

## 8. Safety

Dr. June Cai was the clinical reviewer. Dr. Cai recommends taking an approval action.

This NDA is based on demonstrating bioequivalence to Ambien. The demonstration of safety is therefore primarily by reference to the approved Ambien NDA 019908. The application contains safety data from the four clinical pharmacology studies and published literature.

**Exposures:** These four PK studies enrolled a total of 96 unique healthy volunteers (females = 45; 46.8%). Of these, 72 subjects were aged 18-45 years who were exposed to single doses ranging from 2.5 mg to 10 mg of Zolpimist, and 24 subjects (male and female) were aged  $\geq 65$  years who were exposed to a single dose of 5 mg of Zolpimist.

**Serious Adverse events:** There were no deaths in any study. Only one non-fatal serious adverse event (torsion testis) was reported. Of the seven subjects who withdrew from any of these four studies, three were due to adverse events: two due to vomiting after Ambien 10 mg exposure, and one due to vomiting after Zolpimist 10 mg exposure.

**Common Adverse Events:** The four PK studies compared Zolpimist with Ambien but none of these studies had placebo control. Therefore, the incidence rates were compared between Zolpimist and Ambien. Dr. Cai writes in her review that even though comparison of the adverse events following Zolpimist exposure in these four PK studies with those listed in the Ambien label is limited due to different coding dictionaries used, no new treatment-related adverse events were reported with Zolpimist. There was an apparent relationship between dose and adverse event incidence for both Zolpimist and Ambien.

**Oral soft exams:** In studies 002, 003 and 004, subjects underwent an oral soft tissue exam at screening and at the final visit, and at visits when zolpidem LS was administered – within 30 minutes before dosing and at 2 hours (Studies 002, 003 and 004) and 12 hours (Study 004) after dosing. There was one subject who reported pharyngolaryngeal pain after Zolpimist administration in Study 004. No objective signs of oral irritation were reported in any of the studies.

**Next-day Residual Effects Evaluation:** Dr. Cai notes in her review that during the pre-IND meeting on 8/31/05, the Division told the sponsor that the Agency expects an evaluation of residual drug effects the next morning, and an assessment of combination of sleep drugs. However, these comments were made in the context of middle-of-the-night (MOTN) awakenings indication which the sponsor was interested at that time but is not seeking in this NDA.

**Drowsiness/Sedation seen in Pharmacodynamic evaluation of PK studies:** As noted in my review in clinical pharmacology section 5 of this review, there was a consistent significant effect on drowsiness and less attention with Zolpimist compared to Ambien at 13-15 minutes post dosing but not at later time points. This is also consistent with PK data showing the time to the first detectable concentration and  $\geq 20$  ng/mL was significantly shorter for Zolpimist as compared to Ambien. This transient effect on drowsiness of Zolpimist at 13-15 minutes post

dosing but not at later time points can raise safety concerns if the subject is active and engaged in activities such as driving. However, this risk is mitigated by the instructions in the MedGuide to the patients: Take Zolpimist right before you get in bed, not sooner.

**Literature review:** The sponsor submitted a summary of published literature covering the period from 1/1/06 to 2/29/08, with the following search terms: zolpidem, drug interactions, safety, adverse events, side effects, serious adverse events, sleep driving, anterograde amnesia, nocturnal eating, pseudohallucinations, somnambulism, fatalities, deaths, suicidality, and suicidal ideation. Dr. Cai's review notes one case report of QT-prolongation and Torsades de Pointes reported in a 67 year-old woman who has history of congestive heart failure and prosthetic mitral valve while on zolpidem 10mg and other cardiovascular medications such as captopril, furosemide, warfarin, and amiodarone. The QTc interval was back to initial value once zolpidem discontinued. Dr. Cai opinions that there may be a possible association but is confounded by the patient's significant cardiovascular medical history.

I reviewed this case report which was published in 2006 (*Cardiology*). In this report, a 67 year old female began to experience palpitations after she began using zolpidem. Three weeks later, she was hospitalized and given amiodarone IV for ventricular arrhythmia, but on the fourth day developed Torsades de Points. Zolpidem and amiodarone were immediately discontinued, and she recovered (QT interval returned to baseline). The authors of this report conclude that although amiodarone appeared the most plausible explanation given the common metabolic pathway (CYP3A4) potentiating drug-drug interaction between these two agents, since palpitations were present even before amiodarone was given, there may be a possible hitherto unknown electrophysiological effects due to zolpidem. In the same issue of this journal, an invited editorial comment makes the opposing argument that zolpidem is more likely the offending agent, possibly by an inhibitory effect on potassium channels potentiated by the higher than usually achieved concentration due to the co-administration of amiodarone.

This one case with apparent confounders does not preclude the approval of this application. However, given the potential for adversely affecting the safety profile of zolpidem, this case report does need to be further investigated. I discussed this report with Dr. Alice Hughes, the Division's safety director. As a first step, the Office of Surveillance and Epidemiology has been consulted to search the AERS database and the published medical literature to see if there are other similar reports.

**CSS Review and Abuse potential:** Dr. Sylvia Calderon was the CSS reviewer. CSS agreed with the sponsor that Zolpimist retain Schedule IV of the Controlled Substances Act.

The agency discussed with the sponsor (Telecon on 8/6/08) regarding the abuse and misuse potential of Zolpimist via other routes of administration. Dr. Sylvia Caldron notes the following two broad concerns in her review:

- Zolpimist oral spray shows a 42 minutes earlier Tmax than Ambien immediate release tablets (reference drug) when comparing values reported in the respective labels. Taking into consideration that CNS active drugs with earlier Tmax and onset of action are associated with greater subjective effects such as liking and greater psychomotor impairment, the Zolpimist formulation might be associated with a higher potential for abuse than the Ambien immediate release tablets. Therefore, CSS recommends the Sponsor design a study to evaluate the abuse potential of Zolpimist.

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- CSS requests the Sponsor propose strategies to minimize the predicted increase of the oral abuse of Zolpimist, considering that 1) the number of nonmedical zolpidem related ED mentions in DAWN increased 35 percent from 2004 to 2006; 2) the medical literature indicates that the majority of the cases of zolpidem abuse are associated with the oral route of administration, and 3) Zolpimist provides a more convenient and appealing formulation for oral abuse (because it offers the first oral concentrated (50 mg/mL), sweet and flavored solution of zolpidem tartrate available on the market).

The first comment is based on comparing the T<sub>max</sub> in the Zolpimist NDA with T<sub>max</sub> of Ambien in the current label. However, these two can not be compared as they were done in different studies and so variability is expected. Since the PK studies in NDA are bioequivalent, and there is no statistically significant difference between the T<sub>max</sub> of Zolpimist and Ambien, Dr. Caldron, now agrees that there is no clear basis for this argument.

While I share the concern expressed in the second comment, it is largely theoretical. Without knowing that it in fact is true and understanding the factors associated with such a predicted increase, it would be difficult to propose strategies. Via submission to the NDA on 8/29/08, the sponsor argues that although their research has shown that zolpidem tartrate is a drug where abuse is centered on overuse and dependence but not euphoria, the sponsor acknowledged the Division's concerns, and commits to an intensified post-approval monitoring plan whereby any report of abuse and/or overdose with Zolpimist will be submitted as an expedited adverse event report. This would allow the sponsor to detect and address any signals of potential increased abuse promptly as well as inform the Division of such signals in an expedited manner. After reviewing the proposed post-approval monitoring plan, Dr. Calderon finds this plan acceptable (Memorandum dated 11/25/08). I agree with Dr. Calderon, that the approval letter will need to formally make the sponsor's post-approval monitoring plan as a post-marketing commitment. Regarding the language for the post-marketing commitment, Ms. C. Karwoski (Office of Surveillance and Epidemiology) defers to the Division and CSS (email 12/3/08).

## 9. Advisory Committee Meeting

No Advisory committee meeting was held.

## 10. Pediatrics

PREA requires all applications (or supplements to an application) submitted under section 505 of the Act (21 U.S.C. 355) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (section 505b(a) of the Act). Although Zolpimist is a new dosage form and a new route of administration, this NDA is based on demonstrating bioequivalence to Ambien (the reference drug), and not on any new efficacy data. The proposed label is based on the approved reference listed drug, Ambien. A pediatric study has

already been conducted and described in the Ambien label. This study showed no efficacy in pediatric subjects, and there were more treatment-emergent adverse events such as dizziness, headache and hallucinations in the zolpidem group compared to placebo. Since the above pediatric study has already been conducted for the reference drug, Ambien, the Division, via the Filing Communication dated 1/30/08, granted the sponsor's request for a waiver of pediatric studies for this application for pediatric patients from birth up to 16 years. The Pediatric Review Committee has concurred, and granted waiver in from birth up to 16 years.

## 11. Other Relevant Regulatory Issues

The Division of Scientific Investigation (DSI) conducted inspections of the \_\_\_\_\_ (clinical) and \_\_\_\_\_ (analytical). The clinical audit was based on 100% audit of source data for dosing, blood sampling and handling, concomitant medication, and drug accountability. Following these inspections, DSI issued Form 483. On 9/12/08, the Division of Neurology Products (DNP) received from DSI an evaluation of Form 483 items. Further, on 10/20/08, DSI sent to DNP a completed summary evaluation of \_\_\_\_\_ response to Form 483.

b(4)

DSI identified multiple deficiencies in the conduct of both the pivotal bioequivalence studies that can broadly be divided into two categories – those deficiencies that question the reliability of data generated at specific time points, and those relatively minor deficiencies that taken together call into question the conduct and integrity of the studies:

- **Reliability of data generated at specific time points:** DSI identified several instances of treatment administration documentation that were retrospectively corrected. \_\_\_\_\_ justified these corrections “to reflect information in dispensing logs and drug kits”. DSI found this argument unacceptable as the information in the logs and kits represents *intent* prior to dosing, and the treatment documentation should reflect the *actual* dosing. There were several occurrences of discrepancies between the times of PK sample collection and handling. DSI did not accept \_\_\_\_\_ response that these were transcription errors, as these were the source recordings of sample handling times, not transcribed data. Dosing dates for some subjects differed from source documents and CRF lists (3.B.4). For several subjects, the documentation of the time samples went into freezer appeared to be earlier than the sample was collected, or did not account for the time needed to centrifuge the sample before storage (3.B.5-8). \_\_\_\_\_ did not adequately explain how these discrepancies in time documentation occurred considering that the clocks in the clinic were synchronized.

b(4)

**Reviewer's comments:** Dr. Parepally re-analyzed Study 003 for bioequivalence after excluding the data generated from these specific time points, and finds that Zolpimist 5 mg and 10 mg lingual spray were bioequivalent to the reference Ambien tablets. Since only one subject (#24) had had dosing and sample processing records discrepancy, Dr. Parepally did not perform reanalysis of Study 004. Please see Section 5 of this review for additional details.

b(4)

- DSI also identified the following areas of deficiencies:

- In addition to randomization of subjects, study drugs have to be chosen by the clinical site from drugs provided by the sponsor. The latter did not occur as the study drug kits were preselected with pre-assigned subject numbers assigned by the sponsor. Further, \_\_\_\_\_ failed to retain sufficient reserve sample. Although \_\_\_\_\_ retained remaining unused kits, DSI did not consider them as reserves since the sponsor preselected and pre-numbered the study drug. b(4)
- \_\_\_\_\_ response did not sufficiently establish that the protocol's water restriction was followed. There was no documentation with regard to priming of sublingual spray.
- The source documents provided contradictory information for concomitant drug use; \_\_\_\_\_ failed to adequately address these conflicts. b(4)
- There were discrepancies between the clinic's shipment forms and the samples actually received by the analytical site. \_\_\_\_\_ response partially addressed the discrepancies but did not resolve the inaccuracy for PK time points.
- \_\_\_\_\_ concurred with DSI that IRB approval was not obtained for including additional criteria for subject selection and for collecting blood using direct venipuncture instead of indwelling catheters.

**Reviewer's comments:** None of the above items of deficiency itself calls into question the reliability of the *entire* data generated in the two pivotal bioequivalence studies. Please see additional comments below.

- **DSI conclusions:** The DSI report concludes that multiple issues concerning incomplete or contradictory documentation with respect to dosing, PK sample handling and drug accountability, fail to assure the reliability of source data generated in the pivotal bioequivalence studies (Studies 003 and 004).

**Reviewer's conclusions:** The DSI inspection uncovered deficiencies in multiple areas of the conduct of the two pivotal bioequivalence studies. There is no one single item of deficiency which by itself calls into question the reliability of the *entire* data generated in the two pivotal bioequivalence studies. If the above deficiencies were detected in an audit of only a portion of the bioequivalence studies, then clearly the majority of these deficiencies taken together would question the reliability of the data from the *unaudited* portion of the studies. That is not the situation here as a 100% audit of these two studies was done. The 100% audit of these two studies did, however, uncover specific instances of documentation discrepancies with regard dosing and PK sample handling that clearly question the data generated at those specific time points. As discussed above, when the data from these specific time points were excluded, bioequivalence of Zolpimist 5 mg and 10 mg lingual spray to the reference Ambien tablets is maintained.

## 12. Labeling

The main labeling recommendations are outlined:

- **Clinical recommendations:**
  - **Contraindications of the label should include the following statement:** "Known hypersensitivity to Zolpimist tartrate" as severe hypersensitivity to the drug has been demonstrated [21CFR§201.57(a)(5)] which is described in section 5.2 of the label.

b(4)

- **Clinical Pharmacology:** Changes recommended reflecting the bioequivalence data.
- **Pharmacology-toxicology recommendations**
  - Description of \_\_\_\_\_ should not be allowed in the label.
  - The pregnancy recommendations in section 8 rewritten to more accurately reflect the animal data.
- **Office of Surveillance and Epidemiology / Division of Medication Error Prevention and Analysis (DMEPA),** after a review of the proprietary name, does not object to the use of the proprietary name, Zolpimist.
- **Office of Surveillance and Epidemiology / Division of Risk Management (DRISK)** reviewed the Medication Guide and Patient Instructions for Use (PIFU). After review, DRISK concluded that the Zolpimist Medication Guide was consistent with the approved Ambien Medication Guide, and provided several recommendations that were incorporated into the Medication Guide.

b(4)

### **13. Recommendations/Risk Benefit Assessment**

- **Recommended Regulatory Action**

I recommend Approval for NDA 22196.

- **Risk Benefit Assessment**

Zolpimist 5 mg and 10 mg lingual spray are bioequivalent to the reference Ambien tablets. The sponsor is not seeking any new efficacy claims. There are no new or major safety issues that preclude the approval of this application. There have been several safety concerns with the innovator drug, Ambien, and other drugs in the same class, which have already been minimized or mitigated by strengthening the relevant sections of the label, and the requirement of Medication Guide. Zolpimist label is based on the Ambien label, and therefore, has Medication Guide. In

addition, because Zolpimist is delivered as an oral spray, the label will have Patient Instructions for use to enable safe use of the product. Concerns regarding the lack of child-resistant packaging have now been addressed as discussed under the CMC section of this review. There is a theoretical possibility of a predicted increase of the oral abuse of Zolpimist (discussed in the Safety section 8 of this review memo). Via submission to the NDA on 8/29/08, the sponsor commits to an intensified post-approval monitoring plan whereby any report of abuse and/or overdose with Zolpimist will be submitted as an expedited adverse event report. CSS finds this plan to be acceptable. The Division will formally make this as a post-marketing commitment.

Thus, as discussed above, the benefits of Zolpimist outweigh the risks which are reasonably minimized or mitigated as discussed above.

- **Recommendation for Postmarketing Risk Management Activities**

Medication Guide has been required for the innovator drug, Ambien. Zolpimist label is based on the current approved Ambien label, and will therefore have a Medication Guide.

- **Recommendation for other Postmarketing Study Commitments**

**Required Post marketing Studies:**

None required.

**Post marketing Commitment:**

A post-marketing monitoring plan that will include maintenance of all adverse events in a centralized safety database with expedited reporting of "Events of Interest" as defined in your submission of August 29, 2008 (appended to this letter as Appendix 2). The Individual Case Safety Reports of these events will be submitted as expedited reports, whether or not they meet the regulatory requirements for 15-Day Alert reports. The sponsor will include a discussion in the quarterly periodic report based upon the Standardized MedDRA Query: "Drug Abuse, Dependence and Withdrawal". The sponsor will review data from the Drug Abuse Warning Network and the Toxic Exposure Surveillance System report prepared by the National Poison Data System, and enters these events into the safety database for individual case reporting and aggregate analysis. If a signal suggestive of increase in the abuse potential of Zolpimist is detected, the sponsor commits to taking corrective actions to minimize the abuse.

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Devanand Jillapalli  
12/19/2008 10:16:15 AM  
MEDICAL OFFICER

Russell Katz  
12/19/2008 02:23:27 PM  
MEDICAL OFFICER

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