

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-997

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	March 4, 2009
From	Ronald Farkas, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	21-997
Supplement#	
Applicant	Orexo Pharma Inc.
Date of Submission	05/14/2008
PDUFA Goal Date	March 14, 2009
Proprietary Name / Established (USAN) names	Edluar / zolpidem tartrate
Dosage forms / Strength	Sublingual tablet / 5mg and 10 mg
Proposed Indication(s)	1. Insomnia 2. 3.
Recommended:	Approval

1. Introduction

Zolpidem tartarate sublingual tablets is being developed under section 505(b)(2) by Orexo AB for the treatment of insomnia in adults characterized by difficulties with sleep initiation. To support the application, the sponsor is referencing safety and efficacy information FDA relied on for approval of Ambien® (NDA 19-908), as well as information in the public domain.

The sublingual dosage form is intended to be more convenient for patients than the tablet form.

2. Background

Zolpidem tartrate is a non-benzodiazepine sedative-hypnotic approved in the U.S. as Ambien® tablets in 1992 for the treatment of short term insomnia characterized by difficulties with sleep initiation.

To support the safety and efficacy of this dosage form of zolpidem, the sponsor conducted studies to establish the following:

- Bioequivalence to the Reference Listed Drug (RLD), Ambien® tablets,
- Pharmacodynamic comparability to the RLD
- Local tolerability (sublingual mucosa)

Importantly, the sponsor used 3 different formulations of the sublingual tablet for clinical studies as their development program progressed: 'formulation I' and 'formulation II' were ultimately replaced by a third 'final commercial product.' Pharmacokinetic bridging studies

were used to establish the bioequivalence of final commercial product to RLD Ambien through intermediate comparison of each to formulation II (see *Section 5, Clinical Pharmacology*). An additional 60-day safety study was also conducted with the final commercial product to investigate local tolerability of the oral mucosa.

In contrast, no pharmacodynamic studies were conducted with the final commercial product. Instead, study 002 compared formulation I to a non-U.S. approved formulation of Ambien tablets, and study 006 compared formulation II to RLD Ambien tablets.

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CDTL: Regulatory approval of this NDA is based on bioequivalence to RLD Ambien. The efficacy/pharmacodynamic studies, while supportive, provide only indirect evidence of bioequivalence, particularly since they were not conducted with the final commercial formulation.

3. CMC

Drs. Thomas Wong and Ramesh Sood reviewed the CMC portion of the submission, and recommend approval.

Dr. Wong states that excipients in the formulation are common, compendial grades, and are widely used in the pharmaceutical industry. The applicant refers to DMF — for detailed information on the drug substance. This DMS was reviewed in February 2008 and was found to be adequate. Establishment evaluations were performed and found to be acceptable.

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4. Nonclinical Pharmacology/Toxicology

Pharmacology/toxicology review is pending.

5. Clinical Pharmacology/Biopharmaceutics

Drs. Jagan Parepally and Veneeta Tandon reviewed clinical pharmacology. They recommend approval.

Three different formulations were used during clinical development, including formulation I, formulation II and final commercial formulation. Formulation II was used in the BE study and a second bridging study was conducted between formulation II and final commercial product. Formulation I was used only in pilot BE studies.

CDTL note: Clinical safety and efficacy studies were conducted with formulation II and the final commercial formulation

Two single dose pharmacokinetic (PK)/bioequivalence (BE) bridging studies were designed to show bioequivalence of the sublingual tablets to Ambien, the RLD.

- Study OX22-005 compared 10 mg 'formulation II' of the sublingual tablets to 10 mg Ambien tablets. Formulation II was found problematic to manufacture, leading the sponsor to change excipients in the final commercial product, and necessitating a PK/BE bridging study between formulation II and the final commercial product
- Study OX22-008 compared 10 mg formulation II to the final commercial formulation.

Dr. Parepally finds that formulation II is bioequivalent to Ambien, and that formulation II is bioequivalent to the commercial formulation, establishing a bioequivalence link between the final commercial formulation and Ambien.

Detailed BE findings

Study OX22-005: $AUC_{0-\infty}$ was about 8% higher for formulation II versus Ambien, and C_{max} was about 5% higher. 90% confidence intervals were acceptable for a conclusion of bioequivalence (90% confidence interval between 80% and 125%). T_{max} was earlier for formulation II, 82 minutes versus 90 minutes for Ambien.

Study OX22-008: $AUC_{0-\infty}$ was about 12% higher for the final commercial formulation versus formulation II, and C_{max} was about 8% higher. 90% confidence intervals were acceptable for a conclusion of bioequivalence. T_{max} for both formulations was 120 minutes

Dose proportionality

Study OX22-001 showed that an earlier formulation of sublingual zolpidem, formulation I, was dose-proportional for 5 mg and 10 mg tablets.

Food Effect

A food effect study, OX22-005, was also conducted, finding a lower bioavailability for sublingual zolpidem with a meal compared to under fasting conditions: AUC and C_{max} were decreased by 20% and 30% respectively, and T_{max} was prolonged by 28%, from 82 to 105 minutes. For Ambien, previous studies show food had similar effects on AUC and C_{max} , with decreases of 15% and 25% respectively. T_{max} for Ambien was delayed more by food, by 60%, from 84 to 132 minutes.

Dr. Parepally concludes from this that the sublingual tablets should not be administered with or immediately after a meal.

Absorption time

- T_{first} : Mean time to reach first detectable plasma concentration of zolpidem was 11 minutes for formulation II and 22 minutes for Ambien.
- $AUC_{0-30min}$: At 30 minutes, exposure to drug from formulation II was 40% higher than from Ambien, 766 min.ng/mL versus 545 min.ng/mL. At 60 minutes, exposure was 22% higher for formulation II.

CDTL Discussion:

I agree with Drs. Parepally and Tandon that the PK/BE bridging studies showed in stepwise fashion that formulation II was bioequivalent to the RLD Ambien, and that the final commercial product was bioequivalent to formulation II by the usual criteria based on AUC and Cmax. Measures of absorption time are also considered in bioequivalence determinations if rapid onset of drug effect is necessary for efficacy. The studies suggested some aspects of more rapid absorption of the sublingual tablet compared to the RLD Ambien. The findings thus raise no concern that the sublingual formulation would be less efficacious than the RLD.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

Since this application was based on bioequivalence of the sublingual formulation to RLD Ambien, no statistical analysis of the PD studies below was conducted.

Study 002 was a an open-label, randomized, single-center, 3-period crossover study in 21 healthy volunteers that compared the efficacy and safety of formulation I (5 mg and 10 mg) to Stilnoct® 10 mg, a zolpidem formulation not approved in the U.S. The primary efficacy variable was latency to persistent sleep (LPS) in a post-nap insomnia model. LPS was shorter for formulation I, 10 mg, compared to Stilnoct® 10 mg ($p = 0.03$).

Study 006 was a multi-center, randomized, active-control, double-blind, double-dummy, 2-period crossover study of single doses of formulation II vs. Ambien, conducted in 73 patients with primary insomnia (age 18-65 years). The sponsor intended study OX22-006 to be a superiority study for the sublingual formulation versus Ambien. Study endpoints included sleep initiation (primary endpoint), maintenance, sleep architecture, patient subjective assessments, and next day residual effects. LPS was 20 minutes for formulation II, 10 mg, versus 30 minutes for Ambien 10 mg ($p = 0.001$), compared with baseline of 85 minutes. WASO was essentially the same for both dosage forms.

CDTL: No efficacy studies were conducted with the final commercial product. The PD studies provide supportive evidence that sublingual zolpidem is efficacious, but could not be used to support any future claim that the final commercial product

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8. Safety

201 subjects were exposed to any sublingual formulation (formulation I, formulation II, or final commercial product). Only 60 subjects were exposed to the final commercial product, in a 60-day single-arm study mainly concerned with evaluating local tolerability of the oral mucosa.

Deaths

No deaths occurred.

Serious Adverse Events

Three serious adverse events occurred that are unlikely related to study drug:

- **Ambien:** Spontaneous abortion occurred in a 45-year old woman. She was exposed to a single dose of Ambien in the crossover study (006) about 25 days after reported last menstrual period and negative urine pregnancy test, and withdrawn from the study 2 days later due to positive serum pregnancy test. About 40 days after last menstrual period she presented with metrorrhagia, and miscarriage was diagnosed. No ultrasound or visit to a gynecologist occurred.
- **Final Commercial Product:** Ruptured intervertebral disc occurred in a 57 year old man exposed to final commercial product. Symptoms began before enrollment, but resulted in hospitalization after enrollment.
- **Final Commercial Product:** Asthma exacerbation treated in the emergency room occurred in a 64 year old woman treated with final commercial product. She had a history of asthma. She was not discontinued from the study due to this event.

CDTL: The SAEs are unlikely related to study drug, and do not raise new safety concerns for the sublingual formulation.

Safety/Local tolerability Trial

Study OX22-007 examined local/sublingual tolerability of the final commercial product. The sublingual tablet (10 mg) was self-administered daily for 60 days in 60 subjects age 18-64 years diagnosed with chronic insomnia. A visual inspection of the sublingual mucosa was made 5 times during the study by the investigator. A pill count at each visit was used to estimate compliance. The patient was also contacted by phone between visits for a compliance check and a check of adverse events (AEs) 14 days after the final visit.

Results:

- 1 subject was observed to have mild sublingual erythema <2mm after 35 doses, that was resolved at the next study visit.
- 1 subject experience 'transient paresthesia of tongue' after 33 doses, which resolved in 2 days.

5 patients withdrew due to adverse events unrelated to local tolerability. These were the only dropouts related to adverse events in the development program. The events were similar to those reported in the Ambien label, and did not raise new safety concerns.

Events possibly related to drug include the following:

- Mild intermittent palpitations

- Hallucinations, somnolence, nausea, disequilibrium (patient concomitantly took Tylenol PM)
- Vertigo and disorientation

Efficacy and Safety Trials

- OX22-002: An open randomized three-period, single-dose per period crossover study in 18 healthy subjects to evaluate the hypnotic efficacy and safety of formulation I, 5 mg and 10 mg, compared to a formulation of oral zolpidem not approved in the U.S. (Stilnoct®) 10 mg in healthy volunteers

No adverse events occurred related to local tolerability of the oral mucosa. Adverse events were similar to those reported in the Ambien label.

- OX22-006: A double-blind, randomized, two-period, single-dose per period cross-over study to evaluate the hypnotic effects and safety of formulation II, 10 mg, compared to Ambien 10 mg, in 73 patients with insomnia.

No adverse events occurred related to local tolerability of the oral mucosa. Common adverse events were similar between formulation II and Ambien in the crossover study 006, with no new safety concerns raised. The only adverse event that occurred both at more than 2% with formulation II and that was more common than in Ambien was somnolence: 4% for formulation II and 3% for Ambien.

There were no meaningful differences between formulation II and Ambien for next day subjective assessments of residual effects:

- Bond and Lader Visual Analogue Scale (VAS) - alertness, contentedness and calmness
- Digit Symbol Substitution Test (DSST) - attention and concentration
- Leeds psychomotor tests (MCRT and CFFT)- attention abilities and vigilance

Bioequivalence studies

- OX22-001: 18 subjects exposed to 3 single doses of formulation I
- OX22-004: 12 subjects exposed to single doses of formulation I (10 mg) and formulation II (10 mg)
- OX22-005: 18 subjects exposed to 3 single-doses of formulation II (10 mg) or Ambien
- OX22-008: 19 subjects exposed to single doses of formulation I and final commercial formulation.

In the bioequivalence studies adverse events were similar to those reported in the Ambien label. No adverse events occurred related to local tolerability of the oral mucosa, although 1 subject complained of dry mouth associated with dosing of formulation II.

CDTL: The studies indicate that the sublingual formulation of zolpidem is acceptably safe. There was minimal indication of irritation of the oral mucosa.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

DNP recommended a full waiver for pediatric studies for sublingual zolpidem because evidence strongly suggests that product would be ineffective in all pediatric subpopulations. The PeRC PREA subcommittee reviewed the Orexo full waiver on February 11, 2009, and agreed with DNP to grant a full waiver for this product. PeRC recommended adding language to convey that sublingual zolpidem is "Not recommended for use in pediatrics because safety and effectiveness have not been established." The PeRC notes that this recommendation also reflects the opinion expressed by many advisory committee members at the November 2008 PAC review of Ambien that the language in the label was insufficient to discourage pediatric use.

11. Other Relevant Regulatory Issues

- Controlled Substance Staff review was by Drs. Alicja Lerner and Silvia Calderon.
 - CSS notes that the abuse potential of zolpidem, and concurs that OX22 should remain subject to the controls imposed by Schedule IV of the CSA.
 - CSS is concerned that amnestic effects and rapid dissolution in drinks such as soda and could lead to misuse of the product in criminal acts. CSS therefore recommends the sponsor should do the following:
 - Propose strategies to minimize potential abuse and misuse prior to approval
 - Maintain active surveillance to capture abuse and misuse of the product and report those cases to the Agency as expedited reports whether or not the case as a whole meets the regulatory requirements for a 15-Day Alert report.
 - Provide a list of MedDRA preferred terms that will capture all events of abuse and misuse of the formulation.
 - If, in fact, this new formulation is associated with higher levels of abuse and misuse, the Agency might have to consider the implementation of a Risk Evaluation and Mitigation Strategies (REMS) to maintain a positive benefit to risk ratio.

CDTL: I agree with the concerns of CSS above. As was recently done for Zolpimist, a spray form of zolpidem approved 12/19/2008, CSS agrees that these concerns can be addressed by commitment from the sponsor to do the following:

- **In the postmarketing period submit as Expedited Reports "Adverse Events of Interest" based upon MedDRA preferred terms relating to drug misuse.**
- **Include a discussion in the quarterly periodic report and annual report based upon the Standardized MedDRA Query: "Drug Abuse, Dependence and Withdrawal."**

- **Review data from the Drug Abuse Warning Network (DAWN) and the Toxic Exposure Surveillance System (TESS) report prepared by the National Poison Data System, and to commit to submitting analysis of this information in your quarterly periodic report and annual report.**
 - DSI audits:
 - Two sites were selected from study OX22-006, the PD study, and found to be without major deficiencies.
 - The sites of BE studies OX22-005 and OX22-008 were inspected, with the following deficiencies identified:
 - The requirement for reserve drug samples was not met, such that identity of dosage forms in both studies cannot be assured
 - For study 005, only concentration estimates from the high calibration curve are acceptable.
- CDTL: After reviewing the data with Dr. Parepally I conclude that data from the high calibration curve is adequate to support BE.**
- The sponsor needs to cross-validate assay performance in heparinized human plasma to assure accuracy of concentrations in studies 005 and 008.
- CDTL: The deficiencies in the BE studies do not preclude approval.**

12. Labeling

- Clinical Recommendations
 - Adequate evidence of PK or PD differences between the sublingual formulation and RLD Ambien was not presented to warrant new efficacy claims in labeling
 - New clinical safety data for the sublingual formulation does not raise new safety concerns. Other than data on local oral tolerability, safety data in the label of EDLUAR should reflect current RLD labeling.
- Office of Surveillance and Epidemiology / Division of Medication Error Prevention and Analysis (DMEPA), after a review of the proposed proprietary name, does not object to the use of the proprietary name Edluar.
- Clinical Pharmacology: Changes recommended reflecting the bioequivalence data.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action:
 - I recommend Approval for NDA 21997.
- Risk Benefit Assessment

Edluar 5 mg and 10 mg sublingual tablets are bioequivalent to the reference Ambien tablets. There are no new or major safety issues that preclude the approval of this application. The Edluar label is based on the Ambien label, including Medication Guide.

- Recommendation for Postmarketing Risk Management Activities

None

- Recommendation for other Postmarketing Study Commitments

None

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/s/

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