1, 10.6 | -6.9, 11.7 | - |
| Suicidality | n (%) | 0 | 1 (0.6) | 0 |
| | Treatment Difference | NE | 0.6 | - |
| | 90% Confidence Interval | NE, NE | -8.7, 9.9 | - |

*Ref: Sponsor's Table 46, Other Significant Events, Study 190-246; p. 150/6496; Modified for format only.
Abbreviations: NE=Not Estimable.
Notes: A subject with multiple adverse events of special interest is counted only once per adverse event. Percentages are calculated based on the number of Safety subjects in each treatment group. Adverse events are considered treatment emergent if they occur or increase in severity on or after the date of first dose of study medication. Adverse events with missing start and end dates will be considered treatment emergent.
Reference: Table 14.3.2.1

**Additional Adverse Events of Interest**

In addition to the aforementioned protocol defined adverse events of special interest, Sponsor additionally analyzed the following adverse events- memory impairment, seizures, worsening of depression, parasomnia, and paradoxical reaction.

There were a total of 18 *additional* TEAEs of interest reported for 12/589 (2.0%) eszopiclone-treated subjects for the Phase 3 studies combined and none reported for the Phase 1 studies. None of the additional TEAEs of interest in eszopiclone-treated subjects were serious, 2 were severe (depression, psychomotor hyperactivity), and 5 resulted in subject discontinuation from the study (2 cases of depression, 1 case of somnambulism, 2 cases of psychomotor hyperactivity)

*Memory Impairment*
There were a total of 3 memory impairment TEAEs (PTs of amnesia, memory impairment) reported for 2/589 (0.3%) eszopiclone-treated subjects for the Phase 3 studies combined; none were reported for the Phase 1 studies combined. One event started during 2 mg eszopiclone treatment and 2 events started during 3 mg eszopiclone. There were no placebo-treated or eszopiclone-treated subjects that reported a memory impairment TEAE in Study 190-246. None of the memory impairment TEAEs in eszopiclone-treated subjects were serious, of severe intensity, or resulted in discontinuation from the study.

*Seizure (Convulsion)*
1 seizure TEAE (PT of convulsion) was reported for 1/589 (0.2%) 3 mg eszopiclone-treated subject for the Phase 3 studies combined; none were reported for the Phase 1 studies combined. There were no placebo-treated subjects that reported a seizure TEAE in Study 190-246. There was one 3 mg eszopiclone-treated subject with a TEAE of convulsion ("seizure disorder") that led to a diagnosis of seizure disorder (epilepsy) with initiation of epilepsy treatment; the subject had evidence of prestudy structural brain changes (Subject 190-247-0050-S013). This convulsion TEAE was not serious or of severe intensity, and did not result in discontinuation from the study; however, the new seizure disorder diagnosis and treatment met study exclusion criteria and the subject was withdrawn.

*Worsening of Depression*
There were a total of 2 worsening of depression TEAEs (PT of depression) reported for

2/589 (0.3%) eszopiclone-treated subjects for the Phase 3 studies combined; none were reported for the Phase 1 studies combined. One event started during 2 mg eszopiclone treatment and the other event started during 3 mg eszopiclone. There were no placebo-treated subjects that reported a depression TEAE in Study 190-246. Neither of the depression TEAEs was an SAE. One was of severe intensity (Subject 190-247-0032-S503). Each resulted in discontinuation from the study; Day 6 and Day 317 of 2 mg and 3 mg eszopiclone treatment, respectively (Subject 190-246-0010-S004 and Subject 190-247-0032-S503).

*Parasomnia*

There were a total of 8 parasomnia TEAEs (PT of somnambulism) reported for 3/589 (0.5%) eszopiclone-treated subjects for the Phase 3 studies combined; none were reported for the Phase 1 studies combined. All events started during 2 mg eszopiclone treatment. There were no placebo-treated subjects that reported a parasomnia TEAE in Study 190-246. None of the parasomnia TEAEs in eszopiclone-treated subjects were serious or of severe intensity. One event resulted in discontinuation from the study on Day 120 of 2 mg eszopiclone treatment (Subject 190-247-0031-S505).

*Paradoxical Reaction*

There were a total of 4 paradoxical reaction TEAEs (PT of psychomotor hyperactivity) reported for 4/589 (0.7%) eszopiclone-treated subjects for the Phase 3 studies combined; none were reported for the Phase 1 studies combined. Three events started during 2 mg eszopiclone treatment and 1 event started during 3 mg eszopiclone. There was 1 placebo-treated subject who reported a paradoxical reaction TEAE in Study 190-246 that was not serious or of severe intensity, but did result in discontinuation from the study (Subject 190-246-0089-S002). None of the paradoxical reaction TEAEs in eszopiclone-treated subjects were serious and 1 was of severe intensity (see narrative for Subject 190-247-0040-S502). Two resulted in discontinuation from the study; each on Day 1 of 2 mg and 3 mg eszopiclone treatment, respectively (Subject 190-246-0069-S017 and Subject 190-246-0089-S013).

**Severe Adverse Events (SAE)**

14 severe AEs (events) were reported in 13 subjects (13/663=2.0%) all of which occurred in the Phase 3 studies combined and none in the Phase 1 studies combined. As noted in the Summary of Adverse Events Table for the *pivotal study 190-246*; the overall incidence of severe AE in subjects for *pivotal study 190-246* were: Placebo 2 subjects (1.2%), low-dose eszopiclone 1 subject (0.6%), and high-dose eszopiclone 1subject (0.6%) indicating no dose relationship. The 14 events occurring in 13 subjects were:

1. Event Constipation– this was reported on Day 59 of 3 mg eszopiclone treatment in Study 190-246 (Subject 190-246-0086-S011)

2. Event Respiratory distress- this was reported on Day 88, which was during the single-blind *placebo follow-up* period following 2 mg eszopiclone in Study 190-246 (Subject 190-246-0120-S009)- same patient described under Serious AE
3. Event Tonsillitis (not related & resolved with tonsillectomy)- was reported on Day 20 of 1 mg eszopiclone treatment in Study 190-246 (Subject 190-246-0134-S004)
4. Insomnia was reported on Day 3 of 2 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0002-S501).
5. Dysgeusia was reported on Day 1 of 2 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0023-S502- see narrative below).
6. Depression was reported on Day 317 of 3 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0032-S503).
7. Insomnia was reported on Day 1 of 2 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0032-S506).
8. Psychomotor hyperactivity was reported on Day 12 of 2 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0040-S502).
9. Drowning (accidental) resulted in death on Day 321 approximately 3 weeks following the last known 2 mg eszopiclone dose in Study 190-247 (Subject 190-247-0043-S001- see narrative under death).
10. Ataxia and dizziness were reported on Day 1 of 2 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0043-S508- see narrative below).
11. Headache was reported on Day 318 of 3 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0047-S512).
12. Neutropenia was reported on Day 92 of 2 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0050-S001).
13. Confusional state was reported on Day 8 of 3 mg eszopiclone treatment in Study 190-247 (Subject 190-247-0050-S013).

Of the 14 severe TEAEs in eszopiclone-treated subjects, the following were considered by the Investigator to have a *possible* relationship to study medication- confusional state, depression), *probable* relationship to study medication - neutropenia, psychomotor hyperactivity), or *definite* relationship to study medication- both cases of insomnia, dysgeusia, ataxia, dizziness.

The narratives of patients who experienced severe adverse events that were felt to be clinically relevant (according to this reviewer) and attributable to Lunesta as the most likely cause were:

*Sponsor's Narrative of SAE- Dysgeusia*

"Subject 0023-S502 (2 mg Eszopiclone). Dizziness, Dysgeusia, Abnormal Behavior (Possibly Related, Definitely Related, Definitely Related).

The subject was a 7-year-old white male with ADHD and insomnia, and no other medical history reported. Concomitant medication use included methylphenidate at

study entry. This treatment-naïve subject received open-label 2 mg eszopiclone from 26 July to 07 August 2010.

On 26 July 2010, the first day of the open-label treatment period, the subject experienced the nonserious events of dizziness, strange behavior (both of moderate intensity), and bad after taste (of severe intensity). Study drug was discontinued on 07 August 2010 (Day 13) and the event of dizziness was resolved that same day, while the events of strange behavior and bad after taste resolved on 13 August 2010 (Day 19). The event of dizziness was considered by the investigator as possibly related to study medication, and the events of strange behavior and bad after taste were considered definitely related. Per the investigator's comments, the last contact with the subject was 16 August 2010."

*Sponsor's Narrative of SAE- Ataxia and Dizziness*

"Subject 0043-S508 (2 mg Eszopiclone). Ataxia, Dizziness, Dizziness (Definitely Related, Definitely Related, Definitely Related).

The subject was a 10-year-old white female with ADHD and insomnia, and a medical history significant for tension headache. Concomitant medication use included methylphenidate hydrochloride at study entry. This treatment-naïve subject received open-label 2 mg eszopiclone from 27 September to 21 October 2010.

On 27 September 2010, the first day of the open-label treatment period, the subject experienced the nonserious events of ataxia, dizziness, somnolence, anxiety, and enuresis. The events of ataxia and dizziness were of severe intensity, anxiety and enuresis were of moderate intensity, and somnolence was of mild intensity. Study drug was interrupted, and all events resolved on 28 September (Day 2), except enuresis which resolved on 27 September. The events were considered definitely related to study medication except somnolence, which was considered probably related. On 14 October 2010 (Day 18 into open-label treatment), the subject experienced the nonserious events of morning dizziness and morning somnolence, both of moderate intensity. Study drug was discontinued on 21 October 2010 due to the morning dizziness event. The events were considered resolved on 22 October (Day 26). The events of morning dizziness and morning somnolence were considered by the investigator as definitely related to study medication. The last contact with the subject was 25 October 2010."

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

For the Phase 3 studies combined, 395 (67.1%) eszopiclone-treated subjects experienced at least 1 TEAE. For the Phase 3 studies combined, the most commonly-

reported TEAEs for eszopiclone-treated subjects, by descending frequency, were headache (105 [17.8%] subjects), dysgeusia (72 [12.2%] subjects), dizziness (50 [8.5%] subjects), upper abdominal pain (35 [5.9%] subjects), nasopharyngitis (35 [5.9%] subjects), upper respiratory tract infection (32 [5.4%] subjects), and vomiting (30 [5.1%] subjects).

There was a dose-response relationship for the *overall incidence* of TEAEs for pivotal study **190-246** (74 [46.0%], 97 [59.5%], and 97 [61.0%] subjects in the placebo, low-dose eszopiclone, and high-dose eszopiclone groups, respectively) (Study 190-246 CSR Table 14.3.1.1.1). A dose-response relationship was observed for the following TEAEs: dysgeusia (2 [1.2%], 8 [4.9%], and 22 [13.8%] subjects in the placebo, low-dose eszopiclone, and high-dose eszopiclone groups, respectively); dizziness (3 [1.9%], 6 [3.7%], and 13 [8.2%] subjects, respectively); abdominal discomfort (0 [0%], 4 [2.5%], and 8 [5.0%] subjects, respectively); and nasal congestion (0 [0%], 1 [0.6%], and 4 [2.5%] subjects, respectively) (Study 190-246 CSR Table 14.3.1.1.1).

**Table 7.4.1 A**

**Table***
**Treatment-Emergent Common Adverse Events Study 190-246**
**Double-Blind Treatment Period**
**≥2% of Subjects in Either Eszopiclone Pooled Dose Group and Greater than the Placebo Incidence (ITT Population)**

| MedDRA (version 12.0) Preferred Term | **Pooled High Dose Eszopiclone (N=159)** Subjects n (%) | **Pooled Low Dose Eszopiclone (N=163)** Subjects n (%) | **Placebo (N=161)** Subjects n (%) |
|---|---|---|---|
| Headache | 22 (13.8) | 19 (11.7) | 19 (11.8) |
| **Dysgeusia** | 22 (13.8) | 8 (4.9) | 2 (1.2) |
| **Dizziness** | 13 (8.2) | 6 (3.7) | 3 (1.9) |
| Upper respiratory tract infection | 5 (3.1) | 13 (8.0) | 7 (4.3) |
| Nasopharyngitis | 6 (3.8) | 9 (5.5) | 7 (4.3) |
| Vomiting | 5 (3.1) | 10 (6.1) | 3 (1.9) |
| Abdominal pain upper | 8 (5.0) | 6 (3.7) | 5 (3.1) |
| Abdominal discomfort | 8 (5.0) | 4 (2.5) | 0 |
| Pyrexia | 8 (5.0) | 4 (2.5) | 5 (3.1) |
| Nausea | 7 (4.4) | 4 (2.5) | 6 (3.7) |
| Somnolence | 6 (3.8) | 4 (2.5) | 3 (1.9) |
| Oropharyngeal pain | 3 (1.9) | 6 (3.7) | 4 (2.5) |
| Toothache | 2 (1.3) | 4 (2.5) | 0 |
| Nasal congestion | 4 (2.5) | 1 (0.6) | 0 |
| Urinary tract infection | 4 (2.5) | 1 (0.6) | 1 (0.6) |
| Irritability | 0 | 4 (2.5) | 0 |

*Ref: Copied Sponsor's Table 12, Section 2.7.4, Summary of Clinical Safety; Modified for format only
Abbreviations: CSR = clinical study report; ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities.
Note: Treatment-emergent adverse events were defined as adverse events that occurred or increased in severity on or after the date of first dose of study medication.
Note: A subject with multiple events in a given preferred term was counted only once per preferred term. Note: The table is presented by decreasing frequency of preferred term according to the overall eszopiclone incidence.
Note: Subjects were summarized in the CSR for the safety population according to the treatment actually received (Study 190-246 CSR Section 9.7.1.1); this is equivalent to the SCS ITT population definition. Percentages were calculated based on the number of ITT subjects in each treatment group.
Reference: Study 190-246 CSR Table 14.3.1.8

For the Phase 1 studies combined, 16 (18.8%) eszopiclone-treated subjects experienced at least 1 TEAE. There was no increase in the overall incidence of TEAEs across increasing eszopiclone dose levels (3 [27.3%], 7 [28.0%], 3 [12.5%], and 3 [12.0%] subjects in the 0.6 mg, 1 mg, 2 mg, and 3 mg eszopiclone dose groups, respectively). For the Phase 1 studies combined, the most commonly-reported TEAEs for eszopiclone-treated subjects, by descending overall frequency, were headache (3 [3.5%] subjects), dysgeusia (2 [2.4%] subjects), and abdominal pain (2 [2.4%] subjects). The remaining TEAEs were each reported by a single eszopiclone-treated subject. There was no increase in the incidence of any TEAE across increasing eszopiclone dose levels.

### 7.4.2 Laboratory Findings

*Reviewer Comments*

For pivotal study 190-246; blood and urine samples were processed centrally. All laboratories were to be College of American Pathologists and Clinical Laboratory Improvement Amendments (or equivalent) certified. Subjects were not required to fast prior to clinical laboratory tests. Blood samples for serum pregnancy tests and urine samples for urine pregnancy tests were collected only for female subjects ≥ 8 years of age. Urine samples were collected for urine drug screening, alcohol breath tests were performed, and blood samples for hepatitis B/C screening were collected. Laboratory data were collected at screening (Visit 1), and again at randomization (Visit 3), Visit 7 (pre and post PSG), and end of study (Visit 8).

The same hematology, chemistry, thyroid, coagulation, and urinalysis tests were required in each of the study protocols. The clinical significance of all out-of-range laboratory values was determined by the Investigator, and all CS laboratory abnormalities (or the diagnosis associated with a CS laboratory abnormality) were recorded as adverse events.

In concurrence with the Sponsor, for each study, the mean changes from baseline to the end of the study were small for each hematology, serum chemistry, and numeric

urinalysis parameter. The reported clinically significant lab changes as TEAEs and potentially clinically significant (PCS) values were of low incidence and not clinically worrisome.

### 7.4.3 Vital Signs

*Reviewer Comments*

For pivotal study 190-246; vital sign measurements consisted of supine and standing systolic and diastolic blood pressures, respiration rate, supine and standing heart rates, and oral or auricular body temperature. Height and weight also were captured. Blood pressure and heart rate were taken first with the subject in the supine position after resting for ≥ 5 minutes, and taken again after standing for 2 to 4 minutes. The same arm was used during each assessment of blood pressure and heart rate throughout the study. If a subject developed symptoms consistent with orthostatic hypotension (light headedness, dizziness, or changes in sensorium upon standing) at any point during the study, supine and standing blood pressure and heart rate were collected at that time in the manner described above. Orthostatic hypotension was defined as a decrease of 20 mmHg or more in standing systolic blood pressure (BP) or a decrease of 10 mmHg or more in standing diastolic BP compared to the corresponding supine measurement. Orthostatic tachycardia was defined as a standing heart rate increase of 20 beats per minute or more compared to the supine measurement with a standing heart rate over 100 beats per minute. When feasible, vital signs were obtained prior to performing an ECG and collection of clinical laboratory samples.

In Studies 190-201 and 190-202, sitting and standing systolic and diastolic blood pressures, sitting and standing heart rates, respiration rate, and temperature were collected. Blood pressure and heart rate were taken first with the subject in the sitting position for ≥ 5 minutes, and taken again after standing for 3 minutes.

Individual post baseline vital sign values were evaluated according to sponsor-defined criteria to identify PCS (potentially clinically significant) values. The PCS criteria used were consistent across studies.

In concurrence with the Sponsor, for each study, the mean changes from baseline and the incidence of post baseline values that met PCS criteria were small for each vital sign parameter and did not raise clinical concerns that were worrisome.

### 7.4.4 Electrocardiograms (ECGs)

*Reviewer Comments*

For pivotal study 190-246; all ECGs were obtained in the supine position, after the subject had been resting supine for at least 10 minutes. ECGs were 12-lead with a 10-second rhythm strip. When possible, ECGs were obtained prior to drawing blood

samples. ECGs were centrally over-read at a core lab according to established quality assurance procedures for inter-/intra-reader variability. The interpreted parameters included ventricular rate, PR interval, RR interval, QRS duration, and QT interval. Corrected QT (QTc) was derived using Fridericia's formula [QTc-F = QT / (RR/1000 ms)$^{1/3}$] and Bazett's formula [QTc-B = QT / (RR/1000 ms)$^{1/2}$]. ECG abnormalities also were assessed and categorized (rhythm, conduction, morphology, myocardial infarction, and ST-, T-, and U-wave abnormalities). Clinically significant abnormal ECG findings were to be recorded as AEs.

For each study, the mean changes from baseline were small for each ECG parameter (heart rate, PR interval, RR interval, QRS duration, QT interval, QTc-B interval, and QTc-F interval). No QTc-F intervals > 500 ms were reported in any study. No subjects in any study had an increase in QTc-F of ≥ 60 ms in any study.

### 7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

### 7.4.6 Immunogenicity

Not applicable.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

Not applicable.

### 7.5.2 Time Dependency for Adverse Events

Not applicable.

### 7.5.3 Drug-Demographic Interactions

Not applicable.

### 7.5.4 Drug-Disease Interactions

Not applicable.

### 7.5.5 Drug-Drug Interactions

Drug-drug interactions with eszopiclone were not evaluated in pediatric clinical studies.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

No additional data.

### 7.6.2 Human Reproduction and Pregnancy Data

No additional data.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

No additional data.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

*Abuse and dependence potential*
The abuse and dependence potential of eszopiclone (zopiclone, and its isomer eszopiclone, is listed as a Schedule IV controlled substance) were not evaluated in pediatric clinical studies.

*Overdose*
In pediatric clinical studies, no TEAEs of overdosage with eszopiclone were reported.

*Sponsor's Narrative of Overdose Event from Clinical Study 190-247:*
There was a 12-year old White male (Subject 190-247-0080-S501) with a diagnosis of ADHD, encopresis, and allergies who was "overdosed on eszopiclone for 11 days by

the babysitter" during month 9 of open-label 3 mg eszopiclone treatment. Concomitant medications included loratadine and methylphenidate hydrochloride. The amount of eszopiclone ingested was not recorded; the mother discovered an empty bottle 23 days (23 June 2011) after a bottle containing 35 tablets of 3 mg eszopiclone was dispensed (31 May 2011). No associated adverse event was reported.

During post marketing experience with Lunesta, 2 serious case reports of overdose were reported in pediatric patients (< 18 years of age) from spontaneous sources (see Section 8 of the review).

*Sponsor's Narrative of Post Marketing Overdose Events:*

- "1 intentional overdose case (2006SP002211) of a 17-year-old female, with a medical history significant for bipolar disorder and an unspecified eating disorder, who ingested 18 mg Lunesta in a suicide attempt and was hospitalized. It was unknown if AEs were associated with the incident. In a subsequent suicide attempt when she had already turned 18 years old, she ingested 24 mg Lunesta and fell down a flight of stairs; resolution of the AE was unknown."

- "1 multiple drug overdose case (2009SP002734) of a 4-year-old autistic male whose mother gave him 1 tablet (unknown dose) of Lunesta and ibuprofen (unknown dose) for not sleeping. Approximately 15 minutes later, the mother found her son with many open bottles of unspecified prescription medications. The mother put her son to bed because she did not actually see that her son had taken any of the medications. The child was found deceased the next day. An autopsy with toxicology determined that the child had consumed Lunesta, oxycodone, oxymorphone hydrochloride, and ibuprofen. The levels of oxycodone and oxymorphone hydrochloride were reported to be lethal."

*Reviewer Comments*

Information on overdose from case-review studies from the literature, those reported to poison-control centers and those on racemic zopiclone pharmaceutical poisonings from international sources (racemic zopiclone is available in 80 countries) were reported in the submission (Ref: Sponsor's Submission, Section 5.5, Summary of Clinical Safety, p. 58/71). These are noted.

*Discontinuation/Withdrawal Effects*
Potential discontinuation/withdrawal and rebound effects were evaluated during the 2-week single-blind placebo wash-out period in study 190-246.

The effects of discontinuation/withdrawal of active treatment were assessed in study 190-246 during the 2-week single-blind placebo follow-up (wash-out) period by the evaluation of new adverse events after discontinuation of treatment. Changes in sleep parameters (SL, TST, WASO, and NAASO by actigraphy monitoring) were assessed in

a planned subset of approximately 261 subjects at a subset of clinical sites in Study 190-246 following discontinuation of double-blind therapy (Ref: Study 190-246 CSR Sections 9.1 and 12.5.6).

*New Adverse Events after Discontinuation of Treatment Study **190-246***

A total of 10.3%, 8.2%, and 6.5% of subjects in the high-dose eszopiclone, low-dose eszopiclone, and placebo groups, respectively, reported new TEAEs. The most commonly reported new TEAEs were *headache* (3.2%, 0%, and 0% of subjects in the respective groups) and *upper respiratory tract infection* (1.6%, 0.8%, and 0% subjects in the respective groups; Ref: Sponsor's Table 15- Table of New Treatment-Emergent Adverse Events during the Single-Blind Follow-up Period of Study 190-246-Reported by > 1% of Subjects in Any Treatment Group [Single-Blind Follow-up Population], Section 5.7.1, Summary of Clinical Safety, p. 60/71). There were no reports of insomnia during the 2-week single-blind follow-up period.

Changes in actigraphy sleep parameters following discontinuation of double-blind treatment were additionally measured. According to the Sponsor, none of the actigraphy monitoring parameters had a statistically significant difference between the eszopiclone treatment groups and placebo for discontinuation/withdrawal effects (Ref: Study 190-246 CSR Table 14.3.5.14.1).

*Rebound Effects*
Rebound was defined as the worsening of a subject's sleep pattern after withdrawing from sleep medication compared to baseline. The occurrence of rebound insomnia following abrupt discontinuation was assessed in study 190-246 for the following sleep parameters as measured by actigraphy monitoring: SL, TST, WASO and NAASO. Only the subset of actigraphy subjects who entered the single-blind follow-up period were used for the rebound effects analyses.

For each sleep parameter, the change from baseline to each assessed single-blind follow-up treatment night (up to 14 nights following the end of the double-blind period) was analyzed within each treatment group using a Wilcoxon signed-rank test. According to the Sponsor, the unadjusted *P*-values did not reveal any significant differences between the treatment groups, and there were no consistent patterns between the dose groups and placebo in treatment differences of SL, TST, WASO, and NAASO as measured by actigraphy during the single-blind follow-up period (Ref: Study 190-246 CSR Section 12.5.5). When rebound insomnia was defined as a 20% worsening over the 14 single-blind placebo nights relative to the baseline value, the Sponsor reported that there were incidences of rebound insomnia as measured by actigraphy. However, according to the Sponsor, there was no consistent pattern in comparison between the low- and high-dose groups and placebo, and the actigraphy monitoring parameter unadjusted *P*-values did not reveal any significant differences

between the treatment groups for rebound insomnia (Study 190-246 CSR Section 12.5.5).

***Next-day Performance Effects***
Next-day performance effects were evaluated at each visit during Study 190-246 and at periodic visits during Study 190-247.

For studies 190-246 and 190-247, *objective assessments* that were included in the assessment of next-day performance effects were: Conners' Continuous Performance Test II; and Coding Copy Subtest/Digit Symbol Substitution Test.

For study 190-246, each objective assessment parameter was evaluated for next-day performance effects by comparing eszopiclone groups to placebo for the mean changes from baseline by examining the results for trends across the double-blind visits (Weeks 2, 6, 10, and 12 prePSG), including a comparison of the end of the double-blind period (Week 12 prePSG) to the end of the single-blind placebo period (Week 14). According to the Sponsor, there were no trends across visits for any consistent worsening in eszopiclone dose groups compared with placebo for either objective assessment (Ref: Study 190-246 CSR Tables 14.2.2.16 and 14.2.2.17).

For Study 190-247, each objective assessment parameter was evaluated for next-day performance effects by examining the overall eszopiclone mean changes from baseline for trends across the visits (Months 1, 3, 6, 9, and 12). According to the Sponsor, there were no trends across visits for any consistent worsening for either objective assessment (Study 190-247 CSR Tables 14.2.6 and 14.2.7).

For studies 190-246 and 190-247, *subjective* assessments that were included in the assessment of next-day performance effects were: Parent-/subject-completed sleep questionnaire (daytime alertness, ability to concentrate, physical well-being, ability to function); Pediatric Daytime Sleepiness Scale; Child Behavior Checklist and Pediatric Quality-of-Life Scale (SF-10). According to the Sponsor, there were no trends across visits for any consistent worsening in eszopiclone dose groups for any subjective assessment in both studies or in study 190-246 when compared with placebo.

### 7.7 Additional Submissions / Safety Issues

# 8 Postmarket Experience

The spontaneously-reported US postmarketing experience of pediatric patients (< 18 years of age) with Lunesta (eszopiclone) from *05 April 2005 through 04 January 2012* was presented in the submission. In this period, the US exposure of Lunesta was approximately (b) (4) person years. Over the past 2 years, pediatric patients (< 18 years of age) comprised 0.34% of the total US exposure.

75 individual post marketing events (6 serious events and 69 nonserious events) were spontaneously reported in pediatric patients (< 18 years of age) during this period. The most frequently reported AEs, by descending frequency, were dysgeusia (9 non serious [9/75=12%]), hallucination (7 non serious [7/75=9.3%]), insomnia (6 non serious [6/75=8.0%]), initial insomnia (3 non serious [3/75=4.0%]), somnolence (3 non serious [3/75=4.0%]), drug ineffective (3 non serious [3/75=4.0%]), and vomiting (3 non serious [3/75=4.0%]) reported with an event frequency ranging from 4.0% to 12.0%. The serious adverse event frequency was 8.0% (6/75) of reported events, and included 2 (2.7%) reports of suicide attempt and 2 (2.7%) reports of convulsion. The 6 serious adverse events (MedDRA 14.1 preferred terms) that occurred in 5 subjects were (Ref. Sponsor's Table 17 Summary of Clinical Safety, p 66/71) *Convulsion* (Female, Age 17, daily dose unknown) *Intentional overdose* and *Suicidal attempt* (Female, Age 17, daily dose 18 mg & 24 mg respectively), *Convulsion* (Female, Age 16, daily dose 3 mg), *Suicide Attempt* (Female, Age 15, daily dose unknown) and *Multiple drug overdose* (Male, Age 4, dose unknown).

*Reviewer Comments*

The case of the post marketing serious adverse event of multiple drug overdose is described under section 7.6.4 of the review.

# 9 Appendices

### Appendix Table 1 PK/PD Studies

| Pediatric PK/PD Studies* | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study Number** | **Type of Study** | **Objective(s) of the Study** | **Study Design and Type of Control** | **Test Product(s); Dosage Regimen; Route of Administration** | **Number of Subjects** | **Healthy Subjects or Diagnosis of Patients** | **Duration of Treatment** |
| 190-201 | Phase 1 Pediatric PK/PD Tolerability and Safety | Safety, tolerability, and PK/PD profile of single doses of ESZ in adolescents with ADHD- associated insomnia | Multicenter; open-label; single-dose in-clinic dose escalation study | ESZ; 1, 2, or 3 mg tablet once daily for 1 day; oral administration | 36 M/F enrolled (36 completed) | 12 to 17 year old (inclusive) male and female adolescent subjects with a prior diagnosis of ADHD and insomnia | Single Dose |
| 190-202 | Phase 1 Pediatric PK/PD Tolerability and Safety | Safety, tolerability, and PK/PD profile of single doses of ESZ in children with ADHD-associated insomnia | Multicenter; open-label; single-dose; in-clinic dose escalation study | ESZ; 0.6, 1, 2, or 3 mg tablet once daily for 1 day; oral administration | 49 M/F enrolled (48 completed) | 6 to 11 year old (inclusive) male and female children with a prior diagnosis of ADHD and insomnia | Single Dose |

*Reference: Submission Section 2.5-Clinical Overview, Table 1; Modified for format only
*Abbreviations: ADHD = Attention-deficit hyperactivity disorder; ESZ = Eszopiclone; F = Female; M = Male; PD = Pharmacodynamic; PK = Pharmacokinetic; RND = Randomized

## Appendix Table 2 Phase 3 Studies

| Pediatric Phase 3 Studies* | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Study Number** | **Type of Study** | **Objective(s) of the Study** | **Study Design and Type of Control** | **Test Product(s); Dosage Regimen; Route of Administration** | **Number of Subjects** | **Healthy Subjects or Diagnosis of Patients** | **Duration of Treatment** |
| **190-246 Pivotal** | Phase 3 Pediatric Efficacy and Safety | Evaluation of hypnotic efficacy, next day residual effects and safety of ESZ in children and adolescents with ADHD-associated insomnia. | Multicenter randomized, double-blind, placebo controlled | ESZ; 1 or 2 mg once daily at bedtime for 6 to 11 year old children and 2 or 3 mg once daily at bedtime for 12 to 17 year old adolescents; oral administration | 486 M/F RND (366 completed) | 6 to 11 and 12 to 17 year old (inclusive) male and female children and adolescent subjects with ADHD-associated insomnia | 12 weeks |
| 190-247 | Phase 3 Pediatric Long-term Safety | Long-term safety of ESZ in children and adolescents with ADHD-associated insomnia | Multicenter; long-term open-label extension | ESZ; 2 mg once daily at bedtime for 6 to 11 year old children and 3 mg once daily at bedtime for 12 to 17 year old adolescents; oral administration | 304 M/F enrolled (121 completed) | 6 to 11 and 12 to 17 year old (inclusive) male and female children and adolescent subjects with ADHD-associated insomnia | 1 year |

*Reference: Submission Section 2.5-Clinical Overview, Table 1; Modified for format only
Abbreviations: ADHD = Attention-deficit hyperactivity disorder; ESZ = Eszopiclone; F = Female; M = Male; PD = Pharmacodynamic; PK = Pharmacokinetic; RND = Randomized

## 9.1 Literature Review/References

Not applicable.

## 9.2 Labeling Recommendations

*Reviewer Comments*

The labeling recommendations shown below were discussed with the Agency PeRC committee on Sep 5, 2012.

The inclusion of the following language in the label is recommended:

Highlights- Use in Specific Populations:

Pediatric use: Safety and effectiveness not established. Dizziness, Dysgeusia, Hallucinations and other psychiatric and or nervous system reactions including suicidal ideation and behavior were reported in studies of pediatric patients with Attention-Deficit/Hyperactivity associated insomnia.

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 Attention-Deficit/Hyperactivity (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 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 on placebo (2%).

## 9.3 Advisory Committee Meeting

Not applicable.

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/s/

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RAMESH RAMAN
10/04/2012

RONALD H FARKAS
10/04/2012