CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-997

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-997 SUPPL # HFD # 120

Trade Name Edluar

Generic Name zolpidem tartrate sublingual 5 and 10 mg tabs

Applicant Name Orexo AB

Approval Date, If Known 3/13/09

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505 b2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

In support of this application, the sponsor conducted a bioequivalence study, Study OX22-005, comparing Formulation II (10 mg zolpidem tartrate) with the reference Ambien® in healthy non-elderly adults. Formulation II was found to be bioequivalent to the RLD Ambien®. Time to reach maximum plasma concentration, tmax did not differ significantly from the reference Ambien®. However, Formulation II was not the to-be-marketed or commercial formulation, Therefore, a bridging BE study (Study OX22-008) between Formulation II and the commercial formulation was also conducted. Formulation II was bioequivalent to the commercial formulation, thereby establishing the link between the commercial formulation and the reference Ambien®.

Minor differences between Edluar™ and Ambien® in time to reach first detectable plasma concentration (tfirst) and first detectable plasma concentration (Cfirst) parameters were observed. Zolpidem is detected earlier when administered by the sublingual route vs. the oral route. Mean and standard deviation values for tfirst were 10.7 ± 5 min and 22.4 ± 15 min for Edluar and Ambien® respectively. However, median tfirst values were similar for Edluar and Ambien® [13.5 (range: 5-17) minutes for Edluar and median tfirst values were 15 (range: 5-60) minutes for Ambien®]. There was an overlap in the ranges. The Cfirst for Edluar and Ambien® were 8.4 and 11.8 ng/ml, respectively. The relevant concentrations/exposure necessary for the onset of sleep is not known for zolpidem, hence the significance of these findings cannot be determined.

In summary, Edluar sublingual tablet was bioequivalent to the reference Ambien tablets.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Not for this formulation, but yes for the reference drug via PWR - Ambien

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19908 Ambien 5 and 10 mg tabs

NDA# 21774 Ambien CR 6.25 mg and 12.5 mg controlled release

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☒

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

The sponsor conducted 2 clinical studies. Neither study was for required for clinical data other than safety thus were not essential for approval :

1. OX22-007 was a local/sublingual tolerability study: Single center open label

clinical trial evaluated the local tolerability and safety of EDLUAR 10 mg (FCP, OX22) daily, for 60 days given to 53 patients with chronic insomnia.

2. OX22-006: Multicenter, double-blind, randomized, two period (single night) crossover study was conducted in 73 primary chronic insomnia patients (18-65 years of age) to evaluate the hypnotic effect of single dose zolpidem tartrate sublingual tablet Formulation II (10 mg, OX22) compared to single dose 10 mg Ambien®.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does

not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean

providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form:
Cathy Michaloski (input from Jagan Parepally, PhD and Suhail Kasim, MD
Title: RPM
Date: 3.18.09

Name of Office/Division Director signing form: ODE 1 DNP Russell Katz, MD
Title: Division Director, DNP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Russell Katz
3/18/2009 02:50:36 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: NDA 21-997 (505b2) Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DNP PDUFA Goal Date: 3/14/09 Stamp Date: _____

Proprietary Name: pending

Established/Generic Name: zolpidem tartrate sll

Dosage Form: 5 and 10 mg sl

Applicant/Sponsor: Orexo AB, Sweden

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: insomnia

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☒ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit*	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

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Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

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Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☒ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

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Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the

PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Appears This Way
On Original

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Appears This Way
On Original

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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

/s/

Cathleen Michaloski
3/3/2009 04:45:51 PM

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Memorandum

Date: March 11, 2009 1 pm EST

To: NDA 21-997 Edluar (zolpidem tartrate) sublingual tabs 5 and 10 mg

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Meeting Sponsor: DJA Global Pharma., for Orexo, AB Sweden

Product: EDLUAR (zolpidem tartrate, sl)

From: Cathleen Michaloski, BSN, MPH

Telecon Minutes

FDA Attendees:

Russell Katz, MD Director, DNP

Suhail Kasim, MD Clinical Reviewer

Cathleen Michaloski, Regulatory Project Manager, DNP

Sponsor Attendees:

Damaris DeGraft-Johnson, MSc, President, DJA Global Pharma Inc., US Agent for sponsor, Orexo AB

Harriette Nadler, PhD, VP, Regulatory Affairs, DJA Global Pharma Inc.

Thomas Lundqvist, MSc., Exe. VP, Orexo AB

David Westberg, MSc., Snr. Project Leader, Orexo AB

Åsa Holmgren, MSc., VP, Regulatory Affairs, Orexo AB

Susanne Svensson MSc., Manager, Regulatory Affairs, Orexo AB

Maria Nehlin, Clinical Trial Manager, Orexo AB

T-con Summary:

This is a 505 b2 NDA for a new formulation of zolpidem tartrate, Ambien, the reference product. The formulation is sublingual tabs as opposed to oral tabs. The applicant is relying on the findings of safety and effectiveness from the Ambien approval.

A telecon was held to discuss applicant's proposal to add product specific (EDLUAR) information to the clinical section of the PI (appendix 1).

b(4)

The data in the application do not support inclusion into the label.

Orexo stated they would consider these remarks and get back to us.

Appendix 1

Current Feedback from Orexo AB re: FDA-recommended labeling for Edluar to serve as discussion points with the Agency

The Sponsor acknowledges receipt of the FDA's recommended labeling for Edluar received by email on March 9, 2009 at 6PM and intends to complete the line by line comparison as soon as practically possible. Orexo AB also appreciates the opportunity to speak directly with the Agency on March 11, 2009 and requests knowledge of the aspect(s) to be discussed so that appropriate Sponsor representatives are present.

In addition, the Sponsor proposes that the labeling provided does not reflect the unique product characteristics of Edluar as determined in clinical studies reported in NDA 21-997, particularly, OX22-006 and OX22-007.

b(4)

- Reference is made to Dr. Katz's recent recommendations for post-marketing pharmacovigilance based on faster sublingual absorption/earlier onset of action of Edluar as agreed by the Sponsor.

b(4)

The sublingual tolerability was included in the FDA-recommended labeling, but the earlier onset of action was not included.

- These points are supported by the results from two well-designed studies in insomnia patients, conducted to fully characterize the

profile of the sublingual formulation in terms of safety and efficacy (single dose, OX22-006 and multiple dose OX22-007).

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/s/

Cathleen Michaloski
3/12/2009 04:43:42 PM
CSO

Cathleen Michaloski
3/12/2009 04:44:16 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 26, 2009

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

TO: Russell G. Katz, M.D.
Director, Division of Neurology Products

SUBJECT: Review of EIRs Covering NDA 21-997, Sublinox™ 10mg (Zolpidem tartrate sublingual tablet), Sponsored by Orexo AB, Uppsala, Sweden

At the request of Division of Neurology Products (DNP), the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence studies:

Study 1: **OX22-005** "An open randomized, three-period cross-over study to evaluate the pharmacokinetic profile of sublingual zolpidem for treatment of short-term insomnia." (Pivotal Study)

Study 2: **OX22-008** "An open randomized, two-period cross-over study to assess the bioavailability of two different formulations of sublingual zolpidem for treatment of short-term insomnia." (Bridging Study)

The clinical portions of studies OX22-005 and OX22-008 were

respectively. The analytical portions of both studies were

b(4)

Following the inspection at — Department of Chemistry (1/12-15/09), Form FDA 483 was issued. At conclusion of the inspections at

(1/19-22/09) and (1/12-15/09), no Form 483 was issued. The evaluation of the significant findings at all the inspected sites and response dated February 2, 2009 (attached) to the Form 483 follows: b(4)

Analytical Site:

1. **Failure to include sufficient quality control (QC) concentrations (i.e. at least 3 QC concentrations) for each of the two calibration ranges , to assure that the two calibration ranges accurately measured subject concentrations in Study OX22-005. Similarly, the concurrent validation did not include sufficient QC concentrations.**

The firm used two calibration curves in each run to estimate low and high concentrations. However, in Study OX22-005, the firm did not use sufficient QC concentrations at each calibration curve: only one QC concentration at the low calibration range in 70% of the analytical runs, and two QC concentrations at the high calibration range in all runs. Although, the number of QC concentrations was not optimal, the assay did not reveal problems at the high calibration curve, as the firm used 3-5 replicates at each QC concentration and majority of the replicates were accurate (i.e. within 15% of the nominal) in each analytical run. In total, 96% of QC replicates were accurate. Contrary to response, there was not sufficient QC information to assure accuracy across the low calibration range. Therefore, it is DSI's opinion that only zolpidem concentrations estimated using the high calibration curve are acceptable for review in Study OX22-005. b(4)

Unlike Study OX22-005, in Study OX22-008, the firm included three to four QC concentrations at each of the two calibration ranges.

2. **Failure to validate long-term stability and room temperature stability.**

did not have long-term frozen and room temperature stability data. In their response, stated that the above stability comparisons were done for earlier clinical studies. validated long-term stability for 6 months at -20C and room temperature stability for 4 hours. The above stability data, in addition to freeze-thaw b(4)

data, covers the handling conditions of the subject samples for the above studies.

3. **Greater than 50% of QCs at 0.58 ng/mL were inaccurate in runs 20061115 (Study OX22-005), and 20070915, 20070917 & 20070925 (Study OX22-008). The firm's run acceptance criteria does not address run acceptance when all or greater than 50% of QCs at a given concentration are inaccurate.**

In Study OX22-008, the firm included four QC concentrations at 0.58 (LLOQ), 1.5, 10, and 31 ng/mL for the low calibration curve. Routinely, LLOQ QCs are not required and are not used during study sample analysis; instead QC concentrations are selected at 3 times the LLOQ, the mid assay range and high assay range that adequately reflect the expected study concentrations. In addition to the LLOQ QC, — had the recommended QC concentrations for the low calibration curve in Study OX22-008. While majority of the LLOQ QCs failed in runs 20070915, 20070917 and 20070925 (and other runs in Item 4 below) in Study OX22-008, the remaining QCs at 1.5, 10, and 31 ng/mL were accurate, indicating the runs were not sensitive at the LLOQ. Therefore, the LLOQ for the above runs should be revised to 1 ng/mL. This revision is not likely affect the accuracy of the above runs as the QCs at 1.5, 10, and 31 ng/mL were accurate, and is not likely to impact the data as measurable zolipdem concentrations in the above runs*, with the exception of a couple of study samples, were > 1 ng/mL. Nonetheless, — should revise their current run acceptance criteria to require at least 50% of replicates at each QC concentrations are accurate.

b(4)

4. **Inconsistency in acceptance of calibrators. For example, contrary to the firm's criteria, calibrator "S7" in runs 20070918, and calibrator "S10" in run 20070924 (Study OX22-008) were rejected for estimation of calibration response. Inclusion of the calibrators results in failure of all QCs at 0.58 ng/mL.**

b(4)

— routinely included all calibrators to estimate the calibration curve response. However, in runs 20070918 and 20070924 in Study OX22-008, — deleted calibrators, without justification, to estimate the low calibration curve response. — response that the deleted calibrators were outliers and were excluded to obtain best fit is not acceptable. Contrary to — response, calibrator "S7" in run 20070918 was accurate with no assignable cause for rejection. Also, although

* In run 20070915 in Study OX22-008, study samples with concentrations below 1.5 ng/mL were reanalyzed.

calibrator "S10" was inaccurate in run 20070924, inaccurate calibrators in other runs (e.g. 20070912 and 20070915) were not rejected. should accept calibrators based on accuracy of the calibrators and not based on obtaining best fit. Nonetheless, for reasons cited in Item 3, the LLOQ for runs 20070918 and 20070924 should be revised to 1 ng/mL, and this change is not likely to affect the acceptability of the runs and the resulting data.

5. **Data entries in laboratory notebooks were not always recorded at the time the events occurred. Also, documentation of type of anticoagulant in blank plasma used in the studies and validation were not available. Information obtained from the vendor during the inspection indicates that the anticoagulant in blank plasma (CPD) was different from that in subject plasma samples in Studies OX22-005 and OX22-008 (Sodium Heparin).**

did not cross validate the anticoagulants. In their response, stated that matrix effect experiments and the use of a deuterated internal standard suggest that it is unlikely that the type of anticoagulant will affect assay performance. Although explanation seems logical, needs to provide data to demonstrate assay performance is not altered in heparinized human plasma. stated that in future the same anticoagulant used in study samples will be used for QC preparation.

b(4)

6. **There is no written documentation identifying that the plasma samples were verified to be in a frozen state upon receipt at your facility.**

stated that their SOP required analysts to note any deviation during sample receipt. Since there were no deviations recorded, and since sample transit times between clinical and analytical sites were less than 2 hours, the above finding is not likely to affect sample integrity. Nonetheless, has revised their SOP to verify sample conditions upon receipt.

b(4)

7. **Temperature recording was infrequent in that the temperature of freezers used to store the subject samples are only being monitored weekly.**

Subject plasma samples were stored at -20°C for 37 and 19 days for Studies OX22-005 and OX22-008, respectively. Although the temperature was noted weekly, stated at no point was the temperature close to thawing, and thawing of samples was not noticed on the days samples were removed and processed for analysis.

Clinical Sites:

(Study OX22-005)
(Study OX22-008) b(4)

8. Failure to retain reserve samples at the clinical site or at the independent third party.

Although no Form 483 was issued, review of the EIRs revealed that the clinical sites only received sufficient study drugs to dose the subjects and the reserve samples for Studies OX22-005 and OX22-008 were preselected by the sponsor. This is contrary to the BE regulations (21 CFR 320.38 and 320.63) that require reserve samples be selected by the clinical site, and retained at the clinical site or an independent third party. Although the samples were provided by the sponsor and collected during the inspection, the samples were preselected by the sponsor. Further, the written assurances provided by the clinical sites and the sponsor are not meaningful as the sites did not select the "reserve" samples.

Conclusions

Based on the above findings at the analytical site, DSI conclude the following:

i. Due to the failure to meet the requirement for reserve drug samples, the identity of the dosage forms used in bioequivalence studies OX22-005 and OX22-008 cannot be assured (Item 8).

ii. For Study OX22-005, only concentrations estimated from the high calibration curve ——— are acceptable for Agency review (Item 1). b(4)

iii. —— needs to cross-validate assay performance in heparinized human plasma (Item 5) to assure accuracy of concentrations in Studies OX22-005 and OX22-008.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

Final Classifications:
VAI -
VAI -
VAI -

b(4)

cc:
HFD-45/Vaccari
HFD-48/Subramaniam/Rivera-Lopez/Kaufman/CF
OND/ODEI/DNP/Michaloski
OTS/OCP/DCPI/Parepally
HFR-CE450/Sheehan
HFR-SE1505/Hanks
Draft: SS
Edit: MKY 2/19/09 (anal. Portion)
DSI: O:\BE\EIRCover\21997ore.zol.doc
FACTS

b(4)

15 Page(s) Withheld

8 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative-_____

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: January 13, 2008

TO: Cathleen Michaloski, Regulatory Project Manager
Suhail Kasim, M.D., Medical Officer
Division of Neurology Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-997

APPLICANT: Orexo Ab, Sweden

DRUG: Orexa (zolpidem tartrate)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: Treatment for insomnia

CONSULTATION REQUEST DATE: May 28, 2008

DIVISION ACTION GOAL DATE: March 14, 2009
PDUFA DATE: March 14, 2009

I. BACKGROUND:

NDA 21997 is a 505(b)(2) application for zolpidem tartrate for the proposed indication is for the short-term treatment of insomnia characterized by difficulties with sleep initiation. Zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class. An oral formulation of the reference product Ambien was approved in 1992. The sponsor claims that the sublingual formulation would allow for rapid and consistent drug absorption and is making claims in the label that Orexa (sublingual formulation) has been shown to decrease the time to initiate sleep (sleep latency) in patients with chronic insomnia faster than zolpidem tartrate oral tablets.

The goals of the inspection were to assess adherence to FDA regulatory requirements concerning investigator oversight, protocol compliance, validity of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. The number of subjects randomized and proportion discontinued in a particular site was taken into account in selecting sites for auditing.

Inspection focused on two clinical investigators (CIs) in Russia and France and a contract research organization (CRO) in France. The site in Russia was chosen because this site had the most number of patients enrolled and had an increased frequency of adverse events compared with other sites. The clinical investigator site in France was chosen because this site was the second highest enroller in this study. The site had a large contribution to the treatment effect such that removal of this site's contribution to the endpoint data might affect the efficacy variable. This site had a larger disparity between screening and recruitment of patients compared with other sites. The CRO site was inspected because the source polysomnograms (PSG) used to measure the primary endpoint were located and read at the CRO location.

The protocol inspected was Protocol # OX22-006, entitled "A double-blind, double-dummy randomized, two-period cross-over study to evaluate the hypnotic effects and safety of sublingual zolpidem for the treatment of insomnia." The primary endpoint for this study was latency to persistent sleep (LPS) measured by the polysomnogram (PSG).

II. RESULTS (by Site):

Name of CI or CRO and Location	Protocol # and # of Subjects	Inspection Dates	Final Classification
CI #1 Irina Vlasova, MD Chief of Somnology City Clinic Hospital No.31 Lobachevskiy str. 42, 119 415 Moscow, Russia	Protocol # OX22-006/ 21 subjects	November 10 to 14, 2008	NAI
CI #2 Corinne Staner, MD FORENAP Pharma 27 rue du 4ème RSM 68250 Rouffach, France	Protocol # OX22-006/ 13 subjects	November 17 to 21, 2008	Pending (Preliminary classification VAI)
CRO FORENAP Pharma 24 Rue du 4éme RSM, 68250 Rouffach, France	Protocol # OX22-006	November 24 to 28, 2008	Pending (Preliminary classification NAI)

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Irina Vlasova, MD
   Chief of Somnology
   City Clinic Hospital No.31
   Lobachevskiy str. 42, 119 415
   Moscow, Russia

   a. **What was inspected**: At this site, 24 subjects were screened for Protocol # OX22-006; 21 subjects were randomized and 21 subjects completed the study. An audit of 21 subjects' records was conducted. There were no deaths reported. One subject in the comparator (Ambien) arm experienced a pregnancy and a spontaneous abortion.

   b. **General observations/commentary:** There was no evidence of underreporting of adverse events (AEs). No regulatory violations were noted.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the application for the respective indication.

2. Corinne Staner, MD
FORENAP Pharma
27 rue du 4ème RSM
68250 Rouffach, France

Note: Observations noted for this site are based on communications with the FDA inspector. An inspection summary addendum will be generated if conclusions change upon receipt and review of the establishment inspection report (EIR).

a. **What was inspected**: At this site, 64 subjects were screened for Protocol # OX22-006; 13 subjects were randomized and 13 subjects completed the study. There were no deaths or serious adverse events reported (AEs). An audit of the 13 enrolled subjects' records and 8 of the screen failure records was conducted.

b. **General observations/commentary**: There was no evidence of underreporting of AEs. Inspection revealed the following violations:
   i) The Critical Flicker Fusion Test (CFFT) and the Multiple Choice Reaction Time (MCRT) values were recorded directly on the case report form and no printouts from the machine were generated. As a result, the CFFT and MCRT values recorded in the case report form cannot be verified.
   ii) Because study personnel did not complete the laboratory requisition form accurately, pregnancy tests were not performed for Subject 331-053 at period 2 and Subject 331-061 at the end of study visit.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the application for the respective indication.

3. FORENAP Pharma
24 Rue du 4éme RSM
68250 Rouffach, France

Note: Observations noted for this site are based on communications with the FDA inspector. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

a. **What was inspected**: At this CRO site the FDA inspector reviewed the following:
   i) scoring of PSG's, (i.e. who did the scoring, training of scorers, the

number of times the PSG was scored, was the scoring discussed amongst others) and determined that the software calculated the PSG values based on the scoring.

ii) OREXO's monitoring procedures and their application to the clinical sites

iii) OREXO's quality assurance procedures.

iv) procedures to maintain PSG data integrity.

b. **General observations/commentary**: No objectionable conditions were found.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data (PSG interpretations) generated by this site (CRO) appear acceptable in support of the application for the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections of Dr. Vlasova and FORENAP Pharma found no regulatory violations. The inspection of Dr. Staner found regulatory violations concerning pregnancy testing and lack of source documentation for a secondary endpoint. The data from both clinical sites and from the CRO appear acceptable in support of the application for the proposed indication.

The final classifications for Dr. Staner and for FORENAP Pharma are pending. An addendum to this clinical inspection summary will be forwarded to the review division should there be a change in our assessment of data acceptability or additional observations of clinical and regulatory significance are discovered after reviewing the EIRs.

{See appended electronic signature page}

Susan Leibenhaut, MD
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, MD, MPH
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Susan Leibenhaut
1/14/2009 03:42:38 PM
MEDICAL OFFICER

Constance Lewin
1/21/2009 11:47:40 AM
MEDICAL OFFICER

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 21997 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Established/Proper Name: Zolpidem Tartrate SL Dosage Form: oral lozenge Strengths: 5 and 10 mg		
Applicant: Orexo AB Sweden Agent for Applicant (if applicable): DJA Global Pharma., LLC		
Date of Application: 5/14/08 Date of Receipt: 5/18/08 Date clock started after UN:		
PDUFA Goal Date: ~~May~~ MAR 14, 2009	Action Goal Date (if different):	
Filing Date: 6/28/08 Date of Filing Meeting: 6/25/08		
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A 505b2		
Proposed Indication(s): insomnia		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☐ 505(b)(1) X 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	X Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? ☐ Resubmission after refuse to file? X yes, 3/13/06		
Part 3 Combination Product? No	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)	

Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND #69,200	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	X YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	X YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments:**	☐ YES X NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	X YES ☐ NO
User Fee Status **Comments: small business waiver**	☐ Paid ☐ Exempt (orphan, government) X Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?	☐ YES X NO ☐ YES ☐ NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) **Comments:**	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments**: applic –different route of admin (SL); Clinical and Biopharm studies done	X YES # years requested: ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	X Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☐ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES X NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES X NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	☐ YES X NO

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☐ YES X NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments:**	☐ All paper (except for COL) X All electronic ☐ Mixed (paper/electronic) X CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments:**	X YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	X YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments:**	X YES verify ques sent to spon ☐ NO X YES ☐ NO
Index: Does the submission contain an accurate comprehensive index? **Comments:**	X YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain:	X YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments:**	☐ Not Applicable X YES ☐ NO X YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments:**	X YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.***	X YES ☐ NO

Note: Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..." **Comments:**	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	X Not Applicable (*electronic submission or no CMC technical section*) ☐ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** *Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments:**	X YES ☐ NO
Pediatrics	
PREA *Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes,** does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments:**	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments:**	☐ YES X NO
Prescription Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not applicable** X Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use X MedGuideX X Carton labels X Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments:**	X YES NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments:**	X YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments:**	X YES ☐ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments:**	☐ Not Applicable X YES ☐ NO
REMS consulted to OSE/DRISK? **Comments:**	☐ Not Applicable X YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments:** carton and container consult will be sent; yes for all others	☐ Not Applicable X YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments:**	YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments:**	YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments: Re-sub; was a RTF 3/13/06**	X YES Date(s): 12/16/07 ☐ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments: inform conference 5/31/06**	X YES Date(s): ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments:**	☐ YES Date(s): X NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 6/29/08

NDA/BLA #: 21997

PROPRIETARY/ESTABLISHED NAMES: zolpidem tartrate SL

APPLICANT: Orexo AB Sweden (DJA Global Pharma (US agent))

BACKGROUND: Orexo AB submitted the original NDA 21-997 on Jan. 12, 2006 for the treatment of short-term insomnia and a RTF letter was received on March 13, 2006. The reason for the RTF was that sponsor used the wrong comparator reference drug, Stilnoct (instead of Ambien) in their NDA analysis. Orexo AB has taken actions to address all of the Agency's concerns discussed in the pre-IND meeting (November 16, 2004), pre-IND meeting action item minutes (August 18, 2005), RTF and informal follow-up telecon to the RTF. Because the pharmacokinetic (PK) studies originally compared OX22 to an unapproved zolpidem drug product (Stilnoct) sponsor has resubmitted their data with the proper reference drug (Ambien) for full review and sponsor has relied on the previous finding of safety and efficacy for the proper reference drug, Ambien.

REVIEW TEAM 5/1/06:

Melissa K. Banks, Ph.D. Pharmacologist (DNP)	Division of Neurology Products
Silvia Calderon, Ph.D.	Controlled Substance Staff
Lin Whei Chuang, Ph.D.	Controlled Substance Staff
John Duan, Ph.D.	Clinical Pharmacology Reviewer, OCP
John Feeney, III, M.D.	Team Leader, DNP
Lois M. Freed, Ph.D.	Supervisory Pharmacologist, DNP
Martha Heimann, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Norman Hershkowitz, M.D., Ph.D.	Clinical Reviewer, DNP
Kun Jin, Ph.D. Team Leader	Biostatistics
Russell Katz, M.D. Director	DNP
D. Elizabeth McNeil, M.D.	Clinical Reviewer, DNP
Cathleen Michaloski, MPH	Regulatory Project Manager, DNP
Wayne Mitchell, Esq.	Regulatory Counsel, ORP
Ramana Uppoor, Ph.D. Team Leader	Clinical Pharmacology, OCP

Electronic Submission comments **List comments:**	☐ Not Applicable
CLINICAL; Suhail Kasim, MD - New clinical	☐ Not Applicable

reviewer **Previous reviewers: D. Elizabeth McNeil, MD, Carole Davis, DO** **Comments:**	X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	X YES ☐ NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: X NO ☐ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	X Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Jagan Parepally, PhD - reviewer** **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO

BIOSTATISTICS **Steven Bai, PhD - reviewer** **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Melissa Banks, PhD - reviewer** **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Martha Heimann, PhD – reviewer** **Thomas Wong, PhD - reviewer** **Comments:**	☐ Not Applicable X FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? • Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	Not Applicable ☐ YES ☐ NO ☐ Not Applicable ☐ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for validation of sterilization? **(NDAs/NDA supplements only)**	☐ YES X NO ☐ YES ☐ NO
FACILITY (BLAs only)	☐ Not Applicable ☐ FILE

Comments:	☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Russell Katz, MD Director, DNP; Cathleen Michaloski BSN, MPH - RPM

GRMP Timeline Milestones: on schedule

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): X Standard Review ☐ Priority Review

ACTIONS ITEMS

☐	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
X	Send review issues/no review issues by day 74
☐	Other

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

/s/

Cathleen Michaloski
1/21/2009 12:35:12 PM
CSO

Cathleen Michaloski
1/21/2009 12:35:35 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA # 21997

DJA Global Pharma, LLC
Drug Development & Global Regulatory Consulting
On behalf of: Orexo AB, Sweden
115 Commons Ct.
Chadds Ford, PA 19317

Attention: Damaris DeGraft-Johnson, R.Ph, MSc.
President

Dear Ms. DeGraft-Johnson:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b) (1) of the Federal Food, Drug, and Cosmetic Act for zolpidem tartrate sublingual tablet for the treatment of insomnia.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is **March 14, 2009**.

We also acknowledge receipt of submissions dated June 11, 2008 which contained updated product labeling.

We request that you submit the following information:

Chemistry, Manufacturing and Controls Comments:

1. With regard to the proposed drug product specification, although justifications for the choice of pH for the dissolution medium and the data for paddle speeds of 50 rpm and 100 rpm have been provided for review, the following additional data is needed:

    - Provide dissolution data obtained using an intermediate paddle speed between 50 rpm and 100 rpm.
    - Provide data to demonstrate that the proposed method is adequate and capable of discriminating between acceptable and unacceptable tablet batches.

2. The proposed stability matrix for the first three post approval batches per strength provides for a substantial reduction of testing at the 3, 6, 9, 18, and 24 month time points under long-term storage conditions, and at 3 and 6 months under accelerated conditions. Although a matrix design may be applied to testing of post-approval stability batches, all batches should be tested at the 6 month time point for accelerated stability studies, and at the 0, 12, 24 and 36 month time points for long-term studies.

3. The proposed annual batch stability commitment, which provides for testing at the 0, 12, 24, and 36 month time points only, is not adequate. The protocol should be revised to include additional time points during the first two years.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We are granting you a waiver for pediatric studies up to age 6 and we will defer studies for children ages 6 through 16 years.

If you have any questions, call Cathleen Michaloski, BSN/MPH, Regulatory Project Manager, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director, Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

Russell Katz
7/24/2008 07:42:50 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA #21-997

NDA ACKNOWLEDGMENT

DJA Global Pharma, LLC,
Drug Development & Global Regulatory Consulting
On behalf of: Orexo AB, Sweden
115 Commons Ct.
Chadds Ford, PA 19317

Attention: Damaris DeGraft-Johnson, R.Ph, MSc.
President

Dear Ms. DeGraft-Johnson:

We have received your new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	OX22 (zolpidem tartrate sublingual tablets, 5 and 10 mg tablets)
Review Priority Classification:	Standard
Date of Application:	May 13, 2008
Date of Receipt:	May 14, 2008
Our Reference Number:	NDA # 21-997

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on **July 13, 2008** in accordance with 21 CFR 314.101(a). If we file the application, the **user fee goal date** will be **March 14, 2009.**

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above must be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me, Cathleen Michaloski, BSN, MPH, Regulatory Project Manager, at (301) 796-1123.

Sincerely,

{See appended electronic signature page}

Cathleen Michaloski, BSN, MPH
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

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/s/

Cathleen Michaloski
5/29/2008 01:48:20 PM

ACTION PACKAGE CHECKLIST

Application Information			
BLA # NDA # 21997	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: EDLUAR Established Name: zolpidem tartrate SL Dosage Form: 5 and 10 mg SL tabs		Applicant: Orexo AB Sweden	
RPM: C. Michaloski		Division: DNP	Phone # 301-796-1123

NDAs:	505(b)(2) NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Ambien 19908 oral tabs Provide a brief explanation of how this product is different from the listed drug. New formulation - sublingual tabs ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☒ Confirmed ☐ Corrected Date: 3/12/09

❖ User Fee Goal Date ❖ Action Goal Date (if different)	3/14/2009
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

Appears This Way
On Original

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
- ☐ Fast Track
- ☐ Rolling Review
- ☐ CMA Pilot 1
- ☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
- ☐ Accelerated approval (21 CFR 314.510)
- ☐ Restricted distribution (21 CFR 314.520)

Subpart I
- ☐ Approval based on animal studies

BLAs: Subpart E
- ☐ Accelerated approval (21 CFR 601.41)
- ☐ Restricted distribution (21 CFR 601.42)

Subpart H
- ☐ Approval based on animal studies

NDAs and NDA Supplements:
- ☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☐ No
• Exception for review *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes ☐ No
• OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☒ Included
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☒ Verified
• [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for **each** paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's	☐ Yes ☐ No

notice of certification?

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (3).*

(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)*	3/18/09 CDTL review 3/13/09 Div Director Memo
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	3/14/09
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Patient Package Insert	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	3/14/09
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels)	
• Most-recent division-proposed labels (only if generated after latest applicant submission)	3/14/09
• Most recent applicant-proposed labeling	
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS 1/22/09 and 2/24/09 ☐ DSRCS ☐ DDMAC ☐ SEALD ☒ Other reviews MHT 3/9/09 Abuse Potential rev memo 2/11/09 ☐ Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	3/3/09
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ AIP-related documents • Center Director's Exception for Review memo • If AP: OC clearance for approval	
❖ Pediatric Page (all actions)	☒ Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment Studies	☒ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	ACK ltr 7/24/08 Clin Inspection 1/21/09; 1/14/09 Tradename email to spon 2/3/09 Labeling tcon 3/12/09
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg 5/31/06 after RTF
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	☒ No AC meeting
• Date of Meeting	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)*	T.Wong 1/29/09 R. Sood 2/27/09 (TL)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	5/14/08
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	☐ Not a parenteral product
❖ Facilities Review/Inspection	

❖ NDAs: Facilities inspections (include EER printout)	Date completed: ☐ Acceptable ☐ Withhold recommendation

❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date completed, must be within 60 days prior to AP)*	☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	M.Banks 3/11/09; L.Freed 3/12/09
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	S. Kasim 3/10/09; R.Farkas 3/10/09
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	5/14/08
❖ Clinical consult reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☐ None see section - Labeling
❖ Microbiology (efficacy) reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	
❖ Risk Management Plan review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	3/13/09 Med Guide Only
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☐ Not needed see section Labeling
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	see section-Administrative Ltrs
• Bioequivalence Studies	J.Parepally 2/12/09
• Clin Pharm Studies	
❖ Statistical Review(s) *(indicate date for each review)*	☒ None
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 2/12/09 J. Parepally; 2/12/09 V.Tandon

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

505(b)(2) ASSESSMENT

Revised 3.3.09 CM

Application Information		
NDA # 21997	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Pending (Edluar) Established/Proper Name: zolpidem tartrate SL Dosage Form: oral 5 and 10 mg ODT Strengths: 5 and 10 mg		
Applicant: Orexo AB, Sweden, DJA Global Pharma, LLC (US agent)		
Date of Receipt: 5/14/08		
PDUFA Goal Date: 3/14/09	Action Goal Date (if different):	
Proposed Indication(s): insomnia		

GENERAL INFORMATION

1. Is this application for a drug that is an "old" antibiotic as described in the Guidance to Industry, Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO X

*If "**YES**," proceed to question #3.*

2. Is this application for a recombinant or biologically-derived product and/or protein or peptide product?

YES ☐ NO X

*If "**YES** "contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)

3. List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
NDA 19908 Ambien (zolpidem tartrate)	Two Biopharm studies; specific sections PI changed
	Three clinical studies; specific sections PI changed

4. Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific "bridge" to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Sponsor has conducted a BE study comparing Formulation II with the reference Ambien (Study OX22-005). Formulation II was found to be bioequivalent to the RLD Ambien. However, Formulation II is not to-be-marketed or commercial formulation. Therefore the Sponsor has also conducted a bridging BE study between Formulation II and the commercial formulation (Study OX22-008). Formulation II was bioequivalent to the commercial formulation, thereby establishing the link between the commercial formulation and the reference Ambien.

RELIANCE ON PUBLISHED LITERATURE

5. (a) Does the application rely on published literature to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES x NO ☐

*If "**NO**," proceed to question #6.*

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

Ambien (zolpidem tartrate) x NO ☐

YES

*If "**NO**", proceed to question #6*
*If "**YES**", list the listed drug(s) identified by name and answer question #5(c)*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES X NO ☐

Appears This Way
On Original

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #6-10 accordingly.

6. Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES x NO ☐

*If "**NO**," proceed to question #11.*

7. Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Ambien	19908	yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

8. If this is a supplement, does the supplement rely upon the same listed drug(s) as the original (b)(2) application? N/A

YES ☐ NO

*If "**NO**", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

9. Were any of the listed drug(s) relied upon for this application:
   a. Approved in a 505(b)(2) application?

YES x NO ☐

*If "**YES**", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application: none

   b. Approved by the DESI process?

YES ☐ NO x

*If "**YES**", please list which drug(s).*

Name of drug(s) approved via the DESI process:

   c. Described in a monograph?

YES ☐ NO x

*If "**YES**", please list which drug(s).*

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES ☐ NO x

*If "**YES**", please list which drug(s) and answer question d.1.*
*If "**NO**", proceed to question #10.*

Name of drug(s) discontinued from marketing:

1. Were the products discontinued for reasons related to safety or effectiveness?

YES ☐ NO X

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

10. Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in dosage form, from oral tablet to sublingual lozenge.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

11. (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(**Pharmaceutical equivalents** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES ☐ NO x

*If "**NO**," to (a) proceed to question #12.*

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO X

Appears This Way
On Original

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES ☐ NO X

*If "**YES**" and there are no additional pharmaceutical equivalents listed, proceed to question #13.*
*If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical equivalent(s):

12. (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(**Pharmaceutical alternatives** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

There are 22 generic forms of zolpidem tartrate tablets. Yes X NO ☐

*If "**NO**", proceed to question #13.*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES X NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES X NO ☐

*If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #13.*
*If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note that there are approved generics listed in the Orange Book. Contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

List the patent numbers of all patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

13. Did the applicant address (with an appropriate certification or statement) all of the patents listed in the Orange Book for the listed drug(s)?

There are no unexpired patents for this product in the Orange Book Database. X NO ☐

*If "**NO**", list which patents (and which listed drugs) were not addressed by the applicant.*

Listed drug/Patent number(s):

14. Which of the following patent certifications does the application contain? *(Check all that apply and identify the patents to which each type of certification was made, as appropriate.)*

☐ No patent certifications are required (e.g., because application solely based on published literature that does not cite a specific innovator product or for an "old antibiotic" (see question 1.))

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

X 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s): US PATENT No. 4,382,938 RDL for Ambien; patent has expired

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

N/A NO ☐

YES

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

N/A ☐ NO ☐

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

☐ NO X;

YES N/A

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

There are no agreements betw Orexo and any US partner.

Patent number(s):

If the application has been filed, did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]?

N/A YES ☐ NO ☐

Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

N/A YES ☐ NO ☐

Date Received:

Has the applicant been sued for patent infringement (within 45-days of receipt of the notification listed above)? Note: you may need to call the applicant to verify this information.

N/A ☐ NO ☐

☐ Written statement from patent owner that it consents to an immediate effective date of approval (applicant must also submit paragraph IV certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). N/A

Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents. N/A

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a

statement that the method of use patent does not claim any of the proposed indications. (Section viii statement) N/A

Patent number(s):

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

/s/

Cathleen Michaloski
3/3/2009 04:53:55 PM
CSO

Cathleen Michaloski
3/3/2009 04:54:14 PM
CSO