

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022328Orig1s000**

**OTHER REVIEW(S)**

## 505(b)(2) ASSESSMENT

Application Information		
NDA # 22328	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Intermezzo Established/Proper Name: zolpidem tartrate SL Dosage Form: SL tablets Strengths: 1.75 mg and 3.5 mg oral SL tablets		
Applicant: Transcept Pharma, Inc.		
Date of Receipt: original submission 9/30/08; re-sub 1/14/11; re-sub 9/27/11		
PDUFA Goal Date: 11/27/11		Action Goal Date (if different): 11/23/11
Proposed Indication(s): as needed, middle-of-the- night (MOTN) 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 ☒

*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 ☒

*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)	Three Biopharm studies; specific sections PI changed
	Five 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)

This NDA comprises of the following 3 single-dose pharmacokinetic (PK)/ bioequivalence (BE) bridging studies in healthy adult and elderly subjects. Study ZI-15, provides comparative bioavailability information relative to reference Ambien<sup>®</sup>. Study ZI-14 includes comparative bioavailability of Intermezzo<sup>®</sup> 1.75 mg and 3.5 mg in elderly and adult cohorts. Study ZI-13 provides a bridging link between IND formulation and final commercial formulation used in different studies. Final commercial formulation was used in most of the studies including pivotal BE, pharmacodynamic, and efficacy studies.

**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    ☒    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)    ☒    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 ☒ NO ☐



## 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 ☒ 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 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 ☒

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

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

- c. Described in a monograph?

YES ☐ NO ☒

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

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES ☐ NO ☒

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 ☐

*(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 tablet and for a new method of use, middle of the night insomnia (MOTN). This is also a new indication – middle of the night insomnia –to be taken prn (as necessary).

*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 ☒

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

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? YES ☐ NO

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.*

Yes NO ☐  
X

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)?

There are approx 20 generic drugs approved for zolpidem tartrate. 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 ☒ YES; N/A

YES

- ☐ 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 between Trancept 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):

[Revised 10.16.09 per B.D. Miller; updated 10.24.11](#)

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/s/  
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CATHLEEN B MICHALOSKI  
11/23/2011

## SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 22328
APPLICANT	Transcept Pharmaceuticals, Inc.
PRODUCT NAME	Zolpidem Tartrate (Intermezzo)
SUBMISSION DATE	September 27, 2011
PDUFA DATE	November 25, 2011
SEALD REVIEW DATE	November 22, 2011
SEALD LABELING REVIEWER	Ann Marie Trentacosti

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- ☐ There is no redundancy of information.
- ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- ☐ A horizontal line must separate the HL and Table of Contents (TOC).
- ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- ☐ Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**

- ☒ Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Add space between Highlights Limitation Statement and Product Title Line.

- **Product Title**

- ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

- ☐ The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- ☐ All text in the boxed warning is **bolded**.
- ☐ Summary of the warning must not exceed a length of 20 lines.
- ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- ☐ Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

- ☐ Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:  
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- ☐ All contraindications listed in the FPI must also be listed in HL.
- ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- ☐ For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- ☐ For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”).**”

- **Revision Date**

- ☒ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Revision date is missing.



## Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☒ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.

Section 17 should be listed as “PATIENT COUNSELING INFORMATION” and not “PATIENT COUNSELING INFORMATION and Medication Guide.”
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

### • General Format

- ☐ A horizontal line must separate the TOC and FPI.
- ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- ☒ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

There are no periods after the numbers for the section or subsection headings. For example, the numbers 2. and 2.1. should be replaced with 2 and 2.1 without periods. The numbering needs to be corrected throughout the FPI.

### • Boxed Warning

- ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- ☒ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

Incorrect cross-referencing:

[REDACTED] (b) (4)  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

- **Contraindications**

- ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- ☐ Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.
- ☐ For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”
- ☐ For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- ☐ This section is required and cannot be omitted.
- ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:
  - “See FDA-approved patient labeling (Medication Guide)”
  - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information)”
  - “See FDA-approved patient labeling (Instructions for Use)”
  - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

## SEALD LABELING REVIEW

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ANN M TRENTACOSTI  
11/22/2011

## SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 22328
APPLICANT	Transcept Pharmaceuticals, Inc.
PRODUCT NAME	Intermezzo (zolpidem tartrate)
SUBMISSION DATE	September 27, 2011 (class 1 resubmission)
PDUFA DATE	November 25, 2011
SEALD SIGN-OFF DATE	November 22, 2011
DIRECTOR, STUDY ENDPOINTS AND LABELING STAFF, OND IO	Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed November 22, 2011, have been addressed in the final agreed-upon PI. SEALD has no objection to PI approval at this time.

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/s/  
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LAURIE B BURKE  
11/22/2011

**PMR/PMC Development Template for Intermezzo (Zolpidem Tartrate)**  
**PMR # 1**

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

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PMR/PMC Description: A pharmacokinetic dose-ranging, tolerability, and pharmacodynamic study of Intermezzo in pediatric patients with insomnia related to attention-deficit/hyperactivity disorder (ADHD) ages 6-17 years.

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PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>11/2012</u>
	Study/Clinical trial Completion Date:	<u>05/2016</u>
	Final Report Submission Date:	<u>11/2016</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is part of a PREA requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This study is needed to provide data to select appropriate doses for an efficacy study for Intermezzo in pediatric patients, and to obtain preliminary safety data to inform design of the efficacy study.



3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A pharmacokinetic dose-ranging, tolerability, and pharmacodynamic study in pediatric patients with insomnia related to attention-deficit/hyperactivity disorder (ADHD) ages 6-17 years.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial  
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
☐ Thorough Q-T clinical trial  
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)  
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
☐ Pharmacokinetic studies or clinical trials  
☐ Drug interaction or bioavailability studies or clinical trials  
☐ Dosing trials  
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials  
☐ Immunogenicity as a marker of safety  
☒ Other (provide explanation)  
 This study is needed to provide data to select appropriate doses for an efficacy study for Intermezzo in pediatric patients, and to obtain preliminary safety data to inform design of the efficacy study.
- 

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)  
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
☐ Dose-response study or clinical trial performed for effectiveness  
☐ Nonclinical study, not safety-related (specify)
- 
- ☐ Other
- 

## 5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?  
☒ Are the objectives clear from the description of the PMR/PMC?  
☒ Has the applicant adequately justified the choice of schedule milestone dates?  
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

**PMR/PMC Development Template for Intermezzo (Zolpidem Tartrate)**  
**PMR # 2**

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

---

PMR/PMC Description: A phase 3, multi-center, double-blind, placebo-controlled efficacy and safety study of Intermezzo in pediatric patients with insomnia related to ADHD, ages 6-17 years.

---

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>04/2014</u>
	Study/Clinical trial Completion Date:	<u>04/2017</u>
	Final Report Submission Date:	<u>10/2017</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is part of a PREA requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This double-blind, placebo-controlled study is needed to examine the efficacy of Intermezzo in pediatric patients with insomnia related to ADHD, ages 6-17 years. The study will also provide safety data from the double-blind, placebo-control period.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A phase 3, multi-center, double-blind, placebo-controlled efficacy and safety study in pediatric patients with insomnia related to ADHD, ages 6-17 years

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☐ Pharmacokinetic studies or clinical trials
- ☐ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials
  - ☐ Immunogenicity as a marker of safety
  - ☒ Other (provide explanation)

This study is needed to examine the efficacy of Intermezzo in pediatric patients with insomnia related to ADHD, ages 6-17 years. The study will also provide safety data from the double-blind, placebo-control period.

---

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
- ☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- ☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- ☐ Dose-response study or clinical trial performed for effectiveness
- ☐ Nonclinical study, not safety-related (specify)

---

☐ Other

---

## 5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
- ☒ Are the objectives clear from the description of the PMR/PMC?
- ☒ Has the applicant adequately justified the choice of schedule milestone dates?
- ☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

**PMR/PMC Development Coordinator:**

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

**PMR/PMC Development Template for Intermezzo (Zolpidem Tartrate)**  
**PMR # 3**

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

---

PMR/PMC Description: A phase 3 open-label extension safety study in pediatric patients with insomnia related to ADHD, ages 6-17 years.

---

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>04/2014</u>
	Study/Clinical trial Completion Date:	<u>10/2017</u>
	Final Report Submission Date:	<u>04/2018</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☒ Other

This is part of a PREA requirement.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This study is needed to provide long-term open-label safety data about Intermezzo in the treatment of pediatric patients with insomnia related to attention-deficit/hyperactivity disorder, ages 6-17 years.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☒ Pediatric Research Equity Act
- ☐ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☐ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A phase 3 open-label extension safety study in pediatric patients with insomnia related to ADHD, ages 6-17 years.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial  
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
☐ Thorough Q-T clinical trial  
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)  
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
☐ Pharmacokinetic studies or clinical trials  
☐ Drug interaction or bioavailability studies or clinical trials  
☐ Dosing trials  
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- ☐ Meta-analysis or pooled analysis of previous studies/clinical trials  
☐ Immunogenicity as a marker of safety  
☒ Other (provide explanation)

---

This study is needed to provide long-term safety data for Intermezzo in pediatric patients.

---

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)  
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
☐ Dose-response study or clinical trial performed for effectiveness  
☐ Nonclinical study, not safety-related (specify)

---

☐ Other

---

## 5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?  
☒ Are the objectives clear from the description of the PMR/PMC?  
☒ Has the applicant adequately justified the choice of schedule milestone dates?  
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

**PMR/PMC Development Coordinator:**

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)



**PMR/PMC Development Template for Intermezzo (Zolpidem Tartrate)**  
**PMR # 4**

This template should be completed by the PMR/PMC Development Coordinator and included for **each** PMR/PMC in the Action Package.

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PMR/PMC Description: A study to determine patient compliance with dosing instructions in the setting of actual clinical use.

---

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>04/2013</u>
	Study/Clinical trial Completion Date:	<u>04/2017</u>
	Final Report Submission Date:	<u>12/2017</u>
	Other: <u>Draft Protocol Submission Date</u>	<u>04/2012</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☒ Only feasible to conduct post-approval
- ☐ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

A principle safety concern with this drug is that patients may not follow dosing instructions, as dosing with insufficient sleep time remaining can lead to high residual morning drug levels. Data from controlled clinical trials would not adequately address this question, because study subjects would not adequately represent an actual clinical population, and the study procedures themselves would be likely to affect patient behavior.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A principle safety concern with this drug is that patients may not follow dosing instructions, as dosing with insufficient sleep time remaining can lead to high residual morning drug levels. The goal of the study is to assess the incidence, nature, causes, and consequences of departures from dosing instructions.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- ☐ Accelerated Approval (subpart H/E)
- ☐ Animal Efficacy Rule
- ☐ Pediatric Research Equity Act
- ☒ FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- ☒ Assess a known serious risk related to the use of the drug?
- ☐ Assess signals of serious risk related to the use of the drug?
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- ☐ Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- ☐ Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- ☒ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- ☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study to determine patient compliance with dosing instructions in the setting of actual clinical use. The study should enroll patients representing the clinical population using the drug, and should assess the incidence, nature, causes, and consequences of departures from dosing instructions. The study should include a comparator group that is taking other drugs approved for insomnia characterized by difficulty with sleep maintenance.

Submit a draft protocol approximately 12 months prior to the protocol submission date to allow for time to negotiate the details of the protocol.

Required

- ☐ Observational pharmacoepidemiologic study
- ☐ Registry studies

Continuation of Question 4

- ☒ Primary safety study or clinical trial  
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
☐ Thorough Q-T clinical trial  
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)  
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
☐ Pharmacokinetic studies or clinical trials  
☐ Drug interaction or bioavailability studies or clinical trials  
☐ Dosing trials  
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)  


---

☐ Meta-analysis or pooled analysis of previous studies/clinical trials  
☐ Immunogenicity as a marker of safety  
☐ Other (provide explanation)
- 

Agreed upon:

- ☐ Quality study without a safety endpoint (e.g., manufacturing, stability)  
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
☐ Dose-response study or clinical trial performed for effectiveness  
☐ Nonclinical study, not safety-related (specify)  


---

☐ Other
- 

## 5. Is the PMR/PMC clear, feasible, and appropriate?

- ☒ Does the study/clinical trial meet criteria for PMRs or PMCs?  
☒ Are the objectives clear from the description of the PMR/PMC?  
☒ Has the applicant adequately justified the choice of schedule milestone dates?  
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

☒ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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SALLY U YASUDA  
11/21/2011



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** November 14, 2011

**To:** Russell Katz, MD, Director  
Division of Neurology Products

**Through:** Michael Klein, PhD, Director  
Controlled Substance Staff

**From:** Stephen Sun, MD, Medical Officer  
Controlled Substance Staff

**Subject:** **Topic:**  
Abuse Potential Assessment of New Drug Application re-submission  
**Application:**  
NDA 022328: Intermezzo (zolpidem tartrate) sublingual tablet  
IND 069209  
**Proposed Indication:**  
Use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.  
**Dosages:**  
1.75 mg and 3.5mg sublingual tablets  
**Sponsor:**  
Trancept Pharmaceuticals

**Materials reviewed:**

1. Sun S. Controlled Substance Staff Consult (4/14/2011)
2. Calderon S. CSS Consult (10/20/2009)
3. Beaston PR. CSS Consult (3/25/2008)
4. Trancept Pharmaceuticals. Current proposed product label. 2011.

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# **I. Summary**

## **A. Background**

1. This memorandum is in response to a follow-up CSS consult dated October 3, 2011, for the Division of Neurology Products (DNP) pertaining to NDA022328 for Intermezzo (zolpidem tartrate) sublingual tablets under development by Transcept Pharmaceuticals. CSS was previously consulted on this product from memos dated 4/14/2011, 10/20/2009, and 3/25/2008. In addition to requesting CSS participation in the internal meeting and industry meetings, the consult involves a review of the proposed label. Intermezzo was filed as a 505(b)(2) NDA submission utilizing Ambien<sup>®</sup> as the reference listed drug. Zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class, which interacts with the gamma-aminobutyric acid (GABA) receptor, and is listed in Schedule IV of the Controlled Substances Act (CSA).
2. On October 28, 2009, the Sponsor was issued a Complete Response (CR) letter requesting additional data to demonstrate that the product can be used in a safe manner. The requested data included the following: (1) evidence that driving ability is not impaired when the product is taken as directed, (2) whether patients will be able to consistently use zolpidem according to labeling, (3) the risk of inadvertent dosing with fewer than 4 hours of bedtime remaining, and (4) the risk of inadvertent re-dosing in a single night.
3. Sponsor has resubmitted the materials as a response to issues identified in the Complete Response letter on January 14, 2011.

## **B. Conclusions:**

1. Zolpidem is a well-characterized hypnotic agent indicated for the management of insomnia that is presently classified as a Schedule IV drug. Reports of misuse, abuse, and diversion of this drug are well-known. Zolpidem continues to be under surveillance via the sponsors of the primary reference listed drug, Ambien<sup>®</sup>, the controlled release product Ambien<sup>®</sup> CR, and the respective generic counterparts.
2. In previous CSS consults, concerns about Intermezzo included the following:
  - additive use of this product to an existing hypnotic regimen, e.g. another zolpidem product
  - multiple dosing of this product during a single sleep/wake cycle
  - accidental use and poisoning of children, given the proximity to the bedside
  - frequency of driving, work, and home-related accidents
3. Intermezzo (zolpidem) is proposed for use in middle-of-the-night awakening with availability at 1.75mg and 3.5mg doses. Due to the lower dosing and individual packaging for each of these doses, the risk of misuse, abuse, and addiction are not

likely to be greater than the currently available and lowest 6.25mg zolpidem solid oral product available. Furthermore, the current proposed product language and conversion to single-dose packaging have mitigated some of the concerns.

4. However, the individual packaging of a branded zolpidem could be perceived as having greater street value while its lower doses (1.75 mg and 3.5 mg) could provide prescribers and patients a false sense of assurance that these doses are less abusable. Therefore, there is no recommendation to add any additional active-ingredient specific language to the proposed product label for this product. However, precautionary language on safe-storage of medicines when not in use and safe operation of motorized equipment or vehicles should be included in the individual dose packaging.

### **C. Recommendations:**

1. No change or additional language to “active-ingredient” or zolpidem-specific information in the proposed product label needs to be added to the proposed product label.
2. Highlight appropriate warnings for this formulation to prevent the concomitant use of this drug with other similar hypnotic substances, including those that contain zolpidem, for this proposed product label.
3. Highlight precautions against abuse and diversion (e.g. safe storage for unused medications and safe operation of motorized equipment) for any materials seen by patients and healthcare professionals, including the individual dose packaging and marketing materials.

## **II. Discussion**

### **A. Chemistry**

1. Zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class, which interacts with the gamma-aminobutyric acid (GABA) receptor, and is listed in Schedule IV of the Controlled Substances Act (CSA). Zolpidem is well-characterized; various strengths and formulations of zolpidem are currently marketed in the U.S.
2. In this proposed formulation, Intermezzo is a zolpidem product proposed at 1.75mg and 3.5mg dosage units for use in middle-of-the-night awakening episodes.

### **B. Clinical**

1. No clinical studies on relative abusability between currently marketed zolpidem dosage strengths and Intermezzo were provided for review.

**C. Integrated assessment**

1. Section 9 in the Full Prescribing Information adequately provides information about the risks of zolpidem use with regard to abuse and dependence.
2. Existing national surveillance systems and published studies do not provide sufficient data granularity to distinguish between the relative abusability or misuse profiles amongst the different dosage strengths of zolpidem. Therefore, no comparisons can be made.



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/s/  
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STEPHEN W SUN  
11/14/2011

MICHAEL KLEIN  
11/15/2011

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Direct To Consumer Promotion**

Memorandum

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**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** November 2, 2011

**To:** Cathleen Michaloski, BSN, MPH  
Senior Regulatory Project Manager  
Division of Neurology Products (DNP)

**From:** Meeta Patel, PharmD  
Regulatory Review Officer  
Office of Prescription Drug Promotion, Division of Direct to Consumer  
Promotion (formerly known as Division of Drug Marketing, Advertising,  
and Communications [DDMAC])

**CC:** Robyn Tyler, Acting Group II Leader, DDMAC

**Subject:** NDA 022328  
DDTCP Comments for Intermezzo (zolpidem tartrate sublingual tablets)  
Medication Guide and Instructions for Use

---

DDTCP has reviewed the proposed Medication Guide (MG) and Instructions for Use (IFU) for Intermezzo sublingual tablets. We also reviewed the comments on this MG from the Division of Risk Management (DRISK) dated October 28, 2011 with additional comments from Ron Farkas on October 28, 2011. We agree with DRISK's comments and Ron Farkas' comments and have no additional comments at this time.

Thank you for the opportunity to comment on the proposed Medication Guide and IFU.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or [meeta.patel@fda.hhs.gov](mailto:meeta.patel@fda.hhs.gov).

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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.**  
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/s/  
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MEETA N PATEL  
11/02/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: October 27, 2011

Reviewer(s): Julie Villanueva, PharmD  
Division of Medication Error Prevention and Analysis

Team Leader Irene Z. Chan, PharmD, BCPS  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh  
Division of Medication Error Prevention and Analysis

Drug Name(s): Intermezzo (Zolpidem Tartrate) Sublingual Tablets

Application Type/Number: NDA 022328

Applicant/sponsor: Transcept Pharmaceuticals, Inc.

OSE RCM #: 2011-3730 and 2011-3731

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates the label and labeling for Intermezzo (Zolpidem Tartrate) Sublingual Tablets in response to a request from the Division of Neurology Products (DNP).

### 1.1 REGULATORY HISTORY

This NDA is a 505(b)(2) application. The reference listed drug is Ambien (Zolpidem Tartrate) Tablets: NDA 019908.

DMEPA previously reviewed the labels and labeling of Intermezzo in OSE review # 2008-1770 dated September 3, 2009. The Agency was concerned that dosing errors could occur, such as inadvertent redosing in a single night and inadvertent dosing with less than 4 hours of bedtime remaining. Due to these concerns and increased risk of next day residual effects, a CR letter was sent to the Applicant to address these issues on October 28, 2009.

In response to the CR, the Applicant conducted a driving study and developed a four element packaging system that consisted of a single unit-dose pouch, a dosing time chart, a separate single page patient instructions for use, and a dosing time tool that were submitted on January 14, 2011. DMEPA reviewed the contents of the resubmission in OSE review # 2011-220/221 dated April 15, 2011.

The Agency had remaining concerns about increased risk of next day residual blood levels in certain populations, which were stated in the CR letter dated July 14, 2011.

The Applicant proposed that reducing the recommended dose for women to 1.75 mg and revising the dosing instructions to state that patients (b) (4)

addresses the remaining concern of next day residual effects. Labels and labeling were submitted with the updated dosing information on September 27, 2011.

### 1.2 PRODUCT INFORMATION

Intermezzo is a hypnotic agent indicated for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep. Intermezzo should only be taken if the patient has four hours of bedtime remaining before (b) (4). The recommended dose in men is 3.5 mg, and the total dose should not exceed 3.5 mg per night. The recommended dose of Intermezzo in women, elderly, debilitated patients, or hepatically impaired patients is 1.75 mg, and the total dose should not exceed 1.75 mg per night. Intermezzo will be available in unit-dose pouches containing a sublingual tablet in a foil blister packaged in cartons containing 30 pouches. The recommended storage is between 20°C to 25°C (68°F to 77°F), and the product should be protected from moisture. The blister should only be removed from the pouch if the patient is ready to administer the medication.

## **2 METHODS AND MATERIALS REVIEWED**

Using Failure Mode and Effects Analysis<sup>1</sup> and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following labels and labeling submitted by the Applicant on September 27, 2011:

- Professional Sample
  - Unit-dose Pouch Labeling
  - Unit-dose Carton Labeling
  - Display Carton Labeling (contains five unit-dose cartons)
- Retail Product
  - Foil Blister Labels
  - Unit-dose Pouch Labeling
  - Carton Labeling (contains 30 unit-dose pouches)
- Dosing Time Tool
- Patient Instructions for Use
- Medication Guide
- Insert Labeling (DNP has made changes to the insert labeling on October 26, 2011 as discussed per the internal meeting)

## **3 DISCUSSION OF DEFICIENCIES IDENTIFIED**

A majority of the recommendations from OSE review # 2011-220/221 were implemented by the Applicant; however, the recommendations that were not accepted will be readdressed with the Applicant and are restated in this review. DMEPA's risk assessment of the product's label and labeling submitted by the Applicant, and the insert labeling edited by DNP, identified the following deficiencies:

- Inadequate differentiation between the two strengths on the foil blister label, unit-dose pouch labeling, and carton labeling
- Inappropriate use of negative warnings in labels and labeling
- Inadequate instruction for dispensing the medication guide to the patient in the professional sample carton labeling
- Inappropriate use of error-prone abbreviations, symbols and dose designations in the insert labeling

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

## 4 CONCLUSIONS AND RECOMMENDATIONS

The proposed label and labeling submitted by the Applicant and the insert labeling revised by DNP introduce vulnerability that can lead to medication errors. We advise that the following recommendations be implemented prior to approval:

- A. Unit-dose Pouch Labeling, Patient Instructions for Use, Medication Guide, and Insert Labeling
  - 1. Negative warnings, such as “do not do that” can be misread as an affirmative warning “do this.”<sup>2</sup> The use of negative warnings should be avoided or an affirmative warning should preface the negative warning to prevent misinterpretation. Revise statements, such as, (b) (4) to read “Only take Intermezzo if you have at least 4 hours of bedtime remaining” and “Only take 1 tablet a night,” respectively.
  - 2. (b) (4)
- B. Foil Blister Label, Unit-dose Pouch Labeling, Professional Sample Unit-dose Carton Labeling and Display Carton Labeling, and Retail Product Carton Labeling

The 1.75 mg and 3.5 mg strengths are not well differentiated from one another because they both have (b) (4) that are similar. Modify the colors for increased strength differentiation to prevent selection errors.
- C. Unit-dose Pouch Labeling, Dosing Time Tool, and Patient Instructions for Use

Revise the column heading (b) (4) to read “Take Intermezzo before” to prevent misinterpretation of the negative warning. See Comment A.1.
- D. Professional Sample: Unit-dose Carton Labeling

Revise the statement (b) (4) to read “Attention: Dispense the accompanying Medication Guide and Dosing Time Tool to each patient.” Since the professional samples will be dispensed in the clinic setting, a statement instructing the health care professional to provide the patient with the Medication Guide and Dosing Time Tool is needed.

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<sup>2</sup> Institute for Safe Medication Practices (ISMP). August 12, 2010. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Medication Safety Alert, 15(16).

E. Unit-dose Pouch Labeling

The insert labeling indicates that the unit-dose pouch will contain an NDC number. The current unit-dose pouches provided by the Applicant do not contain the NDC number. Add the NDC number indicated in the insert labeling to the associated unit-dose pouches.

F. Carton Labeling

The statement “Each sublingual tablet contains X mg zolpidem tartrate” should be moved from the principal display panel to the side panel below the statement “Each pouch contains one sublingual tablet.” The statement “Usual Adult Dosage: see accompanying prescribing literature” should be moved from the principal display panel to the side panel. Relocating these statements will help minimize the cluttered appearance on the principal display panel and increase readability.

G. Insert Labeling

1. General Comments

- a. The insert contains strength and dose numerical sequences where the dosage unit does not follow each numerical designation (e.g. 5-20 mg). In these instances, the dash could get overlooked and the strength misinterpreted as 520 mg. Therefore, we recommend that in all such instances the dosage unit follow the numerical strength or dose and the dash be replaced with “to” (e.g., 5 mg to 20 mg). Additionally, revise numerical sequences such as “4, 20, and 100 mg base/kg” to read “4 mg base/kg, 20 mg base/kg, and 100 mg base/kg.”
- b. The symbols  $<$ ,  $\leq$ ,  $>$ ,  $\geq$  were utilized in the insert labeling to represent “less than,” “less than or equal to,” “greater than,” or “greater than or equal to,” respectively. These symbols can be misinterpreted as the opposite of the intended symbol or mistakenly used as the incorrect symbol.<sup>3</sup> In particular, a “ $< 10$ ” can be misread as “40.” As part of a national campaign to decrease the use of dangerous symbols, the FDA agreed to not use such error-prone symbols in the approved labeling of products. Therefore we recommend that  $<$  be replaced with “less than,”  $\leq$  be replaced with “less than or equal to,”  $>$  be replaced with “greater than,” and  $\geq$  be replaced with “greater than or equal to.”

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<sup>3</sup> Institute for Safe Medication Practices (ISMP). ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations. ISMP: 2010.



- c. Trailing zeros were utilized within the insert labeling. Trailing zeros can lead to 10-fold errors in dosing.<sup>3</sup> We recommend removing all trailing zeros with the exception of when it is required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes.
- 2. Highlights of Prescribing Information: Dosage and Administration
  - a. Revise the statement (b) (4) to state “Downward dosing adjustments of CNS depressants may be necessary when taken concomitantly with Intermezzo.”
  - b. Revise the adult dose statement to read “The recommended dose is 1.75 mg for women and 3.5 mg for men, taken only once per night if needed” to be consistent with the Full Prescribing Information.
- 3. Full Prescribing Information: Section 2

Add the statement “Intermezzo should only be taken if the patient has 4 hours of bedtime remaining before the planned time of waking” under Section 2 Dosage and Administration, before Section 2.1 Dosage in Adults. This statement appears in the Highlights of Prescribing Information and therefore should be included in the Full Prescribing Information.
- 4. Full Prescribing Information: Section 2.2

Revise the statement (b) (4)
- 5. Full Prescribing Information: Section 2.3

Add the statement “The Intermezzo dose for men can be decreased from 3.5 mg to 1.75 mg” to immediately follow “Dosage adjustments of CNS depressant drugs...” Section 5.1 refers to the dosage adjustment of Intermezzo, but this information should be clearly stated in the Dosage and Administration section.

If you have further questions or need clarifications, please contact Laurie Kelley, project manager, at 301-796-5068.

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/s/  
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JULIE M VILLANUEVA  
10/27/2011

CAROL A HOLQUIST on behalf of IRENE Z CHAN  
11/02/2011

CAROL A HOLQUIST  
11/02/2011

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Promotion**

**\*\*\*\*Pre-decisional Agency Information\*\*\*\***

## Memorandum

**Date:** October 26, 2011

**To:** Cathleen Michaloski, BSN, MPH  
Senior Regulatory Project Manager  
Division of Neurology Products (DNP)

**From:** Quynh-Van Tran, PharmD, BCPP  
Regulatory Review Officer  
Office of Prescription Drug Promotion, Division of Professional  
Promotion [formerly known as Division of Drug Marketing,  
Advertising, and Communications (DDMAC)]

**Subject:** OPDP Comments on draft Prescribing Information (PI) for  
Intermezzo® (zolpidem tartrate sublingual tablets)

NDA 022328

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This consult is in response to DNP's request for DDMAC's review of the proposed PI for Intermezzo® (zolpidem tartrate sublingual tablets). We appreciate the opportunity to provide comments on the PI.

Please see attached PI with my comments incorporated therein. If you have any questions, please contact Quynh-Van Tran, (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

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QUYNH-VAN TRAN  
10/28/2011

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk  
Management**

**PATIENT LABELING REVIEW**

Date: October 28, 2011

To: Russell Katz, M.D., Director  
**Division of Neurology Products (DNP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Melissa Hulett, MSBA, BSN, RN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management**

From: Robin Duer, MBA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Medication Guide,  
Instructions for Use)

Drug Name: Intermezzo (zolpidem tartrate sublingual tablet)

Application  
Type/Number: NDA 22-328

Applicant: Transcept Pharmaceuticals, Inc.

OSE RCM #: 2011-3729

## 1 INTRODUCTION

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for Intermezzo (zolpidem tartrate sublingual tablet).

This new 505 (b)(2) drug application (NDA) was originally submitted on September 30, 2008 and is indicated for the treatment of insomnia when middle-of-the-night awakening is followed by difficulty returning to sleep. Ambien (zolpidem tartrate), NDA 19-908 is the reference listed drug for Intermezzo.

The Agency issued two Complete Response (CR) letters for Intermezzo, one on October 28, 2009 and one on July 14, 2011. The Agency cited safety concerns with residual morning levels of zolpidem from Intermezzo, particularly if patients dosed themselves with less than 4 hours of bedtime remaining. On September 27, 2011 the Applicant submitted a complete response to the Agency's July 14, 2011 CR letter.

DRISK conferred with DMEPA on October 24, 2011 and a separate DMEPA review of the IFU will be forthcoming.

## 2 MATERIALS REVIEWED

- Intermezzo (zolpidem tartrate sublingual tablet) Medication Guide (MG) submitted on September 27, 2011, revised by the Review Division throughout the review cycle and received by DRISK on October 19, 2011
- Intermezzo (zolpidem tartrate sublingual tablet) Instructions for Use (IFU) submitted on September 27, 2011, revised by the Review Division throughout the review cycle and received by DRISK on October 19, 2011
- Intermezzo (zolpidem tartrate sublingual tablet) Prescribing Information (PI) submitted on September 27, 2011, revised by the Review Division throughout the review cycle and received by DRISK on October 19, 2011
- Ambien (zolpidem tartrate) approved comparator labeling dated April 14, 2010

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the MG and IFU the target reading level is at or below an 8<sup>th</sup> grade level.

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients

with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.
- ensured that the MG and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The MG and IFU are acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG and IFU are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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ROBIN E DUER  
10/28/2011

LASHAWN M GRIFFITHS  
10/28/2011



## Regulatory Project Manager PLR Labeling Review (format)

Date of Review: March 29, 2011  
NDA: 23228  
DRUG: Intermezzo® (zolpidem tartrate, SL)  
1.75 mg and 3.5 mg tablets for sublingual administration  
Indication: for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep

Note: Re-submission following a Complete Response (submitted 1/14/11; due date 7/14/11)

### REVIEW:

The re-submission was reviewed using the PLR tool and the new checklist and MaPP (in draft) provided by SEALD. A brief meeting was held on 3/14/11 with the SEALD reviewer Jun Yan, PharmD and myself.

The following deficiencies were noted in the **Highlights** section:

1. Insert name of drug product in UPPER CASE.
2. Controlled substance IV should be same size font as the text (not superscripted).

Deficiencies in the **Full Prescribing Information** sections:

3. **Contraindications:** Sponsor added new text to the “Contraindications” section: added text underlined:

Observed reactions (b) (4) include anaphylaxis and angioedema.  
(Not consistent with Ambien 19908) This is a clinical review issue.

4. **Adverse Reactions: Clinical Trials:** In the “Clinical trials experience” section, new standard paragraphs have been added by SEALD and these were not included in sponsor label. The statements to be added are:

To begin clinical trials section must have following text:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice”.

If the sponsor inserts a postmarket section, must begin “Postmarket experience” section with following text:

“The following adverse reactions have been identified during post approval use of zolpidem tartrate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure”.

5. **Patient Counseling Information:** Must begin this section with the following statement: “See FDA-approved Medication Guide” (rather than reference at end of paragraph).

Recommendations:

I recommend these deficiencies be communicated to Clinical Reviewer for incorporation with any further changes to PI and then communicated to the sponsor by Day 74 (March 30, 2011).

**Update:** Sponsor has been informed of these edits ( March 29, 2011) and will send in a clean PI within 2 weeks.

**Update:** 10.4.11 Resubmission (9.27.11) contains all the format issues identified in this memo. Not included are the new requirements to standardize the Adverse Reactions text, to remove word “events” and replace with “reactions”. Will notify clinical reviewer.

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Cathleen Michaloski, BSN, MPH  
Regulatory Project Manager  
ODE I DNP

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CATHLEEN B MICHALOSKI  
10/05/2011

**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** 8/8/11

**To:** Cathleen Michaloski, BSN, MPH  
Senior Regulatory Project Manager  
Division of Neurology Products (DNP)

**From:** Quynh-Van Tran, PharmD, BCPP  
Meeta Patel, PharmD  
Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications  
(DDMAC)

**Subject:** NDA 022328  
DDMAC labeling Comments Intermezzo (zolpidem tartrate) 1.75 mg and 3.5 mg sublingual lozenge (sl)

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We acknowledge receipt of February 14, 2011, consult request for the proposed product labeling for Intermezzo® (zolpidem tartrate) sublingual SL (Intermezzo). DDMAC notes that a Complete Response letter was issued on July 14, 2011 and final labeling negotiation was not initiated during the current review cycle. Therefore, DDMAC will provide comments regarding labeling for this application in the next review cycle.

DDMAC requests that DNP submit a new consult request in the next review cycle for Intermezzo. If you have any questions, please contact Quynh-Van Tran at 301-796-0185 or Meeta Patel at 301-796-4284

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QUYNH-VAN TRAN  
08/08/2011

MEETA N PATEL  
08/08/2011

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**REVIEW DEFERRAL MEMO**

**Date:** July 1, 2011

**To:** Russell Katz, M.D., Director  
Division of Neurology Products (DNP)

**Through:** LaShawn Griffiths, MSHS-PH, BSN, RN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management (DRISK)**

Melissa Hulett, MSBA, BSN, RN  
Acting Team Leader, Patient Labeling Reviewer  
**Division of Risk Management**

**From:** Robin Duer, MBA, BSN, RN  
Senior Patient Labeling Reviewer  
**Division of Risk Management**

**Subject:** Review Deferred: Patient Labeling (Medication Guide, Instructions for Use)

**Drug Name(s):** Intermezzo (zolpidem tartrate) Sublingual Tablet

**Application Type/  
Number:** NDA 22-328

**Applicant/Sponsor:** Transcept Pharmaceuticals, Inc.

**OSE RCM #:** 2008-1863 and 2011-1463

This memorandum documents the deferral of our review of Intermezzo (zolpidem tartrate) Sublingual Tablet. On January 14, 2011, the Division of Neurology Products (DNP) requested that the Division of Risk Management (DRISK) review the Patient Labeling (Medication Guide, Instructions for Use) for Intermezzo.

Due to outstanding Clinical deficiencies, DNP plans to issue a Complete Response (CR) letter. Therefore, DRISK defers comment on the Applicant's proposed patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the CR letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/  
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ROBIN E DUER  
07/01/2011

LASHAWN M GRIFFITHS  
07/01/2011



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: April 15, 2011

To: Russell Katz, MD, Director  
Division of Neurology Products

Through: Irene Z. Chan, PharmD, BCPS, Team Leader  
Carol A. Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis (DMEPA)

From: Loretta Holmes, BSN, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Labels, Labeling and Labeling Comprehension Study Review

Drug Name: Intermezzo (Zolpidem Tartrate Sublingual Tablet)

Application Type/Number: NDA 022328

Applicant: Transcept Pharmaceuticals, Inc.

OSE RCM #: 2011-220 and 2011-221

## **1 INTRODUCTION**

This review evaluates the labels, labeling, and labeling comprehension study submitted on January 14, 2011 for Intermezzo (Zolpidem Tartrate Sublingual Tablets). This is a resubmission of the NDA to address the safety concerns raised in the Complete Response letter dated October 28, 2009.

### **1.1 REGULATORY HISTORY**

DMEPA previously reviewed the labels and labeling of Intermezzo in OSE Review 2008-1770, dated September 3, 2009.

This NDA is a 505(b)(2) application. The Reference Listed Drug is Ambien (Zolpidem Tartrate) Tablets.

Given the fact that Intermezzo is to be taken in the middle of the night, concerns were raised by the Agency that dosing errors such as inadvertent redosing in a single night and inadvertent dosing with less than 4 hours of bedtime remaining could occur, both of which could increase the risk of next day residual effects. The Agency was especially concerned about residual effect on driving ability and performance. In the CR letter dated October 28, 2009, the Agency requested the Applicant address these concerns.

To address the safety concerns raised by the Agency, the Applicant conducted a driving study and developed a four element packaging system that consists of a single unit-dose pouch, dosing time chart, separate single page Patient Instructions for Use, and a dosing time tool; all of which were included in this resubmission.

### **1.2 PRODUCT INFORMATION**

Intermezzo is a hypnotic agent indicated for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep. Intermezzo should only be taken if the patient has four hours of bedtime remaining before being active again. The dose of Intermezzo should be individualized. The recommended dose in adults is 3.5 mg. The total Intermezzo dose should not exceed 3.5 mg per night. The recommended dose of Intermezzo in elderly, debilitated patients or hepatically impaired patients is 1.75 mg. Intermezzo will be available in unit-dose pouches containing a sublingual tablet in a foil blister packaged in cartons containing 30 pouches. The recommended storage is between 20°C to 25°C (68°F to 77°F). Protect from moisture. The blister should not be removed from the pouch until the patient is ready to take the tablet inside.

## **2 METHODS AND MATERIALS**

DMEPA reviewed the labels, labeling and labeling comprehension study, "Evaluation of Patient Materials for Intermezzo," submitted by the Applicant on January 14, 2011.

### **2.1 LABELING COMPREHENSION STUDY**

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the labeling comprehension study "Evaluation of Patient Materials for Intermezzo" submitted by the Applicant on January 14, 2011. When reviewing the study, we focused on identifying areas of weakness in the study design that may have affected the utility of the study results.

## 2.2 LABEL AND LABELING RISK ASSESSMENT

DMEPA uses Failure Mode and Effects Analysis (FMEA) to evaluate the labels and labeling of products. This review summarizes our evaluation of the labels and labeling submitted by the Applicant on January 14, 2011 (see Appendices A through G).

- Foil Blister labels: 1.75 mg and 3.5 mg
- Unit-dose Pouch Labeling
  - Trade, 1.75 mg and 3.5 mg
  - Professional Sample, 3.5 mg
- Carton Labeling
  - Trade, 1.75 mg and 3.5 mg (30-count)
  - Professional Sample, 3.5 mg (1-count)
  - (b) (4)
- Dosing Time Tool (Wheel)
- Insert Labeling (no image)
- Patient Instructions for Use
- Medication Guide (no image)

## 3 RESULTS AND DISCUSSION

The following sections describe the findings and assessment of the labeling comprehension study and the label and labeling review.

### 3.1 LABELING COMPREHENSION STUDY

This study was conducted in order to address the Agency's concerns with inadvertent redosing of Intermezzo in a single night and inadvertent dosing with less than four hours of bedtime remaining; both of which could increase the risk of next day residual effects.

To help address the safety concerns, the Applicant developed a proposed 4-element packaging system which includes a unit-dose pouch, dosing time chart, dose timing tool (wheel), and Patient Instructions for Use (PIU). According to the Applicant, these 4-elements were designed to work together to serve as a reminder system at the actual time of dosing in the middle of the night and provide the necessary situational cues to minimize the need for decision making during the middle of the night.

The goal of the study was to refine and optimize the instructions and tools for understanding and ease of use to ensure they are effective in supporting the safe use of Intermezzo and to ensure the materials are effective in communicating how the two potential dosing errors can be avoided.

The study was designed to assess the extent to which consumers understood the information and then were able to apply it to correctly dose themselves in various hypothetical situations. The study was comprised of a series of evaluations designed to test, refine and optimize the materials and assess patient understanding and application of the 4-element packaging system.

#### Methodology

A total of 74 respondents in four states participated over a four month period in the Developmental and Testing Phases of the research.

## Demographics

The study included respondents who had trouble sleeping through the night, that woke up during the night and had difficulty returning to asleep (at least 2 nights per week) and had more than four hours of bedtime remaining. The Developmental Phase included 33 respondents. The mean age was 45.1 years, 42% were female, 48% had graduated college, 42% had come college and 9% completed high school or vocational/technical school.

The Testing Phase included 41 respondents. The mean age was 51.9 years, 66% were female, 54% had graduated college, 39% had some college and 7% had a high school degree or less.

## Materials Tested

Unit-Dose Pouch, Dosing Time Chart (this time chart is on the unit dose pouch and in the Patient Instructions for Use), Dosing Time Tool (a stand alone dosing wheel), and Patient Instructions for Use (PIU)

## Developmental Phase Methodology

The initial phase (Developmental Phase) of the study included four focus groups with a total of 33 respondents. The focus groups were structured to gather individual feedback. Respondents first read the Patient Instructions for Use and answered self-administered knowledge questions to evaluate their understand of the information provided. They were then asked to examine the wheel, unit-dose pouch, Patient Instructions for Use sheet and the dosing time chart (as part of the pouch and PIU) and answer a series of additional self-administered questions. A seven-point scale was used with endpoints that described unfavorable and favorable ratings.

## Testing Phase Methodology

The second phase was the Testing Phase and it included one-on-one in depth interviews utilizing a formal questionnaire to provide more details, independent and quantifiable responses. A total of 41 respondents participated. The research was designed to assess the extent to which consumers understood the information and then were able to apply it to correctly dose themselves in various hypothetical situations. The study objectives were as follows.

Primary Objectives:

- People should not take more than 1 tablet per night.
- People must have 4 hours of sleep remaining before dosing.

Secondary Objectives:

- People should only place one pouch by the bedside before going to bed.
- People should understand how to use the dosing time chart.
- People should understand how to use the dosing time tool (wheel).
- People should understand the consequences of dosing errors (drug effects may remain in the body longer).

## Results

### Developmental Phase Results

Respondents said the PIU, packaging information and dosing time tool were easy to understand and follow. The research did not identify any major issues, concerns or omissions in the materials. The results of the Developmental Phase indicated the

materials were effective and could be enhanced by making minor refinements to format and layout.

#### Testing Phase

Results from the testing phase demonstrated that at least 98% of the respondents understood the primary objectives and at least 90% understood the secondary objectives.

During the testing phase, the Patient Instructions for Use was modified slightly by adding the “use the Dosing Time Chart” to the end of the first bullet under “during the night before you take Intermezzo” section and two of the questions in the Main Questionnaire were slightly revised to align with the Patient Instructions for Use.

Our evaluation of the overall study design determined it was adequate to assess patient understanding and application of the 4-element packaging system. The results appear to support the premise that patients are able to understand and use the 4-element packaging system correctly. However, we have concerns regarding the study subjects. Fifty-one percent of all the respondents were college graduates, about 41% has some college and about 8% of all respondents completed high school or less. Only one respondent was found to meet the low literacy criteria (8th grade level or lower literacy). Therefore, it is unclear whether lower literacy patients will understand and use the 4-element packaging system correctly based on this study.

### 3.2 LABEL AND LABELING RISK ASSESSMENT

Our evaluation of the labels and labeling identified the following deficiencies:

- The strengths are now well differentiated from one another due to the (b) (4)
- The route of administration is not on the pouch or carton labeling.
- The Medication Guide statement is not prominent on the 30-count carton labeling.
- One of the cautionary statements on the pouch lacks prominence.
- The net quantity statement on the 30-count cartons is not optimally worded for clarity.
- The carton contents information is located on a side panel where it is not readily seen.
- Error-prone abbreviations, symbols and dose designations are used in the insert labeling.
- The sequence and presentation of certain information in the Patient Instructions for Use is not optimal.
- The number of medication guides and Dose Timing Tools (2 of each) included in the 30-count carton may not be enough.

We note the unit dose pouch will contain one foil blister although the Applicant submitted the labels (b) (4)

## 4 CONCLUSIONS AND RECOMMENDATIONS

The labeling comprehension study concluded that patients will be able to understand and correctly use the 4-element packaging system. We do note, however, 51% percent of all the respondents were college graduates, about 41% has some college and about 8% of all respondents completed high school or less. Thus, it is unclear if patients with a lower literacy level will be able to understand and properly use the packaging system. DMEPA defers to the Division of

Risk Management for determination regarding the appropriateness of the literacy level at which the Patient Instructions for Use are written.

Our evaluation noted areas where information on the labels and labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1 *Comments to the Division* for discussion during the review team's label and labeling meetings. Section 4.2 *Comments to the Applicant* contains our recommendations for the container label and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

#### 4.1 COMMENTS TO THE DIVISION

The insert contains strength and dose numerical sequences where the dosage unit does not follow each numerical designation (e.g., 5-20 mg). In these instances, the dash could get overlooked and the strength misinterpreted as 520 mg. Therefore, we recommend that in all such instances the dosage unit follow the numerical strength or dose and the dash be replaced with "to" (e.g., 5 mg to 20 mg). Additionally, revise numerical sequences such as "4, 20, and 100 mg base/kg" to read 4 mg, 20 mg, and 100 mg base/kg".

We also noted the symbol ">" (greater than) is used in conjunction with a dose (i.e., >10 mg) and trailing zeros (e.g., 1.0) are also used when specifying a dose. These are considered error-prone symbols and dose designations and appear on the ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations". As part of a national campaign to reduce medication errors related to error-prone medical abbreviations and dose designations, the FDA agreed not to approve labels and labeling that include the use of error prone abbreviations, symbols or dose designations.

#### 4.2 COMMENTS TO THE APPLICANT

##### A. General Comment

The 30-count cartons contain two Medication Guides and two Dose Timing Tools. Please provide your rationale for determining that this number is sufficient.

##### B. General Comment for all pouch and carton labeling

1. The 1.75 mg and 3.5 mg strengths are not well differentiated from one another because (b) (4) Modify the colors used so the two strengths are well differentiated from one another.
2. The route of administration is not present. Add the route of administration to the pouch and carton labeling.

##### C. Pouches (Trade and Professional Sample, 1.75 mg and 3.5 mg)

The statement "If you do not have at least 4 hours of bedtime remaining, **do not take Intermezzo**" is only partially in bold font. The entire statement is important and therefore we recommend the entire statement be placed in bold print (i.e., "**If you do not have at least 4 hours of bedtime remaining, do not take Intermezzo**").

D. Carton Labeling, Trade, 30-count, 1.75 mg and 3.5 mg

The net quantity statement (b) (4) is not optimally worded. For clarity, revise the statement to read “30 Unit-Dose Pouches, Each Pouch Contains 1 Sublingual Tablet”.

E. Carton Labeling, Professional Sample, 1-count, 3.5 mg

Relocate the “Contents Include” information from the side panel to the principal display panel so that patients and healthcare practitioners can readily see what is contained in the carton.

F. Display Carton Labeling, Professional Sample, (b) (4)

1. The Medication Guide statement is not prominent. Increase the size and prominence of the Medication Guide Statement.
2. According to the statement on the carton, each Professional Sample contains (b) (4). This statement is not consistent with the Professional Sample 1-count carton which states the carton contains “1 Dosing Time Tool”. Revise the statement to read “1 Dosing Time Tool” to ensure consistency with the 1-count carton and other labeling.

G. Patient Instructions for Use

1. Label all figures (e.g., Figure 1 or Figure A) and refer to the figures by letter or number in the text at the end of the corresponding step.
2. In the section “During the night before you take Intermezzo” number the steps sequentially. Follow the instructions “Remove the foil blister” with the instructions “Leave the empty pouch where you can see it. It will help remind you that you already took a dose”, for clarity in the sequencing of steps.

5 Page(s) of Draft Labeling have been Withheld in Full as b4  
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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.**  
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/s/  
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LORETTA HOLMES  
04/15/2011

IRENE Z CHAN  
04/15/2011

CAROL A HOLQUIST  
04/15/2011





**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** April 14, 2011

**To:** Russell Katz, MD, Director  
Division of Neurology Products

**Through:** Michael Klein, PhD, Director  
Controlled Substance Staff

**From:** Stephen Sun, MD, Medical Officer  
Silva Calderon, PhD, Team Leader  
Controlled Substance Staff

**Subject:** **Topic:**  
Abuse Potential Assessment of New Drug Application re-submission  
**Application:**  
NDA 022328: Intermezzo (zolpidem tartrate) sublingual tablet  
IND 069209  
**Proposed Indication:**  
Use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.  
**Dosages:**  
1.75 mg and 3.5mg sublingual tablets  
**Sponsor:**  
Transcept Pharmaceuticals

**Materials reviewed:**

1. CSS Consult (3/25/2008)
2. ABL-001: Abuse liability assessment of zolpidem tartrate sublingual lozenge 1.75 mg and 3.5mg (9/8/2008)
3. NDA Submission: Dependence (5.3.5.4.3, 9/8/2008)
4. NDA Submission: Summary of Abuse Potential Information (1.11.4, 9/8/2008)
5. NDA Submission: Table 1: Listing of clinical studies (2.7.6, 9/8/2008)
6. CSS Consult (10/20/2009)
7. Action memo for NDA 22-328 (10/26/2009)
8. Complete response letter for NDA 22-328 (10/28/09)
9. End-of-Review Meeting Minutes (2/18/2010)
10. Middle of the Night (MOTN) hypnotic use among insured Americans with hypnotic prescriptions, (Protocol #70-1029-001; 11/30/2010)
11. NDA Resubmission (1/5/2011)

## **I. Summary**

### **A. Background**

This memorandum is in response to a follow-up CSS consult dated March 25, 2008 and October 20, 2009 for the Division of Neurology Products (DNP) pertaining to NDA022328 for Intermezzo (zolpidem tartrate) sublingual tablets under development by Transcept Pharmaceuticals. In addition to requesting CSS participation in the internal meeting and industry meetings, the consult involves a review of the submitted New Drug Application materials and the proposed label. Intermezzo was filed as a 505(b)(2) NDA submission utilizing Ambien<sup>®</sup> as the reference listed drug. Zolpidem tartrate is a non-benzodiazepine hypnotic of the imidazopyridine class, which interacts with the gamma-aminobutyric acid (GABA) receptor, and is listed in Schedule IV of the Controlled Substance Act (CSA).

On October 28, 2009, the Sponsor was issued a Complete Response letter requesting additional data to demonstrate that the product can be used in a safe manner. The requested data concern: (1) evidence that driving ability is not unacceptably impaired when zolpidem is taken as directed, (2) whether patients will be able to consistently use zolpidem according to labeling, (3) the risk of inadvertent dosing with less than 4 hours of bedtime remaining, and (4) the risk of inadvertent re-dosing in a single night.

Subsequent development discussions were exchanged between the Sponsor and the FDA. Sponsor resubmitted the materials as a response to issues identified in the CR letter on January 14, 2011.

### **B. Conclusions:**

1. Zolpidem is a Schedule IV substance that requires management and handling according to regulations of the CSA; therefore, all respective institutional and legal requirements for schedule substance management pertain. As with all scheduled drugs, all professional- and patient-level safeguards against misuse, abuse, and diversion, including drug disposal, apply.
2. CSS acknowledges the discussion on the similar bioavailability of Intermezzo's zolpidem and Ambien formulations. The product and the reference are likely to have comparable abuse-related profiles; therefore, the abuse evaluation reference to Ambien may suffice in the pre-approval evaluation.
3. As noted in prior consults, Intermezzo may be less appealing for intentional misuse because of its lower dose, relative to other available formulations of 10mg zolpidem units, and its inclusion of excipients that may demonstrate physical sedimentation in common beverages. Despite these known facts, the Schedule IV active ingredient remains a known drug of intentional misuse. We are unable to

determine whether the fast-acting, “sublingual” profile may change the abuse profile, based upon the available clinical data.

4. Safeguards such as the single-dose packaging may likely deter unintentional misuse stemming from multiple dosing during middle-of-the-night awakenings. The time-dosing chart on the label is a helpful separate tool that the Sponsor should consider potentially useful by people who are not exclusively nocturnal sleepers.
5. Unknown variables that remain are postmarketing issues regarding potential medication errors associated with multiple dosing, residual cognitive effects related to impaired activities upon awakening, and misuse, abuse, and diversion concerns that remain unknown in an outpatient setting. Therefore, product-specific post-marketing pharmacovigilance should be stressed.
6. As noted in a prior consult, Intermezzo formulation has features that may limit its potential malicious use in committing criminal acts.

### **C. Recommendations to Sponsor (via Division):**

1. Provide monitoring of selected postmarketing adverse events in addition to current, mandatory pharmacovigilance requirements. The proposed plan will include maintenance of all adverse events in a centralized safety database with expedited reporting of the “Events of Interest” listed below. Individual case safety reports (ICSRs) that include these events will be submitted to the Agency as expedited reports, 15-day reports, for one (1) year unless a renewal is stated. These Events of Interest based on the latest MedDRA terminology are:

#### Specific Preferred Terms:

- Accident
- Accident at home
- Accident at work
- Accidental death
- Fall
- Road traffic accident
- Drug administered at inappropriate site
- Drug administration error
- Incorrect dose administered
- Incorrect route of drug administration
- Wrong technique in drug usage process
- Intentional drug misuse
- Accidental exposure
- Accidental overdose

- Intentional overdose
  - Multiple drug overdose
  - Multiple drug overdose accidental
  - Multiple drug overdose intentional
  - Overdose
  - Drug abuser
  - Substance abuser
  - Dependence
  - Drug dependence
  - Drug tolerance
  - Drug tolerance decreased
  - Drug tolerance increased
2. In addition to expedited reporting of the above events, a discussion in the quarterly periodic report should provide numbers and trends based upon MSSO's Standardized MedDRA Query (SMQ): "Drug Abuse, Dependence and Withdrawal" and accident related events for the entire period the drug is marketed.
  3. Report relevant data from national abuse databases: Drug Abuse Warning Network (DAWN), and the Toxic Exposure Surveillance System (TESS) report prepared by the American Association of Poison Control Centers (AAPCC), currently the National Poison Data System (NPDS), and any additional product-specific databases that are helpful to understanding the use in real-world conditions.
  4. Highlight all essential safeguards to reinforce the appropriate use of the once-daily dosing of this product and to avoid misuse, e.g. concurrent use with other zolpidem products and/or multiple-dosing due to a perceived "lower dose".
  5. Highlight all precautions against misuse, abuse, and diversion for any materials seen by patients and healthcare professionals.
  6. Highlight all concerns about residual effects to mitigate safety risks associated with operation of equipment and vehicles in labeling and educational materials.
  7. Expand the "dosing time chart" information to those who sleep during the day.
  8. Emphasize the language of "single" daily dose; under-emphasize use of the phrase "taken as needed" as it may be perceived as a multiple prn dosing schedule-type of drug

9. Highlight appropriate warnings to prevent the concomitant use of this drug with other similar hypnotic substances including those that contain zolpidem.

## **II. Review**

### **A. Background (previously identified CSS safety risk information)**

1. Noted from the Division's prior consult, 505(b)(2) NDA submission does not differentiate the abuse potential of Intermezzo and marketed Ambien. Intermezzo doses are 1.75mg and 3.5mg sublingual tablets to be taken during middle-of-the-night awakenings, whereas Ambien is the 10mg tablet taken at the beginning of a sleep cycle.
2. From the prior consult, the Intermezzo formulation has features that may limit its potential malicious use in committing criminal acts.
3. Safety issues that may overlap with the potential consequences of the abuse of this formulation include:
  - Unintentional overdosing due to zolpidem-induced impaired cognition and memory
  - Inappropriate dosing due to self-titration (from false perception of lower dose strength), compared to Ambien strength tablets, for sleep induction
  - Misuse via multiple dosing due to repeated awakenings considering that Intermezzo does not decrease the number or length of subsequent MOTN awakenings.
  - Risk of accidents (home, vehicle and work-related) post-awakening due to residual zolpidem levels
  - Product is used with less than the labeled four hours of remaining sleep time
  - Accidental poisoning by children and other members of household if tablets are left at the bedside unattended and has fast-acting, sublingual route of administration

### **B. Integrated abuse potential assessment**

#### **1. Intentional Misuse**

##### **Survey Study on MOTN Awakenings and Prevalence of Drug Use, Report 70-1029-001 (Kessler et al., 2010)**

Additional information: The survey data collected by Kessler et al. (Kessler et al., 2010: Report 70-1029-001), indicate that many hypnotics that are only approved for bedtime use, particularly zolpidem and eszopiclone, are also currently being taken in the middle of the night by a large number of patients. Despite its focus on the profiles of single-dose use subjects, the survey shows an extrapolated population of approximately 450,000 Americans who use hypnotics more than

once per night (based on the results defined in Table 3, 9% of the 1927 surveyed). Therefore, the risks associated with potential over-medication remain as the studies on potential, residual cognitive impairment issues are based on a single-dose sample and the product is proposed on a one-dose-per-night indication. Notably, essential safeguards should be applied to maintain the once-daily dosing of this product and to avoid combinations with other zolpidem products, e.g. regular Ambien of 10mg immediately before bed, then Intermezzo for “breakthrough” awakening.

## **2. Unintentional Misuse**

### **Highway Driving Study (ZI-18)**

ZI-18 is a single-center, double-blind, randomized, placebo-controlled, four-way crossover study conducted in The Netherlands of healthy adult subjects who are assessed their next-morning driving performance after middle-of-the-night administration of zolpidem tartrate sublingual tablet. The four treatment conditions in the study were:

- (1) zopiclone oral capsule 7.5 mg (ZOP) 9 hours before a highway driving test (to serve as a positive control)
- (2) zolpidem tartrate sublingual tablet 3.5 mg 3 hours before a highway driving test (ZST 3h)
- (3) zolpidem tartrate sublingual tablet 3.5 mg 4 hours before a highway driving test (ZST 4h), and
- (4) matching placebo

DNP is presently reviewing the validity and statistical significance of the results. The analysis by Laska et al. was acknowledged. In short, the clinical significance of the submitted results in a controlled setting, e.g. awaken 45 minutes prior to driving, allowing 3 to 4 hours of sleep post-dose, only a single-dose taken during a single sleep cycle, etc. remain unknown in un-monitored settings. Concerns of using prescription drugs while operating motorized equipment remain a public health issue.

## **3. Updated Four-element Unit Dose Packaging**

After receiving comments from the FDA, the (b) (4) that was initially submitted to the NDA was replaced with a four-element risk management strategy to include: (1) unit-dose pouch packaging to remind patients of prior dosing when drowsy, (2) dosing time instructions on the pouch to help patients understand the latest time they can safely take Intermezzo, (3) Patient Instructions for Use, Medication Guide, and a (4) Dosing Time Chart to encourage appropriate use. These multiple measures would help to minimize medication error. Dosing time charts may also want to include information for those who sleep during the day. Precautions to prevent misuse, abuse, and diversion should also be included in the packaging.

## **4. Evaluation of Use of Updated Packaging**

Summary report of patient evaluations of four-element packaging system suggests that the system is effective in enabling patients to understand the risks of taking more than one tablet per night and the minimum requirement precautions of 4 hours after MOTN dosing (Evaluation of Patient Materials for Intermezzo, Transcept Pharmaceuticals, NDA 22-328; Dec 15, 2010).

#### **5. Updated Proposed Labeling**

A comprehensive review of the proposed label can be commented at a separate labeling review. However, some issues that should be addressed include:

- Proper “Schedule IV” designation in the label and related sections highlighting risks of misuse, abuse, and diversion
- Language of “single” daily dose should be emphasized and “taken as needed” should be under-emphasized as it may be perceived as a multiple prn instruction
- Drug should not be taken in combination with other substances that contain zolpidem

#### **6. Review of Proposed REMS Plan and Materials**

The adequacy of the REMS, Medication Guide, and Patient Information, would be detailed by the respective divisions, the submitted materials presently do not highlight the specific risks of unintentional misuse, e.g. keep away from children, nor describe the risks of misuse, abuse, and diversion as with all controlled substances. The street value of a single dosage unit of Ambien<sup>®</sup> has been documented from \$2 to \$10<sup>1</sup> per dosage unit.

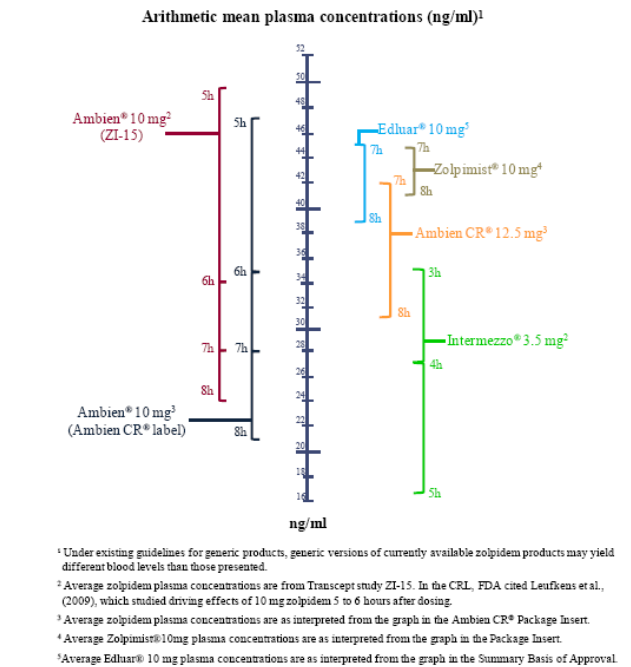
#### **7. Bioavailability Comparisons of Intermezzo with Ambien<sup>®</sup>**

- Cross study comparisons of zolpidem sublingual tablets 3.5 mg blood levels measured at 3 and 4 hours after dosing are mostly below the range of blood levels reported at 7 to 8 hours after dosing of Edluar, Zolpimist and Ambien, which are indicated for sleep onset only. Ambien CR is indicated for sleep onset and sleep maintenance. These data suggest that blood levels at 3 hours after dosing with ZST (off-label use) would not be greater than those anticipated at 7 hours after dosing (on-label) with Ambien CR, Edluar and Zolpimist (see Fig 1).

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<sup>1</sup> Drug Enforcement Administration - National Drug Intelligence Center. National Prescription Drug Threat Assessment. 2009.

**Figure 1: Arithmetic mean pharmacokinetic profiles of Ambien®, Ambien CR®, Zolpimist®, Edluar® and ZST at specified next-morning timepoints after dosing**



- Intermezzo and Ambien show the same Tmax (1.21 h ± 0.85 for Zolpidem sublingual tablets vs. 1.18 h ± 0.86 for Ambien tablets) under fasted conditions. Though a greater absorption of zolpidem from Intermezzo within the first 30 minutes post-dose was observed, both formulations achieve similar Cmax, when the dose is normalized at comparable times post-administration.
- Based on the provided information, the product abuse profile would not likely be different from the reference product.

## 8. Review of Adverse Event Summary Tables (ISS)

Review of their ISS in treatment-emergent AEs related to abuse potential or dependence from 8 clinical studies shows only a modest difference in psychiatric disorders SOC. Nervous system SOC is as expected for a sleep agent and zolpidem is a DEA Schedule IV substance.

System Organ Class Preferred Term	1.0/1.75 MG ZT LOZENGE	3.5 MG ZT LOZENGE	PLACEBO	TOTAL
Number of Subjects	130	436	315	585
Number of Subjects Reporting at least 1 Abuse Potential Adverse Event	8 ( 6.2%)	46 ( 10.6%)	12 ( 3.8%)	59 ( 10.1%)
GASTROINTESTINAL DISORDERS				
NAUSEA	0 ( 0.0%)	10 ( 2.3%)	3 ( 1.0%)	13 ( 2.2%)
VOMITING	0 ( 0.0%)	9 ( 2.1%)	3 ( 1.0%)	12 ( 2.1%)
VOMITING	0 ( 0.0%)	3 ( 0.7%)	0 ( 0.0%)	3 ( 0.5%)
NERVOUS SYSTEM DISORDERS				
SOMNOLENCE	8 ( 6.2%)	39 ( 8.9%)	8 ( 2.5%)	48 ( 8.2%)
DIZZINESS	7 ( 5.4%)	27 ( 6.2%)	5 ( 1.6%)	33 ( 5.6%)
INSOMNIA	2 ( 1.5%)	10 ( 2.3%)	1 ( 0.3%)	13 ( 2.2%)
SEDATION	0 ( 0.0%)	1 ( 0.2%)	0 ( 0.0%)	1 ( 0.2%)
STUPOR	0 ( 0.0%)	1 ( 0.2%)	2 ( 0.6%)	3 ( 0.5%)
STUPOR	0 ( 0.0%)	1 ( 0.2%)	0 ( 0.0%)	1 ( 0.2%)
PSYCHIATRIC DISORDERS				
CONFUSIONAL STATE	0 ( 0.0%)	2 ( 0.5%)	1 ( 0.3%)	3 ( 0.5%)
DISORIENTATION	0 ( 0.0%)	1 ( 0.2%)	0 ( 0.0%)	1 ( 0.2%)
DAYDREAMING	0 ( 0.0%)	1 ( 0.2%)	0 ( 0.0%)	1 ( 0.2%)
DAYDREAMING	0 ( 0.0%)	0 ( 0.0%)	1 ( 0.3%)	1 ( 0.2%)



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/s/  
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STEPHEN W SUN  
04/14/2011

SILVIA N CALDERON  
04/14/2011

MICHAEL KLEIN  
04/14/2011

MEMORANDUM

Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research

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**Date:** October 20, 2009

**To:** Russell Katz, M.D., Director  
Division of Neurology Products

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff

**From:** Silvia Calderon, Ph.D., Pharmacology Team Leader  
Controlled Substance Staff

**Subject:** Abuse potential assessment of Intermezzo (Zolpidem tartrate) sublingual lozenges  
*Indication:* Treatment of insomnia characterized by difficulty returning to sleep after middle-of-the-night (MOTN) awakenings  
*Dosage form and strengths:* Sublingual lozenges of 1.75 mg and 3.5 mg.  
*Submission:* NDA 22-328 (9/30/2008) is located in the DARRTS. The submission includes a section entitled "ABL-001: Abuse Liability Assessment of Zolpidem Tartrate Sublingual Lozenge 1.75 mg and 3.5 mg (9-08-2008)"  
*Materials reviewed:*  
*Modules:* 2.7 Clinical Studies, Section 2.7.2 Summary of Clinical Pharmacological Studies; Section 2.7.4 Summary of Clinical Safety. Appendix B. Report No. TR-013, A comparative study of concentration and appearance of Ambien and Intermezzo in four different beverages. Appendix C. Summary of treatment emergent adverse events by system organ class and MedDRA term. Clinical Pharmacology and Biopharmaceutics Consult (4/5/2009)

**Sponsor:** Transcept Pharmaceuticals Inc.


**- BACKGROUND**

This memorandum summarizes key findings related to the abuse potential assessment of Intermezzo (Zolpidem tartrate) sublingual lozenges by CSS. Intermezzo was filed as a 505(b)(2) NDA submission utilizing Ambien as the reference listed drug. Zolpidem is listed in Schedule IV of the Controlled Substance Act (CSA).

Zolpidem tartrate is a nonbenzodiazepine hypnotic of the imidazopyridine class, which interacts with the gamma-aminobutyric acid (GABA) receptor. Numerous compounds, such as benzodiazepines and barbiturates, with central depressant effects potentiate the actions of GABA at the GABA<sub>A</sub> receptors.

Zolpidem tartrate immediate release 5 mg and 10 mg tablets (Ambien) have been available since 1992 for short term treatment of insomnia. In 2005, Sanofi-Aventis marketed zolpidem tartrate controlled release tablets, 6.25 mg and 12 mg, (Ambien CR).

Transcept's primary objective for developing Intermezzo was to provide a zolpidem formulation with more rapid onset of sleep than that obtained by oral zolpidem so it could be used during MOTN awakening, while maintaining a similar overall safety, efficacy, and abuse liability profile. The Sponsor hypothesizes that most drug from the lozenge is rapidly absorbed through the sublingual mucosa while a lesser amount of the dose is swallowed and absorbed gastrointestinally. The formulation uses a bicarbonate-carbonate buffer system aimed at (b) (4)



The following sections of the Appendix summarize various aspects of the drug product that contribute to assessing its abuse liability.

1. Chemistry
2. Clinical pharmacokinetic and pharmacodynamic studies
3. Solubility and detection of Intermezzo sublingual lozenges in common beverages
4. Abuse and misuse of zolpidem

## CONCLUSIONS

1. The studies to support a 505(b) (2) NDA submission were not designed to differentiate the abuse potential of Intermezzo and Ambien.
2. However, based on currently available information and data in the NDA, CSS concurs that Intermezzo is appropriately scheduled in Schedule IV of the CSA.
3. The Intermezzo formulation has features that may limit its potential malicious use in committing criminal acts.

The abuse potential of zolpidem as well as its amnestic effects<sup>1</sup> in conjunction with rapid dissolution of the tablets and the high solubility of zolpidem tartrate in carbonated drinks, such as Coca Cola and beer, is of concern because it provides a means for the potential misuse of the product in potentially incapacitating a victim by surreptitiously adding the drug to a drink. The addition of intact and crushed Intermezzo tablets to Coca Cola produced an orange froth which stuck to the glass walls. This observed change in the appearance of the drinks after addition of Intermezzo tablets could prevent such criminal use of the drug.

When Intermezzo lozenges were added to beer, an extensive frothing that overflowed the glass was generated, the beer became turbid and particulate matter floated on the top. When crushed Intermezzo lozenges were added to alcohol, the drink became turbid and colored, and sedimentation of the tablets was observed. Upon addition of crushed Intermezzo to water, sediment and turbidity was observed. By comparison, the addition of Ambien tablets to various drinks did not produce the same sort of intense changes in appearance.

4. Intermezzo and Ambien show the same T<sub>max</sub> (1.21 h ± 0.85 for Zolpidem lozenges vs. 1.18 h ± 0.86 for Ambien tablets) under fasted conditions. Though a greater absorption of zolpidem from Intermezzo within the first 30 minutes post-dose was observed, both formulations achieve similar C<sub>max</sub>, when the dose is normalized at comparable times post-administration (see DARRTS, NDA 22-328, Clinical Pharmacology Review, Parepally Jagan Mohan R, July 23, 2009, pages 21-22 and pages 61-68).

5. The new indication for this formulation MOTN awakening raises a number of safety issues that might overlap with the potential consequences of the abuse of this formulation. These factors include:

- The use of the proposed formulation as an add-on medication in the MOTN to Ambien tablets that might have been taken for sleep induction has not been studied.
- Overdosing due to zolpidem-induced impaired cognition and memory

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<sup>1</sup> Anterograde amnesia is seen as an adverse effect of many sedative-hypnotics drugs including benzodiazepines and non-benzodiazepine hypnotics such as zolpidem and zopiclone<sup>1,2,4</sup>. The mechanism of action seems to involve disruption of memory consolidation processes. Due to the fast onset of this action, these drugs are known in forensic medicine to be used to facilitate robbery and sexual-assaults in victims by giving them drinks containing these drugs<sup>1</sup>. Zolpidem related anterograde amnesia is partial or total and starts approximately 30 min after the drug administration and can be seen in up to 50% of patients at 45 min and in 40% patients at 60 min<sup>3</sup>. Zolpidem produces anterograde amnesia in dose-related fashion<sup>4</sup>. Zolpidem was also reported to produce somnambulism such as sleep driving, sleep cooking sleep, sleep shopping followed by amnesia to the event<sup>5</sup>, this number reached 5.1% patients treated for insomnia in one retrospective study<sup>6</sup>.

(<sup>1</sup> Goullé JP and Anger JP. Drug-facilitated robbery or sexual assault: problems associated with amnesia. *Therapeutic Drug Monitoring*. 2004; 26:206-210. <sup>2</sup> Canaday BR..Amnesia possibly associated with zolpidem administration. *Pharmacotherapy* 1996; 16(4):687-9.

<sup>3</sup> Praplan-Pahud J, Forster A, Gamulin Z, Tassonyi E, Sauvanet J.-P. Preoperative sedation before regional anaesthesia. *British Journal of Anaesthesia*. 1990; 64:670-674. <sup>4</sup> Cashman J N, Power SJ, Jones RM. Assessment of a new hypnotic imidazo-pyridine (zolpidem) as oral premedication. *British Journal of Clinical Pharmacology*. 1987; 24:85-92. <sup>5</sup> Dolder CR, Nelson MH. Hypnosedative-induced complex behaviours: incidence, mechanisms and management. *CNS Drugs* 2008; 22(12):1021-1036. <sup>6</sup> Tsai JH, Yang P, Chen CC, Chung W, Tang TC, Wang SY, Liu JK. Zolpidem-induced amnesia and somnambulism: rare occurrences? *European Neuropsychopharmacology*. 2009; (19):74-76.)

- Inappropriate dosing. The lower strength of the lozenges, when compared to the available Ambien strengths, can lead patients to take higher doses than indicated by their physician to make up for the doses of Ambien they might use to take for sleep induction.
- Misuse due to repeated awakenings considering that Intermezzo does not decrease the number or length of subsequent MOTN awakenings. (see DARRTS, NDA 22-328, Cross Discipline Team Leader Review Review, Ronald Farkas, MD, Ph.D., September 3, 2009, pages 6).
- Risk of accidents (home, vehicle and work-related) due to residual zolpidem levels if Intermezzo is used with less than the recommended four hours of remaining sleep time, or if the patients repeat dosing on a subsequent awakening.
- Abuse, misuse or poisoning by children and other members of household if tablets are left at the bedside unattended.

## **RECOMMENDATIONS TO THE DIVISION**

Address the above known serious risks related to the use of the drug. The Sponsor should:

1- Propose and conduct a pharmacoepidemiological study during the post marketing phase to evaluate the safety of the product, with emphasis on overdose in patients already using medications for insomnia, accidental use and poisoning of children, abuse of Intermezzo by members of the household, especially teenagers, and provide frequency of driving, work and home-related accidents which could be related to treatment with Intermezzo.

a- This should include maintenance of active surveillance to capture abuse and misuse of the product and reports of those cases to the Agency as expedited reports whether or not the case as a whole meets the regulatory requirements for a 15-Day Alert report. We view these as serious events.

b.-The study should include a list of MedDRA preferred terms that will capture all events of abuse and misuse of the formulation.

The Agency needs to determine if the above study needs to invoke authorities under Section 505 (o)(3) of FDAAA (post-marketing requirements) or if the study can be required as a post-marketing commitment.

If the proposed study provides a signal that the new formulation is associated with serious events of unintentional overdose, abuse and misuse, it may be appropriate for the Agency to consider additional Risk Evaluation and Mitigation Strategies (REMS), which consists of a Medication Guide, to include a Communication Plan ( letters to healthcare providers about specific risks associated with the formulation) and other Elements to Assure Safe Use (ETASU) such as monitoring the patients using the drug, and to introduce label changes to maintain a positive benefit to risk ratio.

## APPENDIX 1

### I- CHEMISTRY SECTION AND DRUG SOLUBILITY

Chemically, zolpidem tartrate is

(b) (4)

Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol.

The sublingual lozenges are round, uncoated, biconvex, debossed with ZZ on one side and blank on the reverse side. Two strengths of the product will be available, 1.75 mg and 3.5 mg.

The sublingual lozenge size (approximately 8-9 mm in diameter), shape (round) and weight (210 mg) of both strengths are the same. The only difference between both strengths is the color: the 1.75 mg strength sublingual lozenge is yellow, and the 3.5 mg strength sublingual lozenge is beige.

### II- SOLUBILITY AND DETECTION OF INTERMEZZO ZOLPIDEM TARTATE SUBLINGUAL LOZENGES IN COMMON BEVERAGES<sup>2</sup>

The Sponsor conducted a study to determine the solubility and detection of two Intermezzo lozenges (whole and crushed) in water, beer, Coca-Cola. For purposes of comparison, the solubility of two Ambien tablets was determined in the same beverages under the same conditions of the assay. The concentration of the resulting solution and the appearance of the drinks were also evaluated. The Sponsor followed a procedure similar to the one used by Olson et al.<sup>3</sup>

Two 3.5 mg Intermezzo lozenges and two 10 mg Ambien tablets, whole or crushed, were added separately to 300 ml of water, ethanol (Vodka diluted in water to make 12 % v/v ethanol), 330 ml of beer (4.5 % v/v ethanol), and Coca-Cola. Beverages without any added drug served as controls. Samples of one milliliter from the upper (50 ml) layer of each spiked beverage were drawn after 5 min, 10 min, 20 min and 40 min and the concentration of zolpidem tartrate was measured by HPLC (Waters 2685 HPLC system with a Waters 2487 dual wavelength absorbance detector). The amount of drug in 50 mL was calculated. The appearance of the beverages 10 minutes after addition of the drug products was noted.

<sup>2</sup> EDR. NDA 22,328. Appendix B. Report No. TR-013, A comparative study of concentration and appearance of Ambien and Intermezzo in four different beverages.

<sup>3</sup> Olsen V, Gustavsen I, Bramness JG, Hasvold I, Karinen R, Asbjorg S, Christopherson J, Morland J. The concentrations, appearance and taste of nine sedating drugs dissolved in four different beverages. Forensic Science International. 2005;151:171-5

As summarized in **Table 1**, the study showed that the Intermezzo lozenges, either whole or crushed, dissolved best in Coca-Cola. At 10 minutes, the reported concentration of zolpidem tartrate was 5.5 mg/330 mL and 4.6 mg/330 mL respectively. These values indicate that at 10 minutes 66 % to 79 % of zolpidem is dissolved in 330 mL of Coca Cola after the addition of two intact or crushed Intermezzo tablets respectively. The lozenges were less soluble in alcohol and beer and negligibly soluble in water. Similar results were obtained when using Ambien tablets. When added to 330 mL of Coca Cola, at 10 min, only 29 % of zolpidem was solubilized from two intact tablets, whereas 83 % was solubilized from two crushed tablets. The amount of zolpidem solubilized in 330 mL of alcohol from crushed Intermezzo tablets at 5 min corresponded to 35% of zolpidem of the total amount of drug added, whereas at 5 minutes 74 % of zolpidem was extracted from two crushed Ambien tablets in the same volume of alcohol. The same percentage of total amount of drug added (74 %) is extracted from crushed Intermezzo and Ambien tablets in 330 mL of alcohol after 20 min. Intact tablets of Intermezzo and Ambien did not dissolve in alcohol and water.

**Table 1:** Amount of drug in 50 mL expressed in milligrams and as the percentage of total zolpidem tartrate added in various solvents.

<b>Drug in Beverage</b>	<b>Mg of drug in 50 mL 5 min</b>	<b>% of total drug added 5 min in 330 mL drink</b>	<b>Mg of drug in 50 mL 10 min</b>	<b>% of total drug added 10 min in 330 mL drink</b>	<b>Mg of drug in 50 mL 20 min</b>	<b>% of total drug added 20 min in 330 mL drink</b>	<b>Mg of drug in 50 mL 40 min</b>	<b>% of total drug added 40 min in 330 mL drink</b>
Intermezzo in Water (Intact)	0	0	0.058	5.5	0.07	6.6	0.13	12
Intermezzo in Water (Crushed)	0.35	33	0.39	37	0.49	46	0.65	61
Ambien in Water (Intact)	0	0	0	0	0	0	0.02	0.7
Ambien in Water (Crushed)	1.7	56	1.7	56	1.76	58	1.83	60
Intermezzo in Coca Cola (Intact)	0.68	64	0.7	66	0.73	69	0.72	68
Intermezzo in Coca Cola (Crushed)	0.74	70	0.84	79	0.8	75	0.83	78
Ambien in Coca Cola (Intact)	0.28	9	0.88	29	2.16	71	2.84	94
Ambien in Coca Cola (Crushed)	2.41	80	2.51	83	2.66	88	2.63	87
Intermezzo in Beer (Intact)	0.36	34	0.41	39	0.43	41	0.44	42
Intermezzo in Beer (Crushed)	0.27	25	0.30	28	0.34	32	0.49	46
Ambien in Beer (Intact)	0.43	14	1.5	50	2.2	73	2.35	78
Ambien in Beer (Crushed)	0.58	19	0.59	19	1.95	64	2.45	81
Intermezzo in Alcohol (Intact)	0	0	0.05	4.7	0.13	12	0.32	30
Intermezzo in Alcohol (Crushed)	0.37	35	0.62	58	0.78	74	0.83	78
Ambien in Alcohol (Intact)	0	0	0	0	0.02	0.7	0.04	1.3
Ambien in Alcohol (Crushed)	2.2	73	2.16	71	2.25	74	2.16	71



The second part of the study evaluated appearance of four different drinks (water, beer, Coca-Cola and alcohol) at 10 min after the addition of whole and crushed Intermezzo lozenges and Ambien tablets. The most pronounced changes were seen in beer and Coca-Cola. The addition of intact and crushed Intermezzo tablets to Coca Cola produced an orange froth which stuck to the glass walls. When Intermezzo lozenges were added to beer, an extensive frothing that overflowed the glass was observed, the beer became turbid and particulate matter floated on top. When crushed Intermezzo lozenges were added to alcohol, the drink became turbid and colored, and sedimentation of the tablets was observed. Upon addition of crushed Intermezzo to water, sediment and turbidity was observed. Appearance changes of the various drinks were much less pronounced after addition of Ambien tablets; however, changes were noticeable when the tablets were added to alcohol, water and beer.

In conclusion, intact and crushed Intermezzo tablets dissolve well in Coca Cola and beer. Intact Intermezzo and Ambien tablets practically do not dissolve in alcohol and water. Dissolution in water and alcohol is achieved only when the tablets are crushed. Intermezzo lozenges produced a change in physical appearance of beverages. Based on the photos provided by the Sponsor, the appearance changes mediated by Intermezzo were more pronounced than changes caused by Ambien tablets. This observational study seems to indicate that the addition of the drug to common beverages may be detected by individuals. However, the observations are limited to a 10 minute period and no information was provided regarding the appearance of the drinks after a longer time period.

### **III. PHARMACOKINETICS PARAMETERS AS RELATED TO THE ABUSE POTENTIAL EVALUATION OF INTERMEZZO**

Central nervous system (CNS) active drugs with rapid onset of action are associated with greater subjective effects that correlate with a drug's abuse potential as well as psychomotor performance. It is known that the rate of onset and peak of a drug effect correlate with subjective and behavioral pharmacodynamic parameters. De Wit *et al.*<sup>4</sup> showed that higher measures on "euphoria" scales and greater measurements of longer lasting psychomotor impairment are produced by a single dose of diazepam than by the same amount of diazepam dosed at intervals. Though both forms of administration produce similar peak plasma levels, an earlier T<sub>max</sub> was observed for the dose associated with higher liking and psychomotor impairment.

To characterize the rate of absorption, CSS consulted the Office of Clinical Pharmacology, Division of Clinical Pharmacology. CSS requested an evaluation and analysis of the plasma concentrations achieved at earlier times than T<sub>max</sub> after administration of Intermezzo (zolpidem tartrate sublingual lozenges) in comparison to the plasma levels achieved after taking the commercially available Ambien® tablets; an evaluation of the partial AUC (0-T<sub>max</sub>) for both products, and an analysis of how they relate, one to the other. The Division of Clinical Pharmacology concluded that the AUC<sub>0-T<sub>max</sub></sub> was 39% greater for Intermezzo when compared to Ambien. Although, the rate of absorption of this formulation was found to be

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<sup>4</sup> de Wit H, Dudish S, Ambre J. Subjective and behavioral effects of diazepam depend on its rate of onset. *Psychopharmacology* (1993), 112, 324-330)

greater when compared to Ambien tablets as evidenced by a higher  $AUC_{0-T_{max}}$ , both formulations show the same  $T_{max}$  ( $1.21 \text{ h} \pm 0.85$  for Zolpidem lozenges vs.  $1.18 \text{ h} \pm 0.86$  for Ambien tablets) under fasted conditions. As plasma concentrations increase gradually for both formulations, a higher rate of absorption might not be indicative of a higher liking or abuse potential (see DARRTS, NDA 22-328, Clinical Pharmacology Review, Parepally Jagan Mohan R, July 23, 2009, pages 21-22 and pages 61-68).

#### **IV- ABUSE AND MISUSE OF ZOLPIDEM**

The abuse potential of zolpidem had previously been evaluated. The following subsections summarize data from the Drug Abuse Warning Network (DAWN) which contributes to the abuse evaluation of zolpidem as compared to other benzodiazepines, specifically by the number of abuse and misuse emergency department mentions relative to the number of prescriptions.

##### *- Drug Abuse Warning Network (DAWN)*

DAWN is a public health surveillance system that monitors drug-related visits to hospital emergency departments (ED) and drug related deaths reported to DAWN by participating medical examiners and coroners (ME/Cs) to track the impact of drug use, misuse, and abuse in the U.S. The Substance Abuse and Mental Health Administration (SAMHSA) is responsible for DAWN operations. DAWN relies on a national sample of general, non-Federal hospitals operating 24-hour EDs. The sample is national in scope, with oversampling of hospitals in selected metropolitan areas. In each participating hospital, ED medical records are reviewed retrospectively to find the ED visits that are related to recent drug use. All types of drugs- illegal drugs, prescription and over-the-counter (OTC) pharmaceuticals, dietary supplements, and nonpharmaceutical inhalants-are included. Alcohol, when it is the only drug implicated in a visit, is included for patients younger than age 21; alcohol, when it is present in combination with another drug, is included for patients of all ages.

DAWN not only captures ED visits associated with substance abuse/misuse, both intentional and accidental, but includes ED visits related to the use of drugs for legitimate therapeutic purposes.

Eight case types are defined in the new DAWN and each case is assigned into one and only one case type, the first that applies from the following hierarchy: “suicide attempt”, “seeking detox”, “alcohol only (age <21)”, “adverse reaction”, “overmedication”, “malicious poisoning”, “accidental ingestion”, and “other.”

DAWN Live! data 2003-2009, show that the majority of zolpidem related ED visits were associated with the use of higher doses of zolpidem than the prescribed or recommended doses, and with cases of abuse. Under DAWN, these visits are captured under the type of case defined as “Overmedication” and under the type of case identified as “Other”, which captures ED visits associated with recreational use, drug abuse, drug dependence, withdrawal and misuse that can not be classified in any other way. Approximately 38 percent of the zolpidem related ED cases in 2003-2009 were identified as “Overmedication” cases, whereas

15 percent were classified as “Other”. For the same time period, approximately 23 percent of the cases were classified as “Suicide Attempt,” 20 percent were classified as “Adverse Reactions,” and 2 percent represented accidental ingestion.

As reported in DAWN, the nonmedical use of pharmaceuticals captures taking more than the prescribed dose of a prescription pharmaceutical or more than the recommended dose of an OTC pharmaceutical or supplement; taking a pharmaceutical prescribed for another individual; deliberate poisoning with a pharmaceutical by another person; and documented misuse or abuse of a prescription or OTC pharmaceutical or dietary supplement. Nonmedical use of pharmaceuticals may involve pharmaceuticals alone or pharmaceuticals in combination with illicit drugs or alcohol.

DAWN estimates that 536,247 ED visits in 2004, 669,214 ED visits in 2005, 741,425 in 2006 and 855,838 in 2007 involved nonmedical use of prescription or OTC pharmaceuticals or dietary supplements.

Among the pharmaceuticals most frequently implicated in nonmedical use, benzodiazepines as a class increased 52 percent from 2004 to 2007, (from 143,546 to 218,640 estimated visits, respectively). As shown in **Table 2**, the number of estimated visits associated with the nonmedical use of zolpidem increased from 12,792 in 2004 to 18,464 in 2007. For comparison, increases were also reported from 2004 to 2007 of the numbers of estimated ED visits associated with the nonmedical use of benzodiazepines: alprazolam (46,526 ED visits in 2004 vs. 80,313 in 2007), diazepam (15,619 ED visits in 2004 vs. 19,674 in 2007), and lorazepam (17,674 ED visits in 2004 vs. 26,213 in 2007).

For the same period of time, the number of nonmedical ED visits associated with zolpidem rose 44 percent; 73 percent for alprazolam, 26 percent for diazepam and 48 percent for lorazepam. Although ED visits increased for all the benzodiazepines, it is important to note that the number of prescriptions sold for each drug product increased as well. In 2007, over (b) (4) prescriptions for zolpidem were dispensed in the United States [Verispan, Vector One™: National (VONA)]<sup>5</sup>, representing a (b) (4) percent increase of the number of prescriptions dispensed from 2004.

In order to accommodate the differences in availability of each product, we calculated estimates of the nonmedical ED visits per (b) (4) prescriptions sold [Verispan, Vector One™: National (VONA)].<sup>9</sup> As seen in **Table 2**, the rate for ED visits for zolpidem increased from 56 per (b) (4) prescriptions sold in 2004 to 59 per (b) (4) prescriptions sold in 2007. The rate of ED visits per (b) (4) prescriptions sold for zolpidem in 2007 decreased when compared to the same rate calculated for zolpidem in 2006.

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<sup>5</sup> Verispan’s Vector One™: National VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. The Vector One™ database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups.

The number of nonmedical zolpidem related ED visits in DAWN increased 44 percent from 2004 to 2007, whereas the number of dispensed prescriptions increased (b) (4) percent for the same period of time. The number of nonmedical zolpidem related ED cases represents approximately 55 percent of the total zolpidem related cases captured in DAWN. The rate of nonmedical use ED mentions per 100, 000 prescriptions dispensed for zolpidem is lower than that of alprazolam, diazepam and lorazepam for 2004-2007.

**Table 2:** Calculated Rates of Nonmedical ED Visits in DAWN (2004-2007) per (b) (4) Dispensed Prescriptions.

DRUGS	2004	2005	2006	2007
	DAWN TOTAL NONMEDICAL USE ED MENTIONS <sup>1</sup>			
Zolpidem	12,792	14,730	17,257	18,464
Alprazolam	46,526	57,419	65,236	80,313
Diazepam	15,619	18,433	19,936	19,674
Lorazepam	17,674	23,210	23,720	26,213
	PROJECTED PRESCRIPTIONS DISPENSED <sup>2</sup>			
Zolpidem	(b) (4)			
Alprazolam				
Diazepam				
Lorazepam				
	RATES OF NONMEDICAL ED MENTIONS IN DAWN PER (b) (4) PRESCRIPTIONS <sup>3</sup>			
Zolpidem	56	62	65	59
Alprazolam	135	161	168	189
Diazepam	125	145	150	141
Lorazepam	93	120	118	123

<sup>1</sup> Source: SAMHSA, Office of Applied Studies, 2004-2006 DAWN-ED. Nonmedical use cases include the following type of cases: *Overmedication*, *Malicious Poisoning*, and *Other*; <sup>2</sup> Verispan, LLC: Vector One™: National VONA. <sup>3</sup> [DAWN Nonmedical Use ED Mention for specific year X (b) (4)] / Yearly Projected Prescriptions Dispensed

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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.**  
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/s/  
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SILVIA N CALDERON  
10/20/2009

MICHAEL KLEIN  
10/20/2009

### 505(b)(2) ASSESSMENT

Application Information		
NDA # 22328	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Pending (Intermezzo) Established/Proper Name: zolpidem tartrate SL Dosage Form: SL tablets Strengths: 1.75 mg and 3.5 mg oral SL tablets		
Applicant: Transcept Pharma, Inc.		
Date of Receipt: 9/30/08		
PDUFA Goal Date: 10/30/09 3mo exten		Action Goal Date (if different):
Proposed Indication(s): middle of the night (MOTN) 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 ☒

*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 ☒

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

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)	
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99	100

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)	Three Biopharm studies; specific sections PI changed
	Five 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)

This NDA comprises of the following 3 single-dose pharmacokinetic (PK)/ bioequivalence (BE) bridging studies in healthy adult and elderly subjects. Study ZI-15, provides comparative bioavailability information relative to reference Ambien®. Study ZI-14 includes comparative bioavailability of Intermezzo® 1.75 mg and 3.5 mg in elderly and adult cohorts. Study ZI-13 provides a bridging link between IND formulation and final commercial formulation used in different studies. Final commercial formulation was used in most of the studies including pivotal BE, pharmacodynamic, and efficacy studies.

## 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 ☒ 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	<input type="checkbox"/>
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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 ☒ NO ☐





## 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 ☒ 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 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 ☒

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

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

- c. Described in a monograph?

YES ☐ NO ☒

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

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES ☐ NO ☒

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

*(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 tablet and for a new method of use, middle of the night insomnia (MOTN). This is also a new indication – middle of the night insomnia –to be taken prn ( as often as necessary).

*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 ☒

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

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? YES ☐ NO ☐

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.*

Yes NO ☐  
X

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)?

There are 20 generic drugs for zolpidem tartrate .

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;

N/A

YES

- ☐ 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 between Trancept 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):

[Revised 10.16.09 per B.D. Miller](#)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22328	ORIG-1	TRANSCEPT PHARMACEUTICA LS INC	ZOLPIDEM TARTRATE LOZENGE

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/s/

CATHLEEN B MICHALOSKI  
10/16/2009  
b2 assess chgs per BDM





## Memorandum

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### Pre-Decisional Agency Information

**Date:** September 10, 2009

**To:** Cathleen Michaloski  
Regulatory Project Manager  
Division of Neurology Products

**From:** Amy Toscano  
Regulatory Review Officer  
DDMAC

**Subject:** DDMAC comments on Intermezzo® (zolpidem tartrate sublingual tablets)  
PI

---

DDMAC appreciates the opportunity to review the proposed updated PI for Intermezzo (dated 3/2/2009).

Please see attached PI with my comments incorporated therein.

24 Pages of Draft Labeling have been Withheld in Full as b4  
(CCI/TS) immediately following this page

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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.**  
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/s/  
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AMY TOSCANO

09/10/2009

### 505(b)(2) ASSESSMENT

Application Information		
NDA # 22328	NDA Supplement #:S-	Efficacy Supplement Type SE-
Proprietary Name: Pending (Intermezzo) Established/Proper Name: zolpidem tartrate SL Dosage Form: SL tablets Strengths: 1.75 mg and 3.5 mg oral SL tablets		
Applicant: Transcept Pharma, Inc.		
Date of Receipt: 9/30/08		
PDUFA Goal Date: 10/30/09 3mo exten		Action Goal Date (if different):
Proposed Indication(s): middle of the night (MOTN) 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 ☒

*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 ☒

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

INFORMATION PROVIDED VIA RELIANCE (LISTED DRUG OR LITERATURE)	
1	2
3	4
5	6
7	8
9	10
11	12
13	14
15	16
17	18
19	20
21	22
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63	64
65	66
67	68
69	70
71	72
73	74
75	76
77	78
79	80
81	82
83	84
85	86
87	88
89	90
91	92
93	94
95	96
97	98
99	100

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)	Three Biopharm studies; specific sections PI changed
	Five 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)

This NDA comprises of the following 3 single-dose pharmacokinetic (PK)/ bioequivalence (BE) bridging studies in healthy adult and elderly subjects. Study ZI-15, provides comparative bioavailability information relative to reference Ambien®. Study ZI-14 includes comparative bioavailability of Intermezzo® 1.75 mg and 3.5 mg in elderly and adult cohorts. Study ZI-13 provides a bridging link between IND formulation and final commercial formulation used in different studies. Final commercial formulation was used in most of the studies including pivotal BE, pharmacodynamic, and efficacy studies.

## 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 ☒ 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	<input type="checkbox"/>
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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 ☒ NO ☐



## 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 ☒ 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 ☒ 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 ☒

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

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

- c. Described in a monograph?

YES ☐ NO ☒

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

Name of drug(s) described in a monograph:

d. Discontinued from marketing?

YES ☐ NO ☒

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 ☒

*(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 tablet and for a new method of use, middle of the night insomnia (MOTN).*

*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 ☒

*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 ☒

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 ☐ 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 ☒ NO ☐

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?  
YES ☒ 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;  
N/A

YES

- ☐ 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 between Trancept 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):

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22328	ORIG-1	TRANSCEPT PHARMACEUTICA LS INC	ZOLPIDEM TARTRATE LOZENGE

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

/s/

CATHLEEN B MICHALOSKI  
09/08/2009  
b2 assess form



**Department of Health and Human Services**  
**Public Health Service**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**  
**Office of Surveillance and Epidemiology**

Date: September 3, 2009

To: Russell Katz, MD, Director  
Division of Neurology Products

Through: Kristina C. Arnwine, PharmD, Team Leader  
Kellie Taylor, PharmD, MPH, Team Leader  
Denise P. Toyer, PharmD, Deputy Director  
Carol A. Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

From: Loretta Holmes, BSN, PharmD, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Intermezzo (Zolpidem Tartrate) Sublingual Tablets  
1.75 mg and 3.5 mg

Application Type/Number: NDA 22-328

Applicant: Transcept Pharmaceuticals, Inc.

OSE RCM #: 2008-1770

## CONTENTS

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2	METHODS AND MATERIALS .....	3
3	RECOMMENDATIONS .....	3
3.1	Comments to the Division.....	4
3.2	Comments to the Applicant.....	4

## 1 INTRODUCTION

This review is written in response to a request from the Division of Neurology Products for assessment of the proposed labels and labeling of Intermezzo (Zolpidem Tartrate) Sublingual Tablets, NDA 22-328. The container labels, carton and insert labeling were provided for our review and comment.

## 2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the trade (b) (4) labels and carton labeling and the professional sample blister card and carton labeling submitted on the following dates:

- May 12, 2009: Professional sample blister card and trade carton
- May 22, 2009: Trade (b) (4) (back) and professional sample carton
- May 29, 2009: Trade (b) (4) (front)

The Applicant also provided an actual sample of the trade (b) (4) and the professional sample 2-count blister card for our evaluation (see Appendices A through H).

- Trade (1.75 mg and 3.5 mg)
  - (b) (4) Labels (Front and Back), (b) (4)
  - (b) (4)
- Professional Sample (1.75 mg and 3.5 mg)
  - Blister Card, 2-count, Inside and Outside (actual sample)
  - Carton, 5 X 2-count
- (b) (4) package (actual sample)

Additionally, the insert labeling (submitted on March 17, 2009), medication guide and extended container labeling (submitted on July 1, 2009), and the (b) (4) (submitted on July 30, 2009) were reviewed.

## 3 RECOMMENDATIONS

Our evaluation noted areas where information on the blister labels and carton labeling can be improved to minimize the potential for medication errors. We provide comments on the middle-of-the-night dosing concerns expressed by the Division in Section 3.1 *Comments to the Division*. Section 3.2 *Comments to the Applicant* contains our recommendations for the (b) (4) labels and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Laurie Kelley, OSE Project Manager, at 301-796-5068.



### 3.1 COMMENTS TO THE DIVISION

The Division of Neurology Products has concerns that the proposed dosing regimen may lead to medication errors. The concern surrounds the middle-of-the-night dosing regimen and that patients may forget they have taken a dose and, thus, repeat the dose during the night with less than 4 hours of sleep remaining. We agree with the Division and have determined that the

(b) (4)

### 3.2 COMMENTS TO THE APPLICANT

#### A. General Comments for All Labels and Carton Labeling (1.75 mg and 3.5 mg)

1. The colors used to present the 1.75 mg and 3.5 mg strengths use the (b) (4) as well as to display the strength minimizes the effect of color to differentiate the two strengths. Revise the labels and labeling to ensure the two strengths are well differentiated by the use of unique colors that are not present in your trade dress.
2. Increase the prominence of the Medication Guide statement (e.g., use bold print). Refer to 21 CFR 208.24(d). Additionally, the Medication Guide statement should be displayed on the principal display panel of the container labels and carton labeling and revised to read as follows: ‘Dispense the accompanying Medication Guide to each patient’
3. The instructions for how to remove a tablet from the blister may be confused. The terms (b) (4) may not be readily understood by patients. Revise the wording to read: “remove” and “Push tablet through back of blister”, respectively, or similar verbiage.

#### B. Labels and Labeling (3.5 mg)

The 3.5 mg strength labels and labeling have blue print on a faded blue background which makes the print difficult to read. Please revise so that the contrast is improved and the print is easily read.

#### C. Trade (b) (4) Labels, Front and Back, (b) (4)

1. Add a statement: “XX mg per tablet” or “Each tablet contains XX mg” to ensure that healthcare practitioners and patients understand that the strength specified is per each tablet and not per the entire contents of the (b) (4) card.
2. The route of administration and the net quantity statements are combined (i.e., (b) (4)). As currently presented, the statement can be confused as being the dose (b) (4). Separate this sentence into two statements.

3. [REDACTED] (b) (4)

**D. Trade [REDACTED] (b) (4) Labels, Back, [REDACTED] (b) (4)**

The storage instructions are in a too prominent location (central portion of the label). Relocate this information to a less prominent area of the label (e.g., lower portion of the label). This will allow important information such as the route of information and usual dosage statement to be moved up to a more prominent location.

**E. [REDACTED] (b) (4)**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**H. Professional Sample Display Carton Labeling, 5 X 2-count**

1. The statement "Professional Samples..." is not prominent. Increase the prominence of this statement.
2. There is no usual dosage statement. Add a usual dosage statement to the carton labeling.

4 Pages of Draft Labeling have been Withheld in Full as  
b4 (CCI/TS) immediately following this page

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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.**  
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/s/  
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LORETTA HOLMES  
09/03/2009

KELLIE A TAYLOR  
09/03/2009

CAROL A HOLQUIST  
09/03/2009

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

*Memorandum*

---

**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**DATE:** August 27, 2009

**To:** Cathy Michaloski  
Regulatory Project Manager  
Division of Neurology Products

**CC:** Mary Dempsey  
Project Management Officer  
OSE, DRISK

**From:** Sharon Watson, PharmD  
Regulatory Review Officer  
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject:** Drug: Intermezzo (zolpidem tartrate) sublingual tablet  
NDA: 22-328

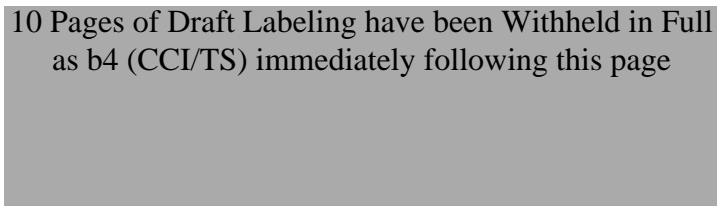
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DDMAC has reviewed the August 14, 2009, DRISK review of the proposed Medication Guide (Med Guide) for Intermezzo from the division's e-room and we offer the following comments. DDMAC's comments are provided directly on the marked up version of this document, attached below.

Thank you for the opportunity to comment on this proposed Med Guide.

If you have any questions or concerns regarding these comments, please contact me.

10 Pages of Draft Labeling have been Withheld in Full  
as b4 (CCI/TS) immediately following this page



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/s/  
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SHARON M WATSON

08/27/2009

# NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # <b>22328</b> BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: <b>Intermezzo</b> Established/Proper Name: <b>Zolpidem Tartrate SL</b> Dosage Form: <b>oral lozenge</b> Strengths: <b>1.75 mg and 3.5 mg</b>		
Applicant: <b>Transcept Pharm Inc.</b> Agent for Applicant (if applicable):		
Date of Application: <b>9/30/08</b> Date of Receipt: <b>9/30/08</b> Date clock started after UN:		
PDUFA Goal Date: <b>July 30, 2009 a three month extension was granted</b>		Action Goal Date (if different): <b>10/30/09</b>
Filing Date: <b>12/11/08</b> Date of Filing Meeting: <b>11/06/08</b>		
Chemical Classification: (1,2,3 etc.) (original NDAs only) <b>N/A 505b2</b>		
Proposed Indication(s): <b>insomnia (middle of the night – MOTN); as needed</b>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file?		
Part 3 Combination Product? <b>No</b>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> 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): <b>IND #69,209</b>	
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>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.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO    <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments: <b>small business waiver</b>	<input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>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).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  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)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO   <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b> Clinical studies done under new method of use (MOTN)</p>	<p><input checked="" type="checkbox"/> YES # years requested: <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>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)).</p> <p>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))?</p> <p><i>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).</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>



4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
If yes, please list below:			
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.			
<b>Format and Content</b>			
Do not check mixed submission if the only electronic component is the content of labeling (COL).  Comments:		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> 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)?  <i>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.</i> Comments:		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
If electronic submission, does it follow the eCTD guidance? <a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
If not, explain (e.g., waiver granted):			

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b> attached to 356h form</p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>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:</p> <p><input type="checkbox"/> legible  <input type="checkbox"/> English (or translated into English)  <input type="checkbox"/> pagination  <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p align="center"><b>Patent Information (NDAs/NDA efficacy supplements only)</b></p>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p align="center"><b>Debarment Certification</b></p>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must</i></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>

<p><b>sign the certification.</b></p> <p><i><b>Note:</b> Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) 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...”</i></p> <p><b>Comments:</b></p>	
<p align="center"><b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b></p>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p align="center"><b>Financial Disclosure</b></p>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p align="center"><b>Pediatrics</b></p>	
<p><b><u>PREA</u></b></p> <p><i>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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li><i>If no, request in 74-day letter.</i></li> <li><b>If yes</b>, 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)</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES (b) (4) spon; DNP may ask for studies. Deferral pending to PeRC.</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<b><u>BPCA (NDAs/NDA efficacy supplements only):</u></b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>  <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?  <b>Comments:</b>	<input checked="" type="checkbox"/> YES sent 5/1/09 <input type="checkbox"/> NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REMS consulted to OSE/DRISK?  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?  <b>Comments:</b> carton and container consult will be sent; yes for all others	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

OTC Labeling	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
Is electronic content of labeling submitted?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	YES <input type="checkbox"/> NO
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input type="checkbox"/> YES <input type="checkbox"/> NO
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?  <b>Comments:</b>	YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting.</i>  <b>Comments:</b>	<input checked="" type="checkbox"/> YES Date(s): 2/6/07 <input type="checkbox"/> NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i>  <b>Comments:</b> inform conference 5/31/06	<input checked="" type="checkbox"/> YES Date(s): 5/1/08 <input type="checkbox"/> NO
Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i>  <b>Comments:</b>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/6/08

NDA/BLA #: 22328

PROPRIETARY/ESTABLISHED NAMES: Intermezzo (zolpidem tartrate SL)

APPLICANT: Transcept Pharma., Inc.

BACKGROUND:

All review disciplines were addressed and there were no issues that would constitute refuse to file. DSI identified clinical sites for inspection. Review is ongoing.

REVIEW TEAM 11/6/08:

Melissa K. Banks, Ph.D. Pharmacologist (DNP)	Division of Neurology Products
Silvia Calderon, Ph.D.	Controlled Substance Staff
Alicja Lerener, Ph.D.	Controlled Substance Staff
Jagan Parepally, Ph.D.	Clinical Pharmacology Reviewer, OCP
Ronald Farkas, MD, Ph.D.	Clinical Team Leader, DNP
Lois M. Freed, Ph.D.	Supervisory Pharmacologist, DNP
Martha Heimann, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Loretta Holmes	OSE Reviewer
Carole Davis, D.O.	Clinical Reviewer, DNP
Kun Jin, Ph.D. Team Leader	Biostatistics
Russell Katz, M.D. Director	DNP
Tristan Massie, Ph.D.	Biostatistics Reviewer
Wendy Wilson, Ph.D.	Chemistry Reviewer
Cathleen Michaloski, MPH	Regulatory Project Manager, DNP
Veneeta Tandon, Ph.D. Team Leader	Clinical Pharmacology, OCP

<b>Electronic Submission comments</b>	<input type="checkbox"/> Not Applicable
<b>List comments:</b>	
<b>CLINICAL; Carole Davis, DO- clinical reviewer</b> <b>Previous reviewers: D. Elizabeth McNeil, MD</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <b>If no, explain:</b>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <b>Comments:</b>  <i>If no, for an original NME or BLA application, include the reason. For example:</i> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>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</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>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?</li> </ul> <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>CLINICAL MICROBIOLOGY</b>  <b>Comments:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>CLINICAL PHARMACOLOGY</b> <b>Jagan Parepally, PhD - reviewer</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>BIOSTATISTICS</b> <b>Tristan Massie PhD - reviewer</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b> <b>Melissa Banks, PhD - reviewer</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b> <b>Martha Heimann, PhD – reviewer</b> <b>Wendy Wilson, PhD - reviewer</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?   <b>If no</b>, was a complete EA submitted?   <b>If EA submitted</b>, consulted to EA officer (OPS)?   <b>Comments:</b> </li> </ul>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?   <b>Comments:</b> </li> </ul>	Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Sterile product?   <b>If yes</b>, was Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>) </li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>FACILITY (BLAs only)</b>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter



<b>Comments:</b>		
<b>REGULATORY PROJECT MANAGEMENT</b>		
<b>Signatory Authority: Russell Katz, MD Director, DNP; RPM - Cathleen Michaloski BSN, MPH</b>  <b>GRMP Timeline Milestones:</b> met  <b>Comments:</b>		
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>		
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:	
X	The application, on its face, appears to be suitable for filing.  <input type="checkbox"/> 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  <input type="checkbox"/> Priority Review	
<b>ACTIONS ITEMS</b>		
<input type="checkbox"/>	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.	
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.	
<input type="checkbox"/>	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.	
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.	
X	Send review issues/no review issues by day 74	
<input type="checkbox"/>	Other	

## **Appendix A (NDA and NDA Supplements only)**

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.

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/s/  
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CATHLEEN B MICHALOSKI

08/25/2009

Reg Filing Memo



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: August 4, 2009

To: Russell Katz, MD, Director  
**Division of Neurology Products**

Through: Jodi Duckhorn, MA, Team Leader  
**Division of Risk Management**

From: Robin Duer, RN, MBA  
Patient Product Information Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Patient Labeling, Medication Guide

Drug Name(s): Intermezzo (zolpidem tartrate) Tablets

Application  
Type/Number: NDA 22-328

Applicant/sponsor: Transcept Pharmaceuticals, Inc.

OSE RCM #: 2008-1863

## **1. INTRODUCTION**

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Intermezzo (zolpidem tartrate) Tablets. Please let us know if DNP would like a meeting to discuss this review or any of or changes prior to sending to the Applicant. DRISK's review of the proposed REMS was provided to DNP under separate cover.

## **2. MATERIAL REVIEWED**

- Draft Intermezzo (zolpidem tartrate) Tablets Prescribing Information (PI) submitted March 17, 2009 and revised by the Review Division throughout the current review cycle.
- Draft Intermezzo (zolpidem tartrate) Tablets Medication Guide (MG) submitted on May 29, 2009.

## **3. RESULTS OF REVIEW**

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

16 Pages of Draft Labeling have been Withheld in Full  
as b4 (CCI/TS) immediately following this page

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/s/  
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ROBIN E DUER  
08/06/2009

JODI M DUCKHORN  
08/06/2009

# MEMORANDUM

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

---

**DATE:** July 22, 2009

**TO:** NDA 22-328  
Division of Neurological Products

**THROUGH:** Suzanne Barone, Ph.D. Team Leader  
Compliance Risk Management and Strategic Problem  
Solving Team  
Division of Compliance Risk Management and  
Surveillance  
Office of Compliance

**FROM:** Kendra Biddick, Consumer Safety Officer  
Compliance Risk Management and Strategic Problem  
Solving Team  
Division of Compliance Risk Management and  
Surveillance  
Office of Compliance

**SUBJECT:** Office of Compliance review and comment on the  
adequacy of the proposed risk evaluation and mitigation  
strategy (REMS) for Intermezzo (zolpidem tartrate  
sublingual tablet, 1.75and 3.5 mg)

This memorandum provides comments and recommendations from the CDER Office of Compliance (OC) on the proposed REMS submitted by Transcept Pharmaceuticals, Inc. for Intermezzo (zolpidem tartrate sublingual tablet, 1.75and 3.5 mg). OC recommendations are listed at the end of the document.

## BACKGROUND

In 2007, the Food and Drug Administration Amendments Act (FDAAA) granted the FDA authority to require risk evaluation and mitigation strategies (REMS) to help ensure that the benefits of a drug outweigh the risks. FDAAA also gave the FDA additional enforcement tools including misbranding charges and civil penalties for sponsors that do not follow requirements of an approved REMS.



Intermezzo (zolpidem tartrate sublingual tablet, 1.75 and 3.5 mg) (NDA 22-328), is indicated for the treatment of insomnia when a middle of the night awakening is followed by difficulty returning to sleep.

1. The goal of the REMS is to effectively communicate to patients the risks involved with Intermezzo (zolpidem tartrate sublingual tablet, 1.75 and 3.5 mg) and how to use Intermezzo safely

The proposed REMS includes a Medication Guide and a timetable for submission of assessments.

## **RECOMMENDATIONS**

Because there has been confusion about the exact due dates for REMS assessments, Compliance suggests the following changes to the Timetable For Assessment of the REMS:

(b) (4)

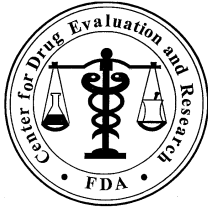


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/s/

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Kendra Biddick  
7/22/2009 03:30:10 PM  
UNKNOWN

Suzanne Barone  
7/22/2009 03:36:01 PM  
UNKNOWN



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: July 17, 2009

To: Russell Katz, MD  
**Division of Neurology Products (DNP)**

Through: Claudia Karwoski, PharmD, Director  
**Division of Risk Management (DRISK)**

Jodi Duckhorn, MA, Team Leader  
**Division of Risk Management**  
Shawna Hutchins, BSN, RN

From: Patient Labeling Reviewer  
**Division of Risk Management**

Subject: DRISK Review of Proposed Risk Evaluation and Mitigation Strategy (REMS)

Drug Name(s): INTERMEZZO® (zolpidem tartrate) sublingual lozenge  
Application Type/Number: NDA 22-328  
Applicant/sponsor: Transcept

OSE RCM #: 2008-1863

## 1. INTRODUCTION

This memorandum is in response to a request by the Division of Neurology Products for the Division of Risk Management (DRISK) to review the proposed Risk Evaluation and Mitigation Strategy (REMS) for INTERMEZZO® (zolpidem tartrate) sublingual lozenge. Please send these comments to the Applicant and request a response within two weeks of receipt. Please let us know if you would like a meeting to discuss these comments before sending to the Applicant. The Medication Guide is being reviewed by DRISK and will be provided under separate cover.

## 2. MATERIAL REVIEWED

- INTERMEZZO® (zolpidem tartrate) sublingual lozenge Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated May 05, 2009
- Proposed INTERMEZZO® (zolpidem tartrate) sublingual lozenge Risk Evaluation and Mitigation Strategy (REMS), submitted July 01, 2009
- INTERMEZZO® (zolpidem tartrate) sublingual lozenge Risk Evaluation and Mitigation Strategy (REMS) Supporting Document submitted July 01, 2009

## 3. CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the elements of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

### Comments to Transcept:



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/s/

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Shawna Hutchins  
7/17/2009 11:24:12 AM  
INTERDISCIPLINARY

Jodi Duckhorn  
7/17/2009 11:31:56 AM  
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski  
7/17/2009 12:32:53 PM  
DRUG SAFETY OFFICE REVIEWER

**M E M O R A N D U M**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** June 5, 2009

**TO:** Cathleen Michaloski, Regulatory Health Project Manager  
Carole Davis, D.O., Medical Officer  
Division of Neurology Drug Products

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

**FROM:** Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch I  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 22-328

**APPLICANT:** Transcept Pharmaceuticals, Inc.

**DRUG:** Sublingual zolpidem tartrate lozenge

**NME:** No

**THERAPEUTIC CLASSIFICATION:** Standard Review (within 7 months)

**INDICATION:** Treatment of insomnia

**CONSULTATION REQUEST DATE:** November 13, 2008

**DIVISION ACTION GOAL DATE:** July 30, 2009

**PDUFA DATE:** July 30, 2009

## I. BACKGROUND:

The sponsor, Transcept Pharmaceuticals, Inc. has submitted a new application using sublingual zolpidem tartrate lozenge for the treatment of patients with insomnia characterized by difficulty to sleep after middle-of-the night (MOTN) awakening.

The review division requested inspection of protocol ZI-06-010 entitled “A randomized, double-blind, placebo-controlled, crossover study of the efficacy and safety of sublingual zolpidem tartrate lozenge in adult patients with insomnia characterized by difficulty returning to sleep after middle-of-night (MOTN) awakening”; and protocol ZI-12 entitled “A randomized, double-blind, placebo-controlled, parallel group study of the efficacy and safety of the zolpidem tartrate sublingual lozenge in adult subjects with insomnia characterized by difficulty returning to sleep after awakening in the middle of the night (MOTN)”. The sponsor submitted results from both protocols in support of NDA 22-328.

The inspection targeted two domestic clinical investigators who enrolled a relatively large number of subjects. Both clinical investigators have expert knowledge in treating insomnia in adults.

## II. RESULTS (by protocol/site):

Name of CI, site #and location	Protocol and # of subjects	Inspection Dates	Final Classification
D. Alan Lankford, Ph.D. Sleep Disorder Center of Georgia 5505 Peachtree Dunwoody, Suite 380 Atlanta, GA 30342 Site # 2 and 18	Protocol ZI-06- 010 16 subjects and ZI-12 14 subjects	1/21-28/09	NAI
Yury Furman, M.D Pacific Sleep Medical Services 6333 Wishire Blvd. Los Angeles, CA 90048 Site # 2	Protocol ZI-12 16 subjects	1/13-15/09	NAI

### Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

1. D. Alan Lankford, Ph.D.  
Sleep Disorder Center of Georgia  
Atlanta, GA 30342

Protocol ZI-12

At this site, a total of 23 subjects were screened, 9 subjects were reported as screen failures, and 14 subjects were randomized and completed the study. Informed consent for all subjects was verified to be signed by subjects prior to enrollment.

Protocol ZI-06-010

At this site, a total of 32 subjects were screened, 16 subjects were reported as screen failures, and 16 subjects were randomized and completed the study. Informed consent for all subjects was verified to be signed by subjects prior to enrollment.

The medical records/source data for all subjects in both protocols were reviewed in depth, including drug accountability, laboratory records, and IRB records, and the source data were compared to case report forms and data listings, including primary efficacy measures and adverse events. Adverse events experienced by subjects were reported to the IRB and the sponsor within the required timeframes. The inspection revealed the investigation was conducted according to the investigational plan. The records reviewed were accurate, and no regulatory violations were found. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

2. Yury Furman, M.D.  
Pacific Sleep Medical Services  
Los Angeles, CA 90048

At this site, a total of 28 subjects were screened, 12 subjects were reported as screen failures, and 16 subjects were randomized and completed the study. Informed consent for all subjects was verified to be signed by subjects prior to enrollment.

The medical records/source data for all subjects were reviewed in depth, including drug accountability records, laboratory records, IRB records, and source documents were compared to data listings, including primary efficacy endpoints and adverse events. Adverse events experienced by subjects were reported to the IRB and the sponsor within the required timeframes.



The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and verifiable. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

#### OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Drs. Lankford and Furman revealed no significant problems that would adversely impact data acceptability.

The data submitted from the inspected sites are acceptable in support of the pending application.

*{ See appended electronic signature page }*

Antoine El-Hage, Ph.D.  
Regulatory Pharmacologist  
Good Clinical Practice Branch I  
Division of Scientific Investigations

#### CONCURRENCE:

*{ See appended electronic signature page }*

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

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/s/

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Antoine El-Hage  
6/11/2009 06:14:05 AM  
PHARMACOLOGIST

Constance Lewin  
6/11/2009 09:27:09 AM  
MEDICAL OFFICER

# NDA/BLA REGULATORY FILING REVIEW

## (Including Memo of Filing Meeting)

Application Information		
NDA # <b>22328</b> BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Intermezzo Established/Proper Name: <b>Zolpidem Tartrate SL</b> Dosage Form: <b>oral lozenge</b> Strengths: <b>1.75 mg and 3.5 mg</b>		
Applicant: <b>Transcept Pharm Inc.</b> Agent for Applicant (if applicable):		
Date of Application: <b>9/30/08</b> Date of Receipt: <b>9/30/08</b> Date clock started after UN:		
PDUFA Goal Date: <b>July 30, 2009</b>		Action Goal Date (if different):
Filing Date: <b>12/11/08</b> Date of Filing Meeting: <b>11/06/08</b>		
Chemical Classification: (1,2,3 etc.) (original NDAs only) <b>N/A 505b2</b>		
Proposed Indication(s): <b>insomnia (middle of the night – MOTN)</b>		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2)
<i>Refer to Appendix A for further information.</i>		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file?		
Part 3 Combination Product? <b>No</b>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> 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): <b>IND #69,209</b>	
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>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.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO    <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments: <b>small business waiver</b>	<input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>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).</i>	
<b>Exclusivity</b>	
Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at:</i> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>  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)]?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO   <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b> Clinical studies done under new method of use (MOTN)</p>	<p><input checked="" type="checkbox"/> YES # years requested: <input type="checkbox"/> NO</p>
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<p><input checked="" type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b></p>	
<p>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> <p>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)).</p> <p>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))?</p> <p><i>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).</i></p>	<p><input type="checkbox"/> Not applicable</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p>

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at:</b> <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a>		<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO	
If yes, please list below:			
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.			
<b>Format and Content</b>			
Do not check mixed submission if the only electronic component is the content of labeling (COL).  Comments:		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> 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)?  <i>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.</i> Comments:		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
If electronic submission, does it follow the eCTD guidance? <a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
If not, explain (e.g., waiver granted):			

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



<p><b>Note:</b> Debarment Certification should use wording in FD&amp;C Act section 306(k)(1) 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...”</p> <p><b>Comments:</b></p>	
<p align="center"><b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b></p>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p align="center"><b>Financial Disclosure</b></p>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><b>Note:</b> Financial disclosure is required for bioequivalence studies that are the basis for approval.</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p align="center"><b>Pediatrics</b></p>	
<p><b><u>PREA</u></b></p> <p><b>Note:</b> 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 &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</p> <p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> <p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li><i>If no, request in 74-day letter.</i></li> <li><b>If yes</b>, 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)</li> </ul> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> (b) (4) spon; DNP may ask for studies. This is pending.</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>



<p><b><u>BPCA</u> (NDAs/NDA efficacy supplements only):</b></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<p align="center"><b>Prescription Labeling</b></p>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not applicable  <input checked="" type="checkbox"/> Package Insert (PI)  <input type="checkbox"/> Patient Package Insert (PPI)  <input type="checkbox"/> Instructions for Use  <input checked="" type="checkbox"/> MedGuide  <input checked="" type="checkbox"/> Carton labels  <input checked="" type="checkbox"/> Immediate container labels  <input type="checkbox"/> Diluent  <input type="checkbox"/> Other (specify)</p>
<p>Is electronic Content of Labeling submitted in SPL format?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> YES  <input checked="" type="checkbox"/> NO</p>
<p>Package insert (PI) submitted in PLR format?</p> <p><b>If no</b>, was a waiver or deferral requested before the application was received or in the submission?  <b>If before</b>, what is the status of the request?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES    sent 5/1/09  <input type="checkbox"/> NO</p>
<p>MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>REMS consulted to OSE/DRISK?</p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>
<p>Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?</p> <p><b>Comments:</b> carton and container consult will be sent; yes for all others</p>	<p><input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES  <input type="checkbox"/> NO</p>

OTC Labeling	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
Is electronic content of labeling submitted?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	YES <input type="checkbox"/> NO
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input type="checkbox"/> YES <input type="checkbox"/> NO
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>  <b>Comments:</b>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?  <b>Comments:</b>	YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? <i>If yes, distribute minutes before filing meeting.</i>  <b>Comments:</b>	<input checked="" type="checkbox"/> YES Date(s): 2/6/07 <input type="checkbox"/> NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <i>If yes, distribute minutes before filing meeting.</i>  <b>Comments:</b> inform conference 5/31/06	<input checked="" type="checkbox"/> YES Date(s): 5/1/08 <input type="checkbox"/> NO
Any Special Protocol Assessment (SPA) agreements? <i>If yes, distribute letter and/or relevant minutes before filing meeting.</i>  <b>Comments:</b>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 11/6/08

NDA/BLA #: 22328

PROPRIETARY/ESTABLISHED NAMES: zolpidem tartrate SL

APPLICANT: Transcept Pharma., Inc.

BACKGROUND:

REVIEW TEAM 11/6/08:

Melissa K. Banks, Ph.D. Pharmacologist (DNP)	Division of Neurology Products
Silvia Calderon, Ph.D.	Controlled Substance Staff
Alicja Lerener, Ph.D.	Controlled Substance Staff
Jagan Parepally, Ph.D.	Clinical Pharmacology Reviewer, OCP
Ronald Farkas, MD, Ph.D.	Clinical Team Leader, DNP
Lois M. Freed, Ph.D.	Supervisory Pharmacologist, DNP
Martha Heimann, Ph.D.	Pharmaceutical Assessment Lead, ONDQA
Loretta Holmes	OSE Reviewer
Carole Davis, D.O.	Clinical Reviewer, DNP
Kun Jin, Ph.D. Team Leader	Biostatistics
Russell Katz, M.D. Director	DNP
Tristan Massie, Ph.D.	Biostatistics Reviewer
Wendy Wilson, Ph.D.	Chemistry Reviewer
Cathleen Michaloski, MPH	Regulatory Project Manager, DNP
Veneeta Tandon, Ph.D. Team Leader	Clinical Pharmacology, OCP

<b>Electronic Submission comments</b>	<input type="checkbox"/> Not Applicable
<b>List comments:</b>	
<b>CLINICAL; Carole Davis, DO- clinical reviewer</b>	<input type="checkbox"/> Not Applicable

<p><b>Previous reviewers: D. Elizabeth McNeil, MD, Carole Davis, DO</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical study site(s) inspections(s) needed?</p> <p><b>If no, explain:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>• Advisory Committee Meeting needed?</p> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>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</i></li> </ul>	<p><input type="checkbox"/> YES</p> <p>Date if known:</p> <p><input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> To be determined</p> <p>Reason:</p>
<p>• 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?</p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Jagan Parepally, PhD - reviewer</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical pharmacology study site(s) inspections(s) needed?</p>	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>

<b>BIostatistics</b> <b>Tristan Massie PhD - reviewer</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Nonclinical</b> <b>(Pharmacology/Toxicology)</b> <b>Melissa Banks, PhD - reviewer</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>Product Quality (CMC)</b> <b>Martha Heimann, PhD – reviewer</b> <b>Wendy Wilson, PhD - reviewer</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> </ul> <ul style="list-style-type: none"> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Sterile product?</li> </ul> <p><b>If yes</b>, was Microbiology Team consulted for validation of sterilization? (<b>NDAs/NDA supplements only</b>)</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>FACILITY (BLAs only)</b>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:		<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>		
<b>Signatory Authority: Russell Katz, MD Director, DNP; RPM -Cathleen Michaloski BSN, MPH</b>  <b>GRMP Timeline Milestones: met</b>  Comments:		
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>		
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:	
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review	
<b>ACTIONS ITEMS</b>		
<input type="checkbox"/>	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.	
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.	
<input type="checkbox"/>	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.	
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.	
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74	
<input type="checkbox"/>	Other	

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 OND ADRA or OND IO.



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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.**  
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/s/

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Cathleen Michaloski  
5/12/2009 03:30:43 PM  
CSO

Cathleen Michaloski  
5/12/2009 03:31:12 PM  
CSO

## STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	2009.002.A.00012
APPLICATION NUMBER	NDA 22,328
LETTER DATE/SUBMISSION NUMBER	September 30, 2008
DATE OF CONSULT REQUEST	February 9, 2009
REVIEW DIVISION	Division of Neurology Products
MEDICAL REVIEWER	Carole Davis
REVIEW DIVISION PM	Cathleen Michaloski
SEALD REVIEWER(S)	Ann Marie Trentacosti
REVIEW COMPLETION DATE	April 2, 2009
ESTABLISHED NAME	Zolpidem tartrate sublingual lozenge
PROPOSED TRADE NAME	Intermezzo
APPLICANT	Transcept Pharmaceuticals, Inc.
ENDPOINT(S) CONCEPT(S)	Sleepiness/Alertness; Insomnia Severity
INSTRUMENT(S)	VAS Rating of Alertness; Morning Sleep Questionnaire; Insomnia Severity Index
INDICATION	Treatment of Insomnia When a Middle of the Night Awakening is Followed by Difficulty Returning to Sleep

### 1 EXECUTIVE SUMMARY

This Study Endpoints and Label Development (SEALD) review is provided as a response to a request for consultation by the Division of Neurology Products regarding NDA 22,328 and use of several patient-reported outcome (PRO) instruments in the support of proposed efficacy and safety claims.

The DSM-IV diagnostic criteria for primary insomnia notes that the predominant complaint is difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month.

The sleep disturbance (or associated daytime fatigue) causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.<sup>1</sup>

Based upon this definition, it appears that a treatment benefit in an insomnia clinical trial can be ascertained by showing an improvement in the sleep disturbance (quantity and quality of sleep), as well as an improvement in the distress or impairment resulting from the insomnia.

NDA 22,328 includes safety and efficacy data to support the indication of the treatment of insomnia when middle of the night awakening is followed by difficulty returning to sleep. The primary endpoint in the pivotal studies (Studies Z1-06-010 and Z1-12) was the latency to return to sleep or persistent sleep after middle of the night awakenings. Both of these endpoints would be useful in ascertaining a clinical improvement in sleep quantity. Correlation of these endpoints with a global assessment of sleep quality would be useful in interpreting the data and understanding from the patient's perspective if the increase in sleep quantity was associated with an overall improvement of quality of sleep as well.

Several patient reported outcome (PRO) instruments were included in Studies Z1-06-010 and Z1-12 in order to evaluate the concepts of next day functioning and next day residual effects of study drug. However, none of these instruments were adequate assessments of either concept.

Next day functioning, is a complex concept which, based on the DSM-IV insomnia criteria, would need to include specific subconcepts and items to show improvement in the distress or impairment resulting from the insomnia. An instrument that assesses next day functioning would most likely be a daily questionnaire that queries patients about their signs and symptoms over the past day; such as important components of physical/mental functioning (e.g. physical endurance, driving ability and reading) and psychological functioning or distress (e.g. irritability).

The VAS Rating of Alertness and Morning Sleep Questionnaire were similar single item questions included as endpoints in Studies Z1-06-010 and Z1-12, respectively. The items asked patients to rate their sleepiness/alertness within 30 minutes of arising in the morning. The instruments included antonymous response options of very sleepy to wide awake and alert.

In addition to the sleepiness/alertness measures, the pivotal studies included other single item measures such as "refreshed sleep" and "ability to function", which were also assessed within 30 minutes of arising.

## STUDY ENDPOINT REVIEW

Information has not been submitted to support the development and content validity of any of these instruments. It is unclear how patients interpret the questions and responses and therefore, how to interpret the data. As single items, these instruments cannot measure or include all of the clinically important aspects of next day functioning and since assessments were obtained 30 minutes after awakening, the instruments cannot effectively measure functioning throughout the remainder of the day. The instruments are not adequate assessments of the clinically significant distress or impairment in social, occupational, or other important areas of functioning, as defined by the DSM-IV and would therefore not adequately support efficacy claims.

As noted above, several PRO instruments, including the VAS Rating of Alertness and Morning Sleep Questionnaire, were also included as measures of next day residual effects (safety endpoints) in the zolpidem clinical studies. The concept of next day residual effects is complex and includes many other subconcepts, such as dizziness that are not captured by these instruments. In addition, comparing mean instrument scores between treatment groups does not identify the most severe events or impact of symptoms. Therefore, the instruments are not adequate measures of safety as posed, for several reasons, but most importantly, because the single item measures do not effectively capture all of the clinically important safety concerns.

## 2 ENDPOINT REVIEW

In this submission, Transcept is seeking an indication through a 505(b) (2) NDA application, of a low-dose zolpidem tartrate sublingual lozenge (1.75 mg and 3.5 mg) for the as-needed treatment of insomnia characterized by difficulty returning to sleep after awakening in the middle of the night. The zolpidem tartrate sublingual lozenge contains the same active ingredient as Ambien but with a 65% lower dose.

The pivotal study reports, which are included in this NDA and pertinent to this review, are Studies Z1-06-010 and Z1-12. Both studies are summarized in the Protocol and Analysis Plan of this review.

SEALD had been requested to review the sleepiness/alertness instruments, Insomnia Severity Index (ISI) and outcome data relevant to these instruments.

### 2.1 Instruments

#### **Treatment Morning Sleep Questionnaire (TMSQ):**

In Study Z1-06-010, the Treatment Morning Questionnaire (See Appendix for a copy of the instrument) was completed by patients 30 minutes after awakening (4.5 hours after the 2<sup>nd</sup> lights-out). In addition to questions about sleep quantity, the instrument includes items concerning the quality of sleep, (b) (4); with response options of poor, fair, good, and excellent.

An analysis of variance and in some cases analysis of covariance was used to analyze the data from the TMSQ in Study Z1-06-010. As noted in the Study Z1-06-010 report, refreshed sleep and ability to function were considered as both efficacy and safety endpoints, which were used as indices of residual sedation.

## STUDY ENDPOINT REVIEW

The level of refreshed sleep and ability to function items from the TMSQ were included as exploratory endpoints in Study Z1-06-010. Based upon the data from Study Z1-06-010, the sponsor proposes labeling claims concerning the improvement of sleep quality and next day function. (See Proposed Labeling section of this review).

*Comments: The TMSQ is comprised of a listing of individual items that does not include a conceptual framework (a diagram that specifies the concepts measured by the scores produced by the instrument and the relationships between items and those concepts measured by an instrument). It is not evident from a review of the instrument itself that the instrument measures a specific concept.*

*Sleep quality is a global assessment of the patient's overall sleep experience and can be useful in describing the patient's immediate sleep experience upon awakening. Sleep quality may be useful as a correlate of sleep quantity in order to define an improved sleep experience for the patient.*

(b) (4)

### **Residual sedation/alertness: VAS Rating of Alertness**

Residual sedation/alertness was assessed as a safety assessment by both the Digital Symbol Substitution Test (DSST) and VAS Rating of Alertness in mornings in Study Z1-06-010. As noted by the sponsor, the DSST is interpreted to measure complex pharmacodynamic activity, short-term memory, and fine motor control. Outcome measures are number of correct substitution during a defined time period (usually 90 seconds or 3 minutes)

The VAS Rating of Alertness instrument consists of a single item in which patients are asked to score the following question:

## STUDY ENDPOINT REVIEW

“How alert do you feel right now?” On a 100 mm VAS, a score of 0 indicates “very sleepy” and a score of 100 indicate “wide awake and alert”.

The response is recorded as the length of the VAS marked.

The VAS Rating of Alertness was completed by patients at the end of the second 4-hour PSG sleeping period, 30 minutes after the patient was awakened.

Evaluation of sedation variables was based on the means of the observations from each treatment period. When the value of 1 night was missing, the value for the other night was used. If both nights were missing, then the observation for the treatment period was set to missing. Mean residual sedation variables were analyzed using ANCOVA.

Based upon the data from Study Z1-06-010, the sponsor proposes labeling claims concerning the next day residual effects as measured by DSST and the VAS sleepiness/alertness scale. The information appears in both the description of Study Z1-06-010 and in the section “Studies pertinent to safety concerns for sedative-hypnotic drugs/Next-Day residual effects”. (See Proposed Labeling section of this review).

*Comments: The VAS Rating of Alertness is not an adequate measure of the “next day residual effects” of treatment (b) (4) Our concerns can be exemplified by the following:*

- *The “next day residual effects” of treatment is a complex concept that includes not only sleepiness, but other concepts, such as dizziness, lightheadedness, and lethargy. The VAS Rating of Alertness is not an adequate measure of this complex concept.*
- *The sponsor has not provided any information concerning the development and validation of the instrument, including score interpretation, to justify this instrument as an adequate measure of sleepiness. It is unclear how to interpret the data. For example, how sleepy or awake are patients when they record a 40 mm response, and how much does this response differ from a 50mm response?*
- *Comparing mean sleepiness scores between treatment groups does not provide sufficient information concerning the most severe events or the impact of the events (functioning). Therefore, this analysis is adequate in delineating safety data.*
- *Labeling missing data as “missing” may introduce bias into the data interpretation, since it is unclear how many patients did not respond to the item because they were too sleepy.*

### **Morning Sleep Questionnaire (MSQ):**

The MSQ was administered to patients in Study Z-1-12 to assess the next morning residual effects and residual sedation during nights study medication was taken; during the nights with middle-of-the night awakenings when study medication was not taken; and averaged over all nights during the 4-week treatment period.

## STUDY ENDPOINT REVIEW

For purposes of safety, subjects were evaluated for IVRS morning ratings of sedation/alertness, as addressed via Question 12 of the IVRS: “On a scale of 1 to 9, with 1 being very sleepy and 9 being wide awake and alert, how sleepy do you feel this morning?” (1 = very sleepy to 9 = wide awake and alert).

(b) (4)

(b) (4)

### **Insomnia Severity Index (ISI):**

The ISI was designed as a brief screening measure of insomnia and an outcomes measure for use in treatment research. The scale includes a 2-week recall period and is composed of seven items that measure the severity of sleep onset and maintenance (middle and early morning awakening) difficulties, satisfaction with current sleep pattern, interference with daily functioning, appearance of impairment attributed to sleep problems, and the degree of concern caused by insomnia.

The ISI (which is a general insomnia questionnaire and not a specific middle-of-the-night awakening questionnaire) was administered at baseline (i.e., the end of the 2-week single-blind screening period [Visit 2]), at Treatment Day 14 (Visit 3), and Treatment Day 28 (Visit 4), or at

## STUDY ENDPOINT REVIEW

the end of treatment if the subject discontinued the study prior to Day 28. It included the following questions in order to evaluate the prior 2 weeks and was scored as shown

The ISI were originally delineated as a secondary endpoint in Study Z1-12. However, Protocol Amendment #2 changed this endpoint from a secondary to an exploratory.

*Comments: The sponsor has not provided any information to support the development or validation of the ISI. However, at face value, the instrument is not an adequate measure of insomnia severity as posed, due to the following:*

- *As a measure of general insomnia, the ISI is not specific for the target population of patients and includes items (e.g. difficulty falling asleep) which are not appropriate for the target population of patients with insomnia due to middle of the night awakenings.*
- *Since a conceptual framework has not been included, it is unclear how each item's score contributes to the overall score and measure of the concept of interest.*
- *The instrument includes an item pertaining to "quality of life". Quality of life is a general concept that implies an evaluation of the effect of all aspects of life on general well-being. Because this term implies the evaluation of nonhealth –related aspects of life (e.g. economic status) it is not an appropriate measure of a treatment benefit and support of labeling claims.*
- *The ISI is not an adequate measure of "daily functioning". "Daily functioning" is a complex concept that cannot be measured by a single item. In addition, the ISI was developed as a measure of overall insomnia and not a measure of each individual subconcept or item which comprise the instrument.*
- *It is unclear if patients can effectively recall their sleep over a 2-week period of time.*

## 2.2 Proposed Labeling

The following section of the proposed Zolpidem label includes reference to the PRO instruments discussed above.



## STUDY ENDPOINT REVIEW

### Section 14.1 Clinical Studies/Controlled Trials Supporting Safety and Efficacy



### 2.3 Protocol and Analysis Plan

NDA 22,328 includes the study reports from two pivotal studies, which are pertinent to this review: Study Z1-06-010, a sleep laboratory study that analyzed objective and subjective outcomes, and Study Z1-12, an outpatient study which analyzed subjective outcomes. The following is a brief description of both studies.

#### **Study Z1-06-010:**

Title: A Randomized, Double-blind, Daytime, 4-way Crossover Study to Evaluate the Pharmacokinetics, Dose Proportionality, Pharmacodynamics, Safety and Tolerability of Three Doses of Sublingual Zolpidem Tartrate Lozenges compared to Placebo in Normal Healthy Volunteers

Study Location: United States

Study Design: This was a multi-center, randomized, double blind, placebo-controlled, 3-period crossover polysomnography (PSG) sleep laboratory efficacy and safety study.

## STUDY ENDPOINT REVIEW

Eligible patients with a history of insomnia as defined by the DSM-IV-TR criteria with a history of middle- of-the night (MOTN) awakenings for at least 4 weeks were enrolled and randomly assigned to one fixed treatment sequence consisting of 3 periods in accordance with a predetermined randomization schedule, whereby patients received zolpidem tartrate lozenge 1.75 mg or zolpidem tartrate lozenge 3.5 mg or placebo during each treatment period. In each treatment period, double-blind study drug was administered after a scheduled MOTN awakening for 2 consecutive nights. Patients were awakened 4 hours after initial lights-out, received study drug, completed a MOTN Awakening Questionnaire (a tool to keep patients awake doing a standardized mental concentration task for a full 30 minutes) , and were kept awake for 30 minutes before returning to bed to sleep for 4 more hours.

PSG was recorded for a total of 8 hours, with a 30-minute interruption in the PSG recording during the scheduled MOTN awakening. At the end of the second 4-hour PSG sleeping period, patients were awakened. Following toilet and dress (30 minutes), they completed a Treatment Morning Sleep Questionnaire (TMSQ) followed by the Digit Symbol Substitution Test (DSST) and Visual Analog Scale for sedation/alertness (VAS) at 4.5 hours after the second lights-out.

### Efficacy Endpoints:

The primary efficacy endpoint was the average latency to persistent sleep after MOTN awakening: ( $LPS_{MOTN}$ ) zolpidem tartrate lozenge 3.5 mg versus placebo.

### Secondary efficacy endpoints included:

- Average Total Sleep Time (TST): zolpidem tartrate lozenge 3.5 mg versus placebo
- Average Sleep Efficiency (SE): zolpidem tartrate lozenge 3.5 mg versus placebo
- Sleep Quality Rating: zolpidem tartrate lozenge 3.5 mg versus placebo (from TMSQ)
- Average Sleep Onset Latency (SOL): zolpidem tartrate lozenge 3.5 mg versus placebo
- Average Subjective TST: zolpidem tartrate lozenge 3.5 mg versus placebo (from TMSQ)
- Average  $LPS_{MOTN}$  zolpidem tartrate lozenge 1.75 mg versus placebo
- Comparison of zolpidem tartrate lozenge between the 1.75 mg and the 3.5 mg doses was considered secondary

### Exploratory efficacy endpoints included:

- Average TST, average SE, Sleep Quality, average SOL, and average subjective TST after MOTN awakening for zolpidem tartrate lozenge 1.75 mg compared to placebo
- Average Number of Awakenings (NAW) after MOTN awakening for zolpidem tartrate lozenge 3.5 mg compared to placebo and zolpidem tartrate lozenge 1.75 mg compared to placebo
- Average Wake Time After Sleep Onset (WASO) based on PSG for zolpidem tartrate lozenge 3.5 mg compared to placebo and zolpidem tartrate lozenge 1.75 mg compared to placebo
- Average Total Sleep Time (TST) during hours 1, 2, 3 and 4, and also during combined hours 1 and 2 and combined hours 3 and 4 based on PSG, for zolpidem tartrate lozenge 3.5 mg compared to placebo and zolpidem tartrate lozenge 1.75 mg compared to placebo
- Level of Refreshed Sleep and Ability to Function ratings for 3.5 mg compared to placebo and 1.75 mg compared to placebo (from TMSQ)

## STUDY ENDPOINT REVIEW

### Safety endpoints included:

- Residual next-morning sedation, assessed by a 90-second DSST and VAS performed 30 minutes after awakening in the morning
- Vital signs (oral temperature, respiration, sitting blood pressure, and heart rate) at screening visit, at PSG screening visit, at pre-dose both days in each treatment period of the study, and prior to discharge at the end of each treatment period
- Physical examination at screening visit and at end of study
- Oral cavity examination for buccal irritation at pre-dose, at the 2-minute time point after study drug dissolution, and at discharge on each treatment morning
- Adverse events (AEs) recorded continuously throughout the study
- Clinical laboratory values (chemistry, hematology, and urinalysis) at screening and at end of study

### Statistical Analyses:

The primary efficacy analysis was between zolpidem tartrate lozenge 3.5 mg and placebo. Comparisons among secondary efficacy endpoints were analyzed in a hierarchical fashion; i.e. analysis of a secondary endpoint was undertaken only if a statistically significant treatment effect was found in the analysis of the preceding variable.

Categorical morning sleep questionnaire ratings (frequency counts) for Sleep Quality, Level of Refreshed Sleep, and Ability to Function were summarized at baseline and for each treatment within period. The Cochran-Mantel-Haenszel test stratified by period with interval scoring was performed to test treatment effects for categorical variables.

### Study Results (Pertinent to Data from Instruments Reviewed):

#### Sleep Quality, Level of Refreshed Sleep and Ability to Function:

Summary statistics and statistical comparisons of overall self-assessment ratings for Sleep Quality, Ability to Function, and Level of Refreshed Sleep (from the TMSQ) after the three treatment periods. Results are shown in Table 1.

As noted by the sponsor, compared to placebo, self assessment of Sleep Quality was significantly improved by zolpidem tartrate lozenge 3.5 mg ( $P < 0.001$ ) but was not significantly different from placebo rating after the zolpidem tartrate lozenge 1.75 mg dose ( $P = 0.116$ ). Post-hoc analyses demonstrated that the difference between doses was also statistically significant ( $P = 0.018$ ). Level of Refreshed Sleep was also significantly improved after zolpidem tartrate lozenge 3.5 mg ( $P < 0.001$ ) and 1.75 mg ( $P = 0.017$ ). Similarly, self-assessment of Ability to Function was significantly improved after zolpidem tartrate lozenge 3.5 mg ( $P = 0.009$ ) and zolpidem tartrate lozenge 1.75 mg ( $P = 0.024$ ), compared to placebo. However, analyses indicated there was no significant difference between doses with regard to self-assessment of Level of Refreshed Sleep or Ability to Function.

## STUDY ENDPOINT REVIEW

**Table 1. Sleep Quality, Level of Refreshed Sleep, and Ability to Function (Morning Sleep Questionnaire)**

	Screening	3.5 mg	1.75 mg	Placebo	P-value <sup>a</sup>
<b>Sleep Quality</b>					
N	82	80	82	81	Overall: < 0.001
Poor	38 (46.3%)	15 (18.8%)	24 (29.3%)	28 (34.6%)	3.5 mg vs. Placebo: < 0.001
Fair	31 (37.8%)	31 (38.8%)	31 (37.8%)	34 (42.0%)	1.75 mg vs. Placebo: 0.116
Good	13 (15.9%)	29 (36.3%)	25 (30.5%)	16 (19.8%)	3.5 mg vs. 1.75 mg: 0.018
Excellent	0 (0.0%)	5 (6.3%)	2 (2.4%)	3 (3.7%)	
<b>Level of Refreshed Sleep</b>					
N	82	80	82	81	Overall: <0.004
Poor	36 (43.9%)	14 (17.5%)	18 (22.0%)	26 (32.1%)	3.5 mg vs. Placebo: < 0.001
Fair	34 (41.5%)	34 (42.5%)	34 (41.5%)	36 (44.4%)	1.75 mg vs. Placebo: 0.017
Good	12 (14.6%)	28 (35.0%)	28 (34.1%)	16 (19.8%)	3.5 mg vs. 1.75 mg: 0.332
Excellent	0 (0.0%)	4 (5.0%)	2 (2.4%)	3 (3.7%)	
<b>Ability to Function</b>					
N	82	80	82	81	Overall: 0.012
Poor	21 (25.6%)	6 (7.5%)	8 (9.8%)	15 (18.5%)	3.5 mg vs. Placebo: 0.009
Fair	35 (42.7%)	33 (41.3%)	35 (42.7%)	34 (42.0%)	1.75 mg vs. Placebo: 0.024
Good	24 (29.3%)	36 (45.0%)	34 (41.5%)	27 (33.3%)	3.5 mg vs. 1.75 mg: 0.355
Excellent	2 (2.4%)	5 (6.3%)	5 (6.1%)	5 (6.2%)	

<sup>a</sup> P-values derived from a repeated measures Cochran-Mantel-Haenszel test with interval scoring. The raw mean score p-value is used.

*Comments: Since “refreshed sleep” and “ability to function” as posed are not adequate measure of a treatment benefit, the data cannot be effectively interpreted. Therefore, although there is a statistically significant difference in score between treatment groups, the clinical meaning of this change is unknown.*

### Residual Sedation and Alertness:

Summary statistics and statistical analysis of the patient scores on the VAS self-assessment of alertness are delineated in Table 2. As noted by the sponsor, there were no statistically significant or clinically significant differences in LS mean scores for either the VAS or the DSST between placebo and zolpidem tartrate lozenge 3.5 mg or zolpidem tartrate lozenge 1.75 mg. The sponsor notes that these data suggest that zolpidem tartrate lozenge 3.5 mg and 1.75 mg do not produce significant residual next-morning sedation or decrements in alertness upon awakening from persistent sleep the morning after dosing.

## STUDY ENDPOINT REVIEW

**Table 2. Morning Visual Analog Scale Self-Assessment of Alertness**

Parameter: VAS	Screening	3.5 mg	1.75 mg	Placebo	P-value
<b>Day 1, Post MOTN Awakening</b>					
N	82	79	81	80	
Mean (SEM)	54.02 ( 2.833)	63.00 ( 2.733)	64.84 ( 2.330)	61.68 ( 2.375)	
Median	51.50	66.00	67.00	63.50	
Min, Max	4.0, 100.0	13.0, 100.0	10.0, 99.0	14.0, 100.0	
<b>Day 2, Post MOTN Awakening</b>					
N	82	80	82	81	
Mean (SEM)	57.29 ( 2.733)	64.48 ( 2.632)	63.40 ( 2.503)	62.99 ( 2.463)	
Median	55.50	68.00	66.00	65.00	
Min, Max	10.0, 98.0	8.0, 99.0	10.0, 100.0	13.0, 100.0	
<b>Mean Days 1 and 2, Post MOTN Awakening</b>					
N	82	80	82	81	
Mean (SEM)	55.66 ( 2.548)	63.56 ( 2.515)	64.25 ( 2.213)	62.35 ( 2.213)	
Median	54.00	66.50	63.25	65.50	
Min, Max	7.5, 97.5	12.0, 98.5	18.5, 99.5	21.5, 99.5	
<b>ANCOVA Analysis<sup>a</sup></b>					
LS Mean		58.86	60.70	59.09	Period: 0.418
95% CI		53.98, 64.18	55.70, 66.15	54.21, 64.41	Sequence: 0.971
					Treatment: 0.626
<b>Comparison to Placebo<sup>b</sup></b>					
Difference in LS Means		1.00	1.03		
95% CI for Difference		0.93, 1.07	0.96, 1.10		
<b>Comparison of zolpidem tartrate lozenge 3.5 mg to 1.75 mg<sup>b</sup></b>					
Difference in LS Means		0.97			
95% CI for Difference		0.91, 1.04			

<sup>a</sup> ANCOVA model with natural logarithmic transformed mean of Day 1 and Day 2 VAS as the response. Sequence, Period, and Treatment as fixed effects; Patient within Sequence as random effect; Average TST pre MOTN Awakening within a period as a covariate and a compound symmetry covariance structure.

<sup>b</sup> Ratio of treatment group LS means was used due to the log transformation of data prior to analysis.

(b) (4)

### Study Z1-12:

**Title:** A Randomized, Double-blind, Placebo-controlled, Crossover Study of the Efficacy and Safety of Trans Oral Zolpidem in Adult Patients with Insomnia Characterized by Difficulty Returning to Sleep after Middle-of-the-Night (MOTN) Awakening

**Study Location:** United States

**Study Design:** This was a multi-center, randomized, double-blind, placebo-controlled, parallel group, outpatient study that utilized middle-of-the-night dosing with study medication (3.5 mg zolpidem tartrate sublingual lozenge or placebo, 1:1 ratio) on an as needed (prn) basis over 28 nights (4 weeks).

The study included a 2-week single-blind screening period prior to the 4-week treatment period. During the 2-week screening period, subjects were instructed to call the IVRS to obtain permission to dose after waking up in the night. At the time of the middle-of-the-night awakening, subjects called the IVRS to answer questions regarding whether they had been awake for at least 10 minutes and still had at least 4 hours remaining in bed, criteria which were required prior to obtaining permission to dose with the placebo sublingual lozenge. If permitted to dose, the subjects immediately took the placebo study medication after the call and returned to

## STUDY ENDPOINT REVIEW

sleep. Each morning (whether or not they had a middle-of-the night awakening or took medication), subjects called the IVRS and responded to questions about their sleep.

During the screening period, subjects were required to demonstrate at least an average of 1 middle-of-the-night awakening per week of  $\geq 60$  minutes in duration, and at least an average of 2 middle-of-the-night awakenings per week of  $\geq 30$  minutes in duration, in which the subject was able to remain in bed for at least 4 hours after the awakening. Eligibility was also determined based on compliance with use of the IVRS, namely that the subject made morning calls to IVRS on at least an average of 5 mornings per week, and demonstrated compliance with the dosing instruction based on whether they had 4 hours remaining in bed.

Eligible subjects were randomized on a 1:1 basis to receive either 3.5 mg zolpidem tartrate sublingual lozenge or placebo lozenge.

At Visits 2 and 3, eligible subjects were provided a 2-week supply of double-blind study medication. Subjects were specifically instructed not to take the study medication at bedtime and to call the IVRS when they had difficulty returning to sleep following a middle-of-the-night awakening of at least 10 minutes in duration and were able to spend 4 additional hours in bed. During the middle-of-the-night IVRS call, subjects responded to questions concerning their middle-of-the-night awakening. After calling the IVRS, if appropriate, subjects self-administered the study medication immediately and attempted to go back to sleep. Subjects were instructed not to take more than one lozenge per night. Each morning (whether or not subjects had middle-of-the-night awakenings or took study medication), the subject called the IVRS. If a subject did not call by a designated time, the IVR system called with an automated reminder message. This automated call gave subjects an option to provide their login and password and place their morning diary call at that time.

After the initial 2 weeks of treatment, subjects returned to the study site for Visit 3 efficacy and safety assessments. Unused study medication was returned. At the end of this visit, subjects received 2 more weeks of drug supply.

The treatment period was 28 days and eligible subjects received a bottle containing 15 lozenges (3.5 mg zolpidem tartrate sublingual lozenge or placebo) at Visit 2 (Randomization or Day 1 of treatment) and at Visit 3 (Day 14 of Treatment Period).

The ISI (which is a general insomnia questionnaire and not a specific middle-of-the-night awakening questionnaire) was administered at baseline (i.e., the end of the 2-week single-blind screening period [Visit 2]), at Treatment Day 14 (Visit 3), and Treatment Day 28 (Visit 4), or at the end of treatment if the subject discontinued the study prior to Day 28.

As part of the exploratory efficacy analysis, the total score from the ISI *without* Question 1, and ISI scores for individual questions were also pre-specified variables. Primary and secondary efficacy end points averaged over each of the 4 treatment weeks, over Treatment Weeks 1 and 2, and over Treatment Weeks 3 and 4 were also exploratory efficacy variables.

## STUDY ENDPOINT REVIEW

### Efficacy Endpoints:

The primary efficacy end point was the latency to sleep onset post MOTN awakening ( $LSO_{MOTN}$ ) averaged over the 4-week period.

### Secondary Endpoints:

The secondary endpoints were also evaluated for the nights on which the subjects took the study medication during the treatment period and are listed by order of hierarchy in which they were analyzed:

- Subjective Total Sleep Time Post-middle-of-the-night Awakening after Dosings ( $sTST_{MOTN}$ ) averaged over the 4-week treatment period
- Subjective Number of Awakenings Post-middle-of-the-night Awakenings ( $sNAW_{MOTN}$ ) averaged over the 4-week treatment period
- Sleep Quality averaged over the 4-week treatment period
- Subjective Wake Time After Sleep Onset Post-middle-of-the-night Awakenings ( $sWASO_{MOTN}$ ) averaged over the 4-week treatment period
- Subjective Number of Awakenings post MOTN awakening ( $sNAW_{MOTN}$ ) averaged over the 4-week treatment period

### Exploratory analyses included:

- Sleep Quality post-middle-of-the-night awakening averaged over the 4-week double-blind treatment period on nights study medication was taken (i.e., assessment of quality of sleep after taking study medication)
- Sleep Quality post-middle-of-the-night awakening averaged over the 4-week double-blind treatment period on nights study medication was not taken (i.e., assessment of quality of sleep for entire night)
- Scores from the Insomnia Severity Index (ISI) at Visit 3 (Treatment Day 14) and at Visit 4 (Day 28/End of Treatment)
- Primary and secondary end points averaged over each of the 4 treatment weeks, averaged over Days 1 to 14 (i.e., Weeks 1 to 2), and averaged over Days 15 to 28 (i.e., Weeks 3 to 4)

### Safety and tolerability endpoints included:

- Change from baseline in residual sedation averaged over the 4 week treatment period
- Vital Signs
- Physical examination results including the oral cavity examinations at each clinic visit
- Adverse events
- Change from baseline in Week 4 chemistry, hematology, and urinalysis results

Morning Sleepiness/Alertness was assessed in three analyses: 1) during nights study medication was taken, 2) during the nights with middle-of-the night awakenings when study medication was not taken, and 3) averaged over all nights during the 4-week treatment period. For each analysis, ANCOVA was used with treatment and pooled site as factors in the model and average baseline Morning Sleepiness/Alertness (during the 2-week screening period) as a covariate. For each analysis, the average baseline Morning Sleepiness/Alertness that was used (as the covariate) was the corresponding baseline for the analysis (i.e., average over all nights during the 2-week

## STUDY ENDPOINT REVIEW

screening, or average over all dosing nights during the 2-week screening period, or average over nights that dosing did not occur over the 2-week screening period).

### Study Results (Pertinent to Data from Instruments Reviewed):

#### Morning Sleepiness/Alertness:

Table 3 represents the results of the Morning Sleepiness/Alertness on dosing nights during the 4-week treatment period. As noted by the sponsor, subjects in the zolpidem tartrate group reported statistically significantly higher scores (i.e. were more awake and alert) than those in the placebo group ( $p=0.0041$ ). Over the double-blind treatment period, mean scores were 5.7 for those treated with zolpidem tartrate sublingual lozenge and 5.2 for those treated with placebo.



## STUDY ENDPOINT REVIEW

**Table 3. Morning Sleepiness/Alertness over the 4-week Treatment Period-Dosing Nights (Safety Population)**

	3.5 mg Zolpidem	Placebo	P-value
Min, Max	1, 9	1, 9	
LS Mean (SE)	5.71 (0.113)	5.31 (0.114)	0.0107 <sup>a</sup>
95% CI of LS Mean	(5.49, 5.94)	(5.08, 5.53)	
			0.2333 <sup>d</sup>
<b>Treatment Week 4 (n)</b>	129	131	
Mean (SE)	5.7 (0.15)	5.3 (0.16)	
Median	6.0	5.2	
Min, Max	1, 9	1, 9	
LS Mean (SE)	5.63 (0.124)	5.37 (0.123)	0.1301 <sup>a</sup>
95% CI of LS Mean	(5.38, 5.87)	(5.13, 5.61)	
			0.2229 <sup>d</sup>
<b>Treatment Weeks 1 to 2 (n)</b>	150	144	
Mean (SE)	5.6 (0.13)	5.1 (0.13)	
Median	5.6	5.0	
Min, Max	1, 9	1, 9	
LS Mean (SE)	5.54 (0.088)	5.13 (0.090)	0.0009 <sup>a</sup>
95% CI of LS Mean	(5.37, 5.71)	(4.95, 5.30)	
			0.1371 <sup>d</sup>
<b>Treatment Weeks 3 to 4 (n)</b>	139	135	
Mean (SE)	5.7 (0.14)	5.3 (0.15)	
Median	5.9	5.2	
Min, Max	1, 9	1, 9	
LS Mean (SE)	5.68 (0.110)	5.36 (0.111)	0.0362 <sup>a</sup>
95% CI of LS Mean	(5.47, 5.90)	(5.14, 5.58)	
			0.2123 <sup>d</sup>

<sup>a</sup>Baseline Residual Sleepiness = Average of Residual Sleepiness values collected during the 2-week placebo single-blind screening period.

<sup>b</sup>The 2-way ANOVA with mean Residual Sleepiness as the response; treatment and pooled site as fixed effects. P-value shown is for 3.5 mg zolpidem versus. placebo.

<sup>c</sup>P-value for pooled site-by-treatment interaction when pooled site-by-treatment interaction was added to the model given in <sup>b</sup>.

<sup>d</sup>ANCOVA model with mean Residual Sleepiness as the response; treatment and pooled site as fixed effects and average residual sleepiness at baseline as a covariate. P-value shown is for 3.5 mg zolpidem versus. placebo.

<sup>e</sup>P-value for pooled site-by-treatment interaction when pooled site-by-treatment interaction was added to the model given in <sup>d</sup>.

To determine if there were differences in morning sleepiness after nights when no study drug was taken, morning sleepiness/alertness was also assessed on non-medication nights and across all nights of the 4-week treatment period. On the nights when medication was taken, patients in the zolpidem tartrate sublingual lozenge group had improved scores compared to the placebo group. There was no significant difference in sleepiness/alertness scores between active and placebo groups on non-dosing nights (5.3 versus 5.1 respectively; p= 0.1801).

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*Comments: As noted by the sponsor, over the double-blind treatment period, mean scores were 5.7 those treated with zolpidem tartrate sublingual lozenge and 5.2 for those treated with placebo. Although this was a statistically significant difference, it is unclear if it was a clinically meaningful difference.*

### Insomnia Severity Index:

As noted by the sponsor, the ISI results showed not statistical differences between study groups. As noted by the sponsor, the mean ISI score at baseline was 18.1 for subjects who took zolpidem tartrate sublingual lozenge versus 18.3 for those who took placebo. At Week 2 and Week 4, the mean scores ranged between 15 and 17 for both treatments. There were no statistically significant differences between the two groups.

*Comments: As noted above, the ISI is a generic measure of insomnia and is not specific for the target population. Therefore, the data cannot be effectively interpreted.*

## 2.4 Key References for Instrument

1. Smith, M, Wegener S. Measures of sleep. Arthritis & Rheumatism (Arthritis Care & Research) 49: S184–S196, 2003

## 3 APPENDICES

### 3.1 Treatment Morning Sleep Questionnaire

Complete within 30 minutes of arising (4.5 hours to 5 hours post-dose)

1. How long did it take you to fall asleep after the second lights-out? \_\_\_\_\_ Hours \_\_\_\_\_ Minutes
2. How long did you sleep after the second lights-out? \_\_\_\_\_ Hours \_\_\_\_\_ Minutes
3. Did you wake up after the second lights-out? ☐ Yes ☐ No
4. If YES, how many times? \_\_\_\_\_
5. If YES, how long did it take you to fall asleep again after each non-scheduled awakening?
 

_____	First non-scheduled awakening
_____	Second non-scheduled awakening
_____	Third non-scheduled awakening
6. How would you rate the quality of your sleep after the second lights-out? (circle *only* one)
 

_____	1 = Poor
_____	2 = Fair
_____	3 = Good
_____	4 = Excellent
7. How refreshing was your sleep after the second lights-out? (circle *only* one)
 

_____	1 = Poor
_____	2 = Fair
_____	3 = Good
_____	4 = Excellent
8. How would you rate your ability to function this morning? (circle *only* one)
 

_____	1 = Poor
_____	2 = Fair
_____	3 = Good
_____	4 = Excellent

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### 3.2 Insomnia Severity Index (ISI)

1. Over the past 2 weeks rate the severity of your insomnia problem(s).

	None	Mild	Moderate	Severe	Very Severe
Difficulty falling asleep:	0	1	2	3	4
Difficulty staying asleep:	0	1	2	3	4
Problem waking up too early:	0	1	2	3	4

2. Over the past 2 weeks how satisfied/dissatisfied were you with your sleep pattern?

Very Satisfied					Very Dissatisfied
0	1	2	3		4

3. Over the past 2 weeks to what extent did you consider your sleep problem to interfere with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc)

Not at all Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

4. Over the past 2 weeks how noticeable to others do you think your sleeping problem was in terms of impairing the quality of your life?

Not at all Noticeable	Barely	Somewhat	Much	Very Much Noticeable
0	1	2	3	4

5. Over the past 2 weeks how worried/ distressed were you about your sleep problem?

Not at all	A Little	Somewhat	Much	Very Much
0	1	2	3	4

*Guideline for Scoring/ Interpretation:*

*Total score ranges from 0—28*

*Add scores for all seven items (1a + 1b + 1c + 2 + 3 + 4 + 5)*

*0—7 = No clinically significant insomnia      8—14 = Sub threshold Insomnia*

*15—21 = Clinical Insomnia (moderate severity) 22—28 = Clinical Insomnia (severe)*

## STUDY ENDPOINT REVIEW

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this page is the manifestation of the electronic signature.**  
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/s/

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Ann Marie Trentacosti  
4/2/2009 02:21:42 PM  
MEDICAL OFFICER

Laurie Burke  
4/3/2009 05:34:03 PM  
INTERDISCIPLINARY

## DSI CONSULT: Request for Clinical Inspections

**Date:** November 13, 2008

**To:** Constance Lewin, M.D., M.P.H, Branch Chief, GCP1  
Joseph Salewski, Acting Branch Chief, GCP2

**Through:** Leslie K. Ball, M.D., Director  
Division of Scientific Investigations  
Russell Katz, MD Director, Division of Neurology Products

**From:** Cathleen Michaloski, MPH, Regulatory Project Manager  
Carole Davis, DO, Clinical Reviewer  
Division of Neurology Products, HFD-120

**Subject:** **Request for Clinical Site Inspections**  
Application: NDA 22328  
Sponsor: Transcept Pharmaceuticals, Inc.  
Drug: Intermezzo- *still under review in DMETS*

### **Protocol/Site Identification:**

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

This NDA provides data for the following: *New treatment for insomnia – 505 b2 applicant*

This drug (*is not*) a New Molecular Entity (NME)

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
Martin Scharf, PhD Tri-State Sleep Disorders 1275 East Kemper Road Cincinnati, OH 45246 P 513-671-3101 F 513-671-4159	ZI-06-10 ZI-12	20, site 5 19, site 16	insomnia

Site # (Name,Address, Phone number)	Protocol #	Number of Subjects	Indication
D. Alan Lankford, PhD Sleep Disorders Center of Georgia 5505 Peachtree Dunwoody Suite 380 Atlanta, GA 30342 P 404 256 6545 F 404 257 0592	ZI-06-010 ZI-12	16, site 2 14, site 18	insomnia
Yury Furman Pacific Sleep Medical Services 6333 Wilshire Blvd. Los Angeles, CA 90048 P 323-653-3434 F 323-653-6281	ZI-12	16, site 2	insomnia

**Domestic Inspections:**

We have requested inspections because (please check all that apply):

- ☒ Enrollment of large numbers of study subjects
- ☐ High treatment responders (specify):
- ☐ Significant primary efficacy results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ☒ Other (specify): Involved in both pivotal studies

**International Inspections:**

We have requested inspections because (please check all that apply):

- ☐ There are insufficient domestic data
- ☐ Only foreign data are submitted to support an application
- ☐ Domestic and foreign data show conflicting results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ☐ Other (specify):

**Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.**

**Goal Date for Completion: within 7 months (PDUFA is 7/30/09)**

We request that the inspections be performed and the Inspection Summary Results be provided by April 15, 2009. We intend to issue an action letter on this application by July 30, 2009.



**Note to Investigator:**

**Please see attached sponsor audit reports for the 2 pivotal studies (ZI-06-010, and ZI-12)- these will be sent separately.**

Study ZI-06-010 was a single-dose, 2 consecutive nights trial with 5 US sites (total of 82 subjects).  
Study ZI-12 was a 4 week prn (as needed) trial with 25 US sites (total of 295 subjects).

Should you require any additional information, please contact Cathy Michaloski 796-1123.  
Clinical reviewer is Carole Davis 301-796-1930.

Concurrence: (as needed)

*(Name, title)*, Medical Team Leader

*(Name, title)*, Medical Reviewer

*(Name, title)*, Division Director (for foreign inspection requests only)

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/s/

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Cathleen Michaloski  
11/13/2008 02:30:47 PM